Low Calorie Sweeteners: Science and Controversy
Conference Proceedings

Richard D. Mattes, MPH, PhD, RD

Correspondence:

Richard D. Mattes, MPH, Ph.D., R.D.
Distinguished Professor of Nutrition Science
Director of Public Health Graduate Program
Director, Ingestive Behavior Research Center
Purdue University, 113 Stone Hall
Department of Nutrition Science
700 W State Street
West Lafayette, IN 47907-2059
765-496-2791 ph (morning)
765-494-0662 ph (afternoon)
765-496-1168 fax
mattes@purdue.edu

Introduction

This Special Issue summarizes the sixth biennial international conference hosted by the Ingestive Behavior Research Center (IBRC) at Purdue University. The conference was held September, 22-24, 2015 on the Purdue campus. The theme was: High Intensity Sweeteners: Science and Controversy. The goals were to: 1) review current knowledge on the mechanisms and functions of sweet taste; 2) critically assess the evidence related to low calorie sweetener (LCS – the term preferred by conference attendees) effects on: gut function; the microbiome; brain reward systems and energy balance; and 3) Identify future directions for LCS research and applications.

The role of LCS in a healthful diet has been contentious for over 135 years. Controversy arose with the discovery itself of the first LCS, saccharin, and has been ongoing for issues related to the safety of LCS and their efficacy for weight management. Saccharin was discovered initially by the chemist Ira Remsen in 1878 at Johns Hopkins University. However, it was accidentally re-discovered in 1879 by his post-doctoral student, Constantine Fahlberg, while working on derivatives of coal tar products. Fahlberg's origin is itself less than clear, being referenced as American [1], Russian [2] and German-American [3] in different sources. Remsen was not interested in commercializing saccharin, but Fahlberg filed a patent and claimed to be the sole discoverer, much to the displeasure of Remsen. Through the end of the 1800s and beginning of the 1900's, use of saccharin began to grow raising concern by Harvey Wiley, the primary driver of the 1906 Pure Food and Drug Act and founder of the Food and Drug Administration (FDA). Wiley questioned the safety of saccharin and in 1908 proposed banning its use in the food supply. He appealed to then president Theodore Roosevelt to support a ban. However, Roosevelt was not convinced of the harm and is famously reported as stating, "Anyone who

says saccharin is injurious to health is an idiot. Dr. Rixey gives it to me every day” (reportedly as an approach to moderate his weight) [3]. Despite extensive review by multiple regulatory bodies [e.g., 4, 5 see paper by Ashley in this supplement] and clearance by all of them, questions about the safety of LCS persist [6,7].

LCS are widely used to moderate energy intake and body weight, but their efficacy for this purpose has also been the subject of continuous acrimony, often attributable to less than faithful interpretations of the literature by proponents of different perspectives. For example, an American Cancer Society survey of 78,694 females revealed a small, but statistically higher percentage of individuals reporting weight gain among those who used LCS in the year preceding enrollment in the study [8]. This was widely interpreted as evidence that LCS promote weight gain. At the other extreme, a clinical trial designed to assess the efficacy of aspartame to promote weight loss reported no difference in weight loss among 82 aspartame users compared to 81 non-users over a 19 week intervention, but aspartame users gained less weight over the 36 month follow-up period [9]. This was often cited as evidence supporting the efficacy of aspartame for weight loss. However, these were not the conclusions reached by either of the investigators of the two studies. For the Cancer Society study, Stellman and Garfinkle concluded, “These data do not support the hypothesis that long-term AS [aspartame] use either helps in losing weight or prevents weight gain” and for the clinical trial, Blackburn et al., concluded, “...the use of aspartame-containing foods and beverages is as effective at promoting weight loss as the same diet, exercise, and behavior program devoid of aspartame-containing products.” Much of the confusion was bolstered by exposition of extreme views in the scientific community and the media.

The unsettled questions prompted considerable new research through the 1990s and early 2000s. Most of the work entailed preload design trials to assess the effects of LCS on appetite

and short-term trials to measure effects on food intake. A clear evolution of thinking is apparent from the conclusions of reviews on the topics by researchers in the field at the time. These are summarized in Table 1 and Table 2 for appetite and food intake outcome, respectively. Both reveal an early view that LCS were potentially counter-productive for weight loss because they could stimulate appetite and food intake. However, reports then transitioned through uncertainty to a view that LCS were not problematic. Interestingly, the conclusions regarding effects of LCS on body weight were not tightly tied to views about their effects on appetite and energy intake. During this period, published conclusions initially reflected a belief that the evidence linking LCS and body weight was weak and did not support claims that they promote weight gain. Later reports suggested that they may be either ineffective or effective for weight loss and moved to the conclusion that the outcome will be determined by how they are actually used in the diet. That is, if LCS are substituted for energy-yielding sweeteners leading to lower total energy intake, they may aid weight management but this is not likely if they are simply added to the diet without a net reduction of energy intake (as many consumers use them).

