High Intensity Sweeteners and Energy Balance

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Rationale for NNS Use

- Economics
- Sensory properties of foods
- Health
<table>
<thead>
<tr>
<th>Year</th>
<th>Grams per capita</th>
<th>% of pop. Consuming</th>
<th>Grams per consumer</th>
<th>Grams per capita</th>
<th>% of pop. Consuming</th>
<th>Grams per consumer</th>
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<td>381</td>
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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)
FIG. 1. The effect of consuming water (dotted line), glucose (circles), acesulfame-K (diamonds), aspartame (squares) and saccharin (triangles) on ratings of hunger, desire to eat, fullness and prospective consumption during one hour after the loads. Statistically significant (t-test, \( p < 0.05 \)) changes from baseline (i.e., ratings made immediately before the loads were consumed) are indicated by closed symbols. See text for statistical analysis comparing the effects of the different preloads.
Figure 1  Change in hunger ratings over the 90 minutes following ingestion of 200 ml of water, plain soup broth (non-nutritive) or soup broth containing polyose (200 kcals) on 3 separate days by the same 20 individuals.
Effects of NNS on Appetite

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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)

In 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 off 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 both energy intakes and bodyweight (de la Hunty, Giibson et al. 2006)

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


**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. \( \bar{x} \pm \text{SEM} \) 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.”
Mechanisms By Which NNS May Stimulate Appetite

• Cephalic Phase Stimulation
• Nutritive and Osmotic Effects
• Gut peptide Response
• Palatability
Cephalic Phase Responses

**Stimulus**
- Cognition
- Sound
- Appearance
- Odor / Tactile
- Taste / Tactile

**Site**
- Thermogenic system
- Salivary glands
- Cardiovascular system
- Renal System
- Pancreas
- Gastrointestinal tract

**Effect**
- Increased thermogenesis.
- Increased salivary flow/ altered salivary composition.
- Increased heart rate and mesenteric flow/ decreased cardiac output and stroke volume.
- Compensatory changes in diuresis and natriuresis.
- Increased digestive enzyme secretion and hormone release.
- Increased acid and digestive enzyme secretion, motility, gut hormone release and pressure.
FIGURE 3. Mean ± SE cephalic phase insulin release of 10 normal weight men after consumption of (1) water (upper graph), (2) cherry-flavored beverage sweetened with aspartame (middle graph), and (3) cherry-flavored beverage sweetened with aspartame and a peanut butter sandwich.
FIG. 2. The effect of equilibrated D-glucose on the release of insulin. Four different concentrations of the glucose (II: 277 mM, n=8; III: 555 mM, n=9; IV: 1110 mM, n=12; V: 2220 mM, n=9) were applied on the tongue as sweet stimuli. Plasma concentrations of insulin 3 min after the stimulation were indicated. Values are means±SEM. *p<0.01, **p<0.005 and ***p<0.001; significantly different from the value without stimulation (I: n=8).

Fig. 2. (a) Effect of taste stimulation with sucrose on plasma insulin concentrations from baseline (μIU/mL) of healthy humans (n = 20) (means, S.E.M.) after subjects sipped and spat out the solutions after 45 s. An arrow indicates t = 0 min. Significant differences (*) were found between concentration before stimulation and 5 min after sucrose stimulation (p < 0.05). (b) Effect of taste stimulation with saccharin on plasma insulin concentrations from baseline (μIU/mL) of healthy humans (n = 20) (means, S.E.M.) after subjects sipped and spat out the solutions after 45 s. An arrow indicates t = 0 min. Significant differences (*) were found between concentration before stimulation and 5 min after sucrose stimulation (p < 0.05).
Potential Effects of Cephalic Phase Responses to NNS

• Increase Intake
  – Stimulates insulin release
Positive AUC = 100; Total AUC = 100
Positive AUC = 120; Total AUC = 92
Difference 20 8
Potential Effects of Cephalic Phase Responses to NNS

• Increase Intake
  – Stimulates insulin release

• Decrease Intake
  – Stimulates insulin release
Fig. 2a. The effect of intraventricular insulin (100 μU/kg/day) on food intake in free feeding baboons (35). Note the progressive effect of a constant infusion and the delayed recovery time. b The effect of intraventricular insulin (100μU/kg/day) on body weight. Same six baboons as 2A. Note that body weight recovers sooner than food intake.
Carbohydrate and Appetite, Food Choice, Energy Balance and Body Weight

↑ GI ↑ Insulin ↓ Glucose

↑ Hunger ↑ Intake +EB ↑ Wt

↓ GI ↓ Insulin ↓ Leptin
Fig. 2. Mean ± SE venous glucose concentrations (top) and plasma insulin concentrations (bottom) during euglycemic iv infusions of control (■), low-dose insulin (0.8 mU·kg⁻¹·min⁻¹; □), and high-dose insulin (1.6 mU·kg⁻¹·min⁻¹; ▲); n = 14 subjects.

Fig. 3. Change from baseline in ratings of hunger (top) and fullness (bottom) during euglycemic iv infusions of control (■), low-dose insulin (□), and high-dose insulin (▲); n = 14. Significant effect of time on hunger and fullness [P < 0.01 by analysis of variance (ANOVA)] but no significant effect of treatment on either hunger or fullness.

Fig. 4. Mean ± SE venous glucose concentrations (top) and plasma insulin concentrations (bottom) during iv infusion of 25% glucose (○) and euglycemic iv infusions of control (■), low-dose insulin (□), and high-dose insulin (▲); n = 12.

Fig. 5. Change from baseline in ratings of hunger (top) and fullness (bottom) during iv infusion of 25% glucose (○) and euglycemic iv infusions of control (■), low-dose insulin (□), and high-dose insulin (▲); n = 12. Significant effect of time on hunger and fullness (P < 0.01 by ANOVA) but no significant effect of treatment on either hunger or fullness.

Mechanisms by which NNS may Stimulate Appetite

• Cephalic Phase Stimulation
• Nutritive and Osmotic Effects
• Gut peptide Response
• Palatability
Figure 1 Gastric emptying profile of orally administered sucrose and maltose solutions and unsweetened water control. ANOVA followed by Tukey's procedure indicates that the emptying rates of both sucrose and maltose are significantly slower than that of water from $t=30$ min ($P<0.05$) and the emptying rate of maltose is significantly slower than sucrose for the majority of time points from $t=40$ to $t=160$ min ($P<0.05$).

Lavin et al., Int'l J Obes 2002;26:80-86.
Bergh et al., Physiol Behav 2003;78:143-147.
Mechanisms by which NNS may Stimulate Appetite

- Cephalic Phase Stimulation
- Nutritive and Osmotic Effects
- Gut peptide Response
- Palatability
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 sucralose (▲, 1 mM, S arrowhead) added at 30 min and of phloretin added at 40 min (■, 1 mM P arrowhead): effect on sucralose-stimulated glucose absorption (0–40 min) of phloretin added at 40 min (○). B, concentration dependence of stimulation of glucose absorption by sucralose; 20 mM glucose and sucralose were perfused in the absence (□, 0–40 min) and presence (■, 40–80 min) of 1 mM phloretin.
Fig. 5. Perceptions of hunger (A) and fullness (B) following intragastric infusion of equisweet 500-ml solutions of glucose (560 mosmol/kgH₂O), fructose (290 mosmol/kgH₂O), saccharin [50 mg (0.2 μM)], aspartame [200 mg (0.67 μM)], and water (volumetric control). There was an effect of time, but no differential effect of treatment, on perceptions on hunger or fullness. Data shown are mean (SE); n = 8.
Brown et al., Diabetes Care 2009;32:2184-2186.
Mechanisms by which NNS may Stimulate Appetite

- Cephalic Phase Stimulation
- Nutritive and Osmotic Effects
- Gut peptide Response
- Palatability
Palatability Effects on Appetite

• Enhances motivation to eat
  – Hill et al., Appetite 1984;5:361
  – Yeomans et al., Appetite 1997;29:61

• No Effect on motivation to eat
  – Yeoman & Symes Appetite 1999;32:383

• Diminishes motivation to eat
  – Warwick et al., Physiol Behav 1993;53:553
  – DeGraaf et al., Physiol Behav 1999;66:681
Glendinning et al., Appetite 2010;101:331-343.
FIG. 2. Hedonic ratings of individual sucrose likers to sucrose, glucose, and fructose solutions.
Mechanisms By Which NNS May Stimulate Energy Intake

- Stimulate fat intake
- Informed use increases intake
- Loss of signal fidelity
- Water effects
- Activation of reward systems
- Training the palate
- Inherent liking
Table 4. Change in the composition of the diet resulting from the covert substitution of sugar with aspartame (n = 10) or aspartame with sugar (n = 4); mean values ± SD

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<td>Period I</td>
<td>Period II</td>
<td>Period I</td>
<td>Period II</td>
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<tr>
<td>Energy (kcal)</td>
<td>3226 ± 625</td>
<td>2966 ± 520**</td>
<td>3517 ± 635</td>
<td>3782 ± 785*</td>
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<tr>
<td>Carbohydrate (kcal)</td>
<td>1838 ± 403</td>
<td>1447 ± 293†</td>
<td>1715 ± 330</td>
<td>2108 ± 445***</td>
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<tr>
<td>Fat (kcal)</td>
<td>850 ± 230</td>
<td>945 ± 251†</td>
<td>1151 ± 288</td>
<td>1093 ± 307</td>
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<td>Protein (kcal)</td>
<td>487 ± 72</td>
<td>528 ± 54†</td>
<td>598 ± 76</td>
<td>534 ± 85</td>
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<td>Alcohol (kcal)</td>
<td>51 ± 7</td>
<td>46 ± 5</td>
<td>53 ± 5</td>
<td>47 ± 4</td>
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Value differs from that for Period I: *p < 0.05; **p < 0.02; ***p < 0.01; †p < 0.001.
FIGURE 2. Mean (± SEM) change from baseline of reported fat intake for control (○), reduced-fat (□), and reduced-sugar (△) groups.
Mechanisms By Which NNS May Stimulate Energy Intake

- Stimulate fat intake
- Informed use increases intake
- Loss of signal fidelity
- Water effects
- Activation of reward systems
- Training the palate
- Inherent liking
**MEAN (SD) DAILY ENERGY INTAKE BY INDIVIDUALS WHO WERE KNOWLEDGEABLE REGARDING THE COMPOSITION OF AN EXPERIMENTAL BREAKFAST CEREAL AND THOSE WHO WERE NAIVE IN THIS RESPECT DURING BASELINE AND EXPERIMENTAL PERIODS**

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<th>Kcal Intake</th>
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<tr>
<td>Baseline (informed) (n = 12)</td>
<td>2400 ± 711</td>
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<tr>
<td>Baseline (naive) (n = 12)</td>
<td>2356 ± 625</td>
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<td>Aspartame (informed) (n = 12)</td>
<td>2488 ± 540</td>
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<td>Aspartame (naive) (n = 12)</td>
<td>2299 ± 417</td>
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<tr>
<td>Sucrose (informed) (n = 12)</td>
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<td>Sucrose (naive) (n = 12)</td>
<td>2229 ± 350</td>
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<tr>
<td>Plain (informed) (n = 12)</td>
<td>2393 ± 456</td>
</tr>
<tr>
<td>Plain (naive) (n = 12)</td>
<td>2208 ± 233</td>
</tr>
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</table>

Mattes Physiol Behav 1990;47:1037-1044.
Mechanisms By Which NNS May Stimulate Energy Intake

• Stimulate fat intake
• Informed use increases
• Loss of signal fidelity
• Water effects
• Activation of reward systems
• Training the palate
• Inherent liking
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.

Fig. 3. Effects of energy 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 pale bars on the left represent consumption after the AS preload, the dark bars on the right represent consumption after the NS preload. Significant differences (p < 0.05) between LASB and HASB, independent of preload.

Mechanisms By Which NNS May Stimulate Energy Intake

- Stimulate fat intake
- Informed use increases intake
- Loss of signal fidelity
- Water effects
- Activation of reward systems
- Training the palate
- Inherent liking
Figure 1. Mean (± SEM) intake of flavored food (top three panels) and fluid (bottom panel) by groups of 11 rats given 0.2% saccharin, 0.9% NaCl, or a mixture of the two, during the first 2 h of the dark period. (The open bars in the top three panels show food intake with water as the only available fluid; the shaded bars show food intake with both water and solution available). □, Saccharin; ●, NaCl; ▲, Saccharin + NaCl.
Mechanisms By Which NNS May Stimulate Energy Intake

- Stimulate fat intake
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| Correlations between sensitivity to punishment and sensitivity to reward scales and each of the nine subscales of the food cravings questionnaires-trait version |
|-------------------------------------------------|-----------------|-----------------|
| Sensitivity to punishment | Sensitivity to reward |
| 1. Plans or intentions to eat | 0.13 | 0.32** |
| 2. Anticipation of positive reinforcement from eating | −0.01 | 0.25* |
| 3. Anticipation of negative reinforcement from eating | 0.10 | 0.25* |
| 4. Lack of control over eating | 0.03 | 0.24* |
| 5. Thoughts or preoccupation with food | 0.17 | 0.21* |
| 6. Craving as a physiological state or hunger | 0.07 | 0.29** |
| 7. Emotions experienced before or during food cravings | 0.04 | 0.23* |
| 8. Environmental cues that may trigger food cravings | 0.15 | 0.28** |
| 9. Guilt from cravings and/or for giving into them | −0.12 | 0.11 |

*p < 0.05, **p < 0.005.
Fig. 1. Fitted sensitivity to reward by BMI, for a hypothetical group composed equally of males and females. The “rug plot” