LOW CALORIE SWEETENERS AND NUTRITION: NEW DEVELOPMENTS AND REALITY CHECKS

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Purdue University
West Lafayette, IN, USA
High Intensity Sweeteners: Science and Controversy

Ira Remsen
Chemist
1901-1912 President of Johns Hopkins

Constantin Fahlberg
Chemist, Post-Doctoral Fellow
Johns Hopkins
High Intensity Sweeteners: Science and Controversy

Theodore Roosevelt
President 1901-1909

Harvey Wiley
Founded FDA, Pure Food and Drug Act 1906
Anyone who says saccharin is injurious to health is an idiot. Dr. Rixey gives it to me every day.”
<table>
<thead>
<tr>
<th>RELATIVE WEIGHT AT START (N)</th>
<th>USE ARTIFICIAL SWEETENER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>VERY LOW (17,416)</td>
<td>11.9 32.3</td>
</tr>
<tr>
<td>LOW (15,901)</td>
<td>14.9 39.0</td>
</tr>
<tr>
<td>AVERAGE (15,425)</td>
<td>18.5 41.5</td>
</tr>
<tr>
<td>HIGH (15,263)</td>
<td>22.2 41.9</td>
</tr>
<tr>
<td>VERY HIGH (14,689)</td>
<td>28.2 31.9</td>
</tr>
</tbody>
</table>

Fig. 2. Percentage of women who gained or lost weight or whose weight did not change during the 1-year period prior to enrollment in the study, according to artificial sweetener use. Percentages are adjusted for age in 5-year intervals.

(N=78,694 Females)
FIGURE 1. Percentage change in body weight over 175 wk for women participating in a comprehensive weight-control program with (aspartame) and without (no-aspartame) aspartame-containing products. \( \bar{x} \pm SEM \) for each treatment group at 1-wk intervals during 19 wk of active weight loss and at the end of 36 mo of maintenance and follow-up.
CONCLUSIONS

• Stellman & Garfinkel
  • “These data do not support the hypothesis that long-term AS [aspartame] use either helps in losing weight or prevents weight gain.”

• Blackburn et al.
  • “…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.”
Effects of NNS on Appetite

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. (Rogers and Blundell 1989)

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. (Renwick 1994)

Reports of a small increase in subjective appetite when aspartame is added to water have come from two laboratories. This small transient effect seems specific to the addition of aspartame to water and has not been found in studies utilizing familiar beverages... (Anderson and Leiter 1996)

Artificial sweeteners do not increase energy intake or ratings of hunger (Benton 2005)

No stimulation of appetite was observed following the consumption of intense sweeteners in such foods as ...(Bellisle and Drewnowski 2007)
Effects of NNS on Energy Intake

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. (Rogers and Blundell 1989)

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 (Rolls 1991)

Any slight effect on perceived hunger has not been translated into an increase in food ingestion… (Renwick 1994)

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. (Drewnowski 1995)

Artificial sweeteners do not increase energy intake or ratings of hunger (Benton 2005)

Most studies that have measured food intakes following ingestion of aspartame-sweetened preloads, as compared to sucrose, reported no significant effects (Bellisle and Drewnowski 2007)
Effects of NNS on Body Weight

… it has little impact on the controls of food intake and body weight (Rolls 1991)

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. (Renwick 1994)

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. (Anderson and Leiter 1996)

Consequently, it does appear to be difficult to undereat (diet) simply by substituting artificial sweeteners for carbohydrates (Blundell and Green 1996)

There has been no satisfactory study that has considered the value of artificial sweeteners in long-term weight maintenance (Benton 2005)

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 (de la Hunty, Gibson et al. 2006)

Their ultimate effect will depend on their integration within a reduced energy diet. (Bellisle and Drewnowski 2007)
RECENT ADVANCES

• Microbiota
• Neural imaging
• Sweet receptors in the GI tract
RECENT PROVOCATIVE QUESTIONS

• Oral sensing – activation of reward centers
• Microbiota – carbohydrate metabolism, energy extraction
• Gut peptide secretion – appetitive signaling
• Disrupted learning – stimulation of appetite and energy intake
• Epidemiological studies – positive association between HIS use and BMI
SWEET ADDICTION - CONSIDER

- Was food less palatable earlier in time?
- If highly processed foods are addictive because they are rapidly absorbed, why is fat implicated?
- There is no evidence linking any specific nutrient or food to addictive behavior – any food can be rewarding when hungry
- There is an order of magnitude difference in dopamine response to drugs of abuse compared to food
- Best estimates are addiction is present only in <5% of the population, so does not account for obesity prevalence
- Binge Eating Disorder is not reliably linked to Food Addiction
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Table 1. Characteristics of experimental animals.

<table>
<thead>
<tr>
<th></th>
<th>Chow</th>
<th>High Fat</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Water</td>
<td>Aspartame</td>
</tr>
<tr>
<td>Final weight (g)</td>
<td>488±5.5</td>
<td>453±13.2</td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td>7.1±0.5</td>
<td>11.9±1.0†</td>
</tr>
<tr>
<td>Liver triglycerides (mM)</td>
<td>17.7±1.6</td>
<td>16.8±0.9</td>
</tr>
<tr>
<td>Food consumption (kcal/day)</td>
<td>132.1±2.3</td>
<td>109.5±8.0†</td>
</tr>
<tr>
<td>Fluid consumption (ml/day)</td>
<td>42.4±1.3</td>
<td>47.7±3.9†</td>
</tr>
<tr>
<td>Sweetener consumption (mg/kg/day)</td>
<td>---</td>
<td>7.0±0.5</td>
</tr>
<tr>
<td>Fasting blood glucose (mM)</td>
<td>5.4±0.2</td>
<td>6.9±0.4†</td>
</tr>
<tr>
<td>Plasma Insulin (pmol/l)</td>
<td>143.1±13.8</td>
<td>143.8±27.5</td>
</tr>
<tr>
<td>Plasma free fatty acids (mM)</td>
<td>0.24±0.03</td>
<td>0.25±0.02</td>
</tr>
<tr>
<td>Plasma GIP (pmol/l)</td>
<td>12.2±2.8</td>
<td>8.4±2.4</td>
</tr>
</tbody>
</table>

Food and fluid consumption were recorded during week 7 of the diet. Glucose was measured in the fasted state, all others including plasma free fatty acids, liver triglycerides and plasma insulin were measured from samples taken at sacrifice (non-fasting). All data includes n = 9–12 animals/group, data is represented as mean ± SE. *p<0.05 for diet (chow vs. high fat) within fluid treatments (water, aspartame). †p<0.05 for fluid (water vs. aspartame) within diet (chow, high fat). Data from the water controls (chow, high fat) were part of a shared control group that has been previously published [15]. Permission to reuse the data in this table was obtained from Elsevier.

doi:10.1371/journal.pone.0109841.t001

Palmnas et al., PLOSone 2014;9:e109841
Palmnas et al., PLOSone 2014;9:e109841
Suez et al., Nature 2014 doi:10.1038/nature13793
RECENT PROVOCATIVE QUESTIONS

- Oral sensing – activation of reward centers
- Microbiota – carbohydrate metabolism, energy extraction
- Gut peptide secretion – appetitive signaling
- Disrupted learning – stimulation of appetite and energy intake
- Epidemiological studies – positive association between HIS use and BMI
Jang et al., PNAS 2007;104:38:15069-15074.
Figure 1. Artificial sweeteners and glucose stimulate glucose absorption

A, effect on 20 mM glucose absorption of sucrrose (▲, 1 mM, S arrowhead) added at 30 min and of phloretin added at 40 min (◼, 1 mM P arrowhead): effect on sucrrose-stimulated glucose absorption (0–40 min) of phloretin added at 40 min (●). B, concentration dependence of stimulation of glucose absorption by sucrrose; 20 mM glucose and sucrrose were perfused in the absence (■, 0–40 min) and presence (◼, 40–80 min) of 1 mM phloretin.

Human Participants (BMI ~18kg/M²) Fasting
Intraduodenal infusion of sucralose (4mM, 600 ml, ~14mg/kk) + glucose (~30g) + 3-OMG (~3g) over 2.5 hours

Ma et al., Br J Nutr 2010,104:803-806
Human Participants (Obese: BMI ~ 40kg/m²) Fasting
Oral ingestion of sucralose (2 mM, 60 ml, ~0.64 mg/kg) + glucose (~75g): OGTT

Pepino et al., Diabetes Care 2013;36:2530-2535
Human Participants (BMI ~26kg/m²), Fasting
Oral ingestion of 8 oz caffeine-free diet soda (sucralose/Ace-K blend) + glucose (~75g), OGTT

Brown et al., Diabetes Care 2009;32:2184-2186
Human participants (BMI ~30.3kg/m²), Fasted
Oral ingestion of 24mg of sucralose in 200ml water; 72mg or aspartame in 200ml of water or 200ml of water before 75g CHO OGTT

Temizkan et al., Eur J Clin Nutr 2014; doi:10.1038/ejcn.2014.208
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Figure 1. Mean calories consumed of a sweet, chocolate-flavored pre-meal (open bars) and of a subsequent lab chow test meal (cross-hatched bars) for rats that were given prior training with different sweet tastes that were consistently paired with calories (Group Consistent) and for rats that were trained with sweet tastes that were inconsistently paired with calories (Group Inconsistent). Error bars depict standard error of the mean (s.e.m.).

Figure 5. Total energy intake during 14 days of consumption of sweet predictive or sweet nonpredictive yogurt diets in Experiment 2. Error bars represent standard error. *p < .05.
Fig. 2. Effects of sweet taste on measures of cumulative energy intake across the day in HASB and LASB. Hashed bars represent LASB, solid bars represent HASB. In each pair, the dark bars on the left represent consumption after the W preload, the pale bars on the right represent consumption after the AS preload. □ Significant differences (p < 0.05) between W and AS preloads in LASB, no differences in HASB. # Significant differences (p < 0.05) between LASB and HASB, independent of preload.

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HIS Prospective Cohort Studies - Substitute HIS for NS in Foods or Beverages

**Figure 4.** Forest plots derived from random effects models summarizing results from the meta-analysis of prospective cohort studies that examined LCS intake and change in BMI (A) or body weight (B). The squares represent the mean correlation within each study, with 95% CIs represented by horizontal lines. Square size is proportional to the weight of each study. Diamonds represent the WGMС. Reference numbers are shown in parentheses. *P < 0.05. LCS, low-calorie sweetener; ref, reference; WGMС, weighted group mean correlation.
RCT trials - Replacement of NS with HIS

All Participants

Age

Sex

Food Form
# HIS Prospective Cohort Studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Follow-up (months)</th>
<th>Sample size</th>
<th>Weight (%)</th>
<th>Change in BMI per year [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fowler et al, 2008 (M+F, adult)</td>
<td>96</td>
<td>3371</td>
<td>13.4</td>
<td>0.03 [ 0.01 , 0.04 ]</td>
</tr>
<tr>
<td>Chen et al, 2009 (M+F, adult)</td>
<td>18</td>
<td>810</td>
<td>0.7</td>
<td>-0.09 [-0.17 , -0.01 ]</td>
</tr>
<tr>
<td>Vanselow et al, 2009 (M+F, adult)</td>
<td>60</td>
<td>2294</td>
<td>9.6</td>
<td>0.00 [-0.01 , 0.02 ]</td>
</tr>
<tr>
<td>Pan et al, 2013 (F, adult) - NHS</td>
<td>48</td>
<td>50013</td>
<td>20.1</td>
<td>-0.01 [-0.01 , -0.01 ]</td>
</tr>
<tr>
<td>Pan et al, 2013 (F, adult) - NHS II</td>
<td>48</td>
<td>52987</td>
<td>19.8</td>
<td>-0.01 [-0.01 , -0.01 ]</td>
</tr>
<tr>
<td>Pan et al, 2013 (M, adult) - HPS</td>
<td>48</td>
<td>21988</td>
<td>19.8</td>
<td>0.00 [-0.01 , 0.00 ]</td>
</tr>
<tr>
<td><strong>RE estimate for sub-group</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sig. test of ES = 0: Z = -0.841 , p = 0.400</td>
<td></td>
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<tr>
<td>Het.: p &lt; 0.001 , I^2 = 88.9 %</td>
<td></td>
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<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berkey et al, 2004 (M, children)</td>
<td>12</td>
<td>5067</td>
<td>0.5</td>
<td>0.12 [ 0.02 , 0.21 ]</td>
</tr>
<tr>
<td>Berkey et al, 2004 (F, children)</td>
<td>12</td>
<td>6688</td>
<td>0.8</td>
<td>0.05 [-0.02 , 0.12 ]</td>
</tr>
<tr>
<td>Striegel-Moore et al, 2006 (F, children)</td>
<td>120</td>
<td>2371</td>
<td>15.0</td>
<td>0.00 [-0.01 , 0.01 ]</td>
</tr>
<tr>
<td>Laska et al, 2012 (M, children)</td>
<td>24</td>
<td>276</td>
<td>0.1</td>
<td>-0.06 [-0.29 , 0.18 ]</td>
</tr>
<tr>
<td>Laska et al, 2012 (F, children)</td>
<td>24</td>
<td>286</td>
<td>0.1</td>
<td>0.05 [-0.18 , 0.28 ]</td>
</tr>
<tr>
<td><strong>RE estimate for sub-group</strong></td>
<td></td>
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<tr>
<td>Sig. test of ES = 0: Z = 1.213 , p = 0.225</td>
<td></td>
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<tr>
<td>Het.: p = 0.069 , I^2 = 54.1 %</td>
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<tr>
<td><strong>Overall RE estimate</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.00 [-0.01 , 0.00 ]</td>
</tr>
<tr>
<td>Het.: p &lt; 0.001 , I^2 = 82.1 %</td>
<td></td>
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<tr>
<td>Sig. test of ES = 0: Z = -0.600 , p = 0.549</td>
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</table>

Change in BMI per year (kg/m^2/year)
## Longer-Term Intervention Trials (LCS vs Sugar)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Follow-up (months)</th>
<th>Sample size</th>
<th>Weight (%)</th>
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<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanders et al, 1988 (M+F)</td>
<td>3</td>
<td>59</td>
<td>7.4</td>
<td>-0.40 [-2.75, 1.95]</td>
</tr>
<tr>
<td>Blackburn et al, 1997 (F)</td>
<td>40</td>
<td>163</td>
<td>11.5</td>
<td>-5.10 [-6.29, -3.91]</td>
</tr>
<tr>
<td>Raben et al, 2002 (M+F)</td>
<td>2.5</td>
<td>41</td>
<td>11.8</td>
<td>-2.60 [-3.71, -1.49]</td>
</tr>
<tr>
<td>Reid et al, 2007 (F)</td>
<td>1.25</td>
<td>66</td>
<td>12.4</td>
<td>-0.45 [-1.39, 0.49]</td>
</tr>
<tr>
<td>Njike et al, 2009 (M+F)</td>
<td>6</td>
<td>77</td>
<td>13.9</td>
<td>-0.09 [-0.49, 0.31]</td>
</tr>
<tr>
<td>Reid et al, 2010 (M+F)</td>
<td>1.25</td>
<td>53</td>
<td>11.9</td>
<td>-0.49 [-1.58, 0.60]</td>
</tr>
<tr>
<td>Tate et al, 2012a (M+F)</td>
<td>6</td>
<td>210</td>
<td>11.8</td>
<td>-0.80 [-1.90, 0.30]</td>
</tr>
<tr>
<td>Maersk et al, 2012a (M+F)</td>
<td>6</td>
<td>22</td>
<td>5.6</td>
<td>-1.20 [-4.25, 1.85]</td>
</tr>
<tr>
<td><strong>RE estimate for adult subgroup</strong></td>
<td></td>
<td></td>
<td></td>
<td>-1.41 [-2.62, -0.20]</td>
</tr>
<tr>
<td>Sig. test of ES = 0; Z = -2.280, p = 0.023</td>
<td></td>
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<tr>
<td>Het.: p &lt; 0.001, I² = 90.5 %</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Ruyter et al, 2012 (M+F)</td>
<td>18</td>
<td>641</td>
<td>13.7</td>
<td>-1.02 [-1.52, -0.52]</td>
</tr>
<tr>
<td><strong>Overall RE estimate for LES vs sugar-sweetened beverages</strong></td>
<td></td>
<td></td>
<td></td>
<td>-1.35 [-2.28, -0.42]</td>
</tr>
<tr>
<td>Sig. test of ES = 0; Z = -2.854, p = 0.004</td>
<td></td>
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<tr>
<td>Het.: p &lt; 0.001, I² = 89.2 %</td>
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</tbody>
</table>

**Mean difference (kg)**

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Rogers et al., Int J Obes 2015; doi: 10.1038/ijo.2015.177
### Longer-Term Intervention Trials (LCS vs Water)

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<tr>
<td>Tate et al, 2012b (M+F)</td>
<td>6</td>
<td>213</td>
<td>38.7</td>
<td>-0.60 [-1.77, 0.57]</td>
</tr>
<tr>
<td>Maersk et al, 2012b (M+F)</td>
<td>6</td>
<td>25</td>
<td>10.0</td>
<td>-0.50 [-3.42, 2.42]</td>
</tr>
<tr>
<td>Peters et al, 2014 (M+F)</td>
<td>3</td>
<td>303</td>
<td>51.4</td>
<td>-1.86 [-2.72, -1.00]</td>
</tr>
</tbody>
</table>

**Overall RE estimate for LES vs water**

Sig. test of ES = 0: Z = -2.479, p = 0.013
Het.: p = 0.197, I² = 38.4 %
Figure 2 (a) Fitted model for group mean percent body weight change over time using a polynomial mixed effects model, which was fit to the weekly weight data expressed as percent change from the individual baseline weight, and an intention-to-treat analysis. Error bars represent the standard error of the mean. \( P < 0.001 \) for between-group comparisons at all time points. (b) Fitted model for group mean percent body weight regained from point of maximum weight loss using an intention-to-treat analysis. \( P < 0.001 \) for difference in velocity of weight regain between groups.

Figure 3 Percentage of participants who achieved at least 5% weight loss. Results based on \( \chi^2 \) analysis. Analysis includes those participants who dropped out of the study, using the baseline observation carried forward. This analysis mimics the clinical setting. Difference = 0.1865 or 18.65% difference between groups with 90% CI (0.1065-0.2735), \( n = 154 \) for NNS, \( n = 149 \) for water. \( *P < 0.001 \).
SUMMARY

• The sweetness of LCS may activate brain reward centers, but the implications for ingestive behavior and body weight are questionable.

• Cohort studies suggest LCS consumption is associated with higher BMI, but RCT’s indicate LCS use is associated with lower BMI.

• Multiple mechanisms have been proposed implicating LCS use with increased energy intake, but strong evidence is available for none.