It may have appeared that some resolution on the efficacy of LCS for weight management was emerging, but this was not the case. Advances in understanding of human physiology and research capabilities raised new questions. Neural imaging technologies permitted monitoring of brain activity in response to oral exposure and ingestion of LCS. Though not uniformly observed [19], differential responses to LCS and natural sugars in brain reward centers [20, 21] raised new questions about their behavioral and biological effects. Sweet receptors, labeled such because they were first identified in the oral cavity, were discovered throughout the GI tract and in the periphery [22]. Their presence on intestinal enteroendocrine cells and evidence that LCS may elicit the release of gut peptides [23] and alter glucose transport in cell culture studies [24, 25] suggested LCS were not as metabolically inert as previous believed. Greater awareness of the importance of the microbiota in GI function and overall health also prompted

new questions as early trials suggested LCS altered bacterial populations and possibly glycemic responses [26, 27]. Adding to this, meta-analyses yielded conflicting outcomes with prospective cohort trials suggesting LCS use was associated with higher BMI while randomized controlled trials showed the opposite [28]. Thus, there was new scientific substrate for further deliberation. Indeed, the lack of clarity on the role of LCS in the diet was reinforced by the recent report for the Dietary Guidelines Committee [29] who concluded that:

Moderate and generally consistent evidence from short-term RCTs conducted in adults and children supports that replacing sugar-containing sweeteners with low-calorie sweeteners reduces calorie intake, body weight, and adiposity. DGAC Grade: Moderate

Long-term observational studies conducted in children and adults provide inconsistent evidence of an association between low-calorie sweeteners and body weight as compared to sugar-containing sweeteners. DGAC Grade: Limited

However, there is insufficient evidence (due to a paucity of data) to recommend the use of low-calorie sweeteners as a strategy for long-term weight loss and weight maintenance. Since the long-term effects of low-calorie sweeteners are still uncertain, those sweeteners should not be recommended for use as a primary replacement / substitute for added sugars in foods and beverages.

The uncertainty in the scientific community, existence of widespread overweight/obesity nationally and globally, and questions about whether LCS use is more likely to be part of the problem or solution prompted the decision to host an international conference on the role of LCS in a healthful diet. The topic is not new or novel. Symposia on this issue have been held at numerous professional meetings, but without apparent effect with respect to reaching a

consensus view. Often these symposia were designed to present one perspective or to showcase opposing views without a mechanism to resolve them. To move the field forward, the IBRC hosted a conference with a different format. Twenty-one speakers and discussants from five countries were invited to critically assess the state of LCS science in an open forum with over 100 registered attendees.

To set the stage, the conference opened with a plenary lecture on the ecology of sweetness where Gary Beauchamp presented evidence supporting the fundamental importance of sweet taste in the behavior and biology of most, but not all (carnivores), species. This was followed by a presentation on the regulatory processes related to sweeteners by Ashley Roberts who outlined the long history of scrutiny applied to the safety of LCS by many international agencies and uniform clearance by these bodies. Allison Sylvetsky next presented the most recent data on trends in LCS use emphasizing their ubiquity in the food supply and difficulty in quantifying intake levels. The discovery of the sweet receptor in 2001 [30] opened new research on the mechanisms of sweet detection. Grant Dubois reviewed the emerging evidence that a single receptor, the T1R2+T1R3 heterodimer, likely accounts for the detection of the wide array of sweet compounds through their binding to multiple sites on the receptor. However, the possibility of additional detection mechanisms is not excluded [e.g., 31]. Presentations on the role of LCS in energy balance and learning mechanisms rounded out the general overview portion of the conference. Peter Rogers argued that while LCS influence appetitive sensations, these sensations are not strong predictors of ingestive behavior. This may be attributable, in part, to findings described by Ivan De Araujo that sweetness is not as effective a motivator of ingestive behaviors when uncoupled from the delivery of energy.

The conference then turned to a series of four debates on the topics of LCS and 1) gut digestive and endocrine function (presenters: Chris Beglinger and John McLaughlin); 2) the microbiota

(presenters: Jane Shearer and Soraya Shirizi-Beechy); 3) brain reward pathways (presenters: Nicole Avena and John Glendinning); and 4) energy balance (presenters: Sharon Fowler and John Peters). The unique aspect of the debates was that speakers presenting opposing views shared their presentations with the other speaker in their session ahead of the conference. Thus, each was aware of the evidence the other planned to present. This allowed them time to develop insightful rebuttal questions before the conference and each presenter was provided time after the formal presentations to query the other presenter and respond to the questions put to them. Questions were then fielded from the attendees. It was expected this would raise the probability that the best science would emerge and provide a basis for formulating a more objective understanding of the evidence related to LCS use. To track the impact of the debates, all in attendance were asked to rate their view of the science on each of the session topics before and after the debate through an electronic voting program. Interpretation of the impact of the presentations and discussion must be made cautiously because variable numbers of registered attendees voted before and after each session, but it was apparent that shifts in thinking occurred. For example, three shifts of greater than 15% were observed. For the session on gut endocrine effects, the percent of respondents indicating LCS disordered glucose absorption declined from 24% to 5%. The number of attendees indicating they were unsure if LCS alter the microbiota increased from 15% to 37% after the complexity of the issue was revealed by the presentations and discussion. Additionally, there was an increase from 42% to 58% of the attendees responding that LCS did not promote disordered eating through activation of brain reward pathways. Thus, the format seemed to be effective at stimulating new thinking.

The meeting concluded with a session on identifying the remaining gaps in knowledge and most promising new research areas. During this session, the question of what terminology should be used for these sweeteners was discussed. There is no consensus in the literature with reference to high intensity sweeteners, high potency sweeteners, low calorie sweeteners, sugar

substitutes, artificial sweeteners and others. No one term was viewed as fully accurate or desirable, but the consensus view was that the preferred term should be low calorie sweeteners. The primary justification was that the term reasonably captures the functional property of the compounds and may be the most easily understood by consumers.

This special issue includes papers by each of the invited speakers as well as a transcription of the most pertinent points raised during discussion periods that followed the presentations. The papers were all peer-reviewed and the fidelity of the discussion transcription was reviewed by the presenters.

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Table 1

Effects of Low Calorie Sweeteners on Appetite
<p>All studies including a comparison between different sweetness levels (same caloric value – the addition principle) have revealed a stimulatory effect of sweetness on hunger and/or food intake. [10]</p> <p>A review of published data shows that although intense sweeteners have been shown to increase hunger ratings in some studies in humans, this has not been a consistent and reproducible observation. [11]</p> <p>Reports of a small increase in subjective appetite when aspartame is added to water have come from two laboratories^{15,16}. This small transient effect seems specific to the addition of aspartame to water and has not been found in studies utilizing familiar beverages... [12]</p> <p>Artificial sweeteners do not increase energy intake or ratings of hunger [13]</p> <p>No stimulation of appetite was observed following the consumption of intense sweeteners in such foods as ... [14]</p>

Table 2

Effects of Low Calorie Sweeteners on Energy Intake
<p>All studies including a comparison between different sweetness levels (same caloric value – the addition principle) have revealed a stimulatory effect of sweetness on hunger and/or food intake. [10]</p> <p>Aspartame has not been found to increase food intake; indeed, both short term and long-term studies has shown that consumption of aspartame-sweetened foods or drinks is associated with either no change or a reduction in food intake. [15]</p> <p>Any slight effect on perceived hunger has not been translated into an increase in food ingestion... [11]</p> <p>There is no evidence that the addition of an intense sweetener to a plain stimulus promotes appetite or results in increased food consumption during some later meal. [16]</p> <p>Artificial sweeteners do not increase energy intake or ratings of hunger. [13]</p> <p>Most studies that have measured food intakes following ingestion of aspartame-sweetened preloads, as compared to sucrose, reported no significant effects. [14]</p>

Table 3

Effects of Low Calorie Sweeteners on Body Weight
<p>... it has little impact on the controls of food intake and body weight. [15]</p> <p>The published database does not support the concept that the consumption of intense sweeteners results in a paradoxical increase in calorie intake and body weight. [11]</p> <p>It seems unlikely, however, that the availability of intense sweeteners, and the food and beverages that contain them, has had any impact on the prevention of weight gain. [12]</p> <p>Consequently, it does appear to be difficult to under eat (diet) simply by substituting artificial sweeteners for carbohydrates. [17]</p> <p>there has been no satisfactory study that has considered the value of artificial sweeteners in long-term weight maintenance. [13]</p> <p>The meta-analyses demonstrate that using foods and drinks sweetened with aspartame instead of sucrose results in a significant reduction in both energy intakes and bodyweight. [18]</p> <p>Their ultimate effect will depend on their integration within a reduced energy diet. [14]</p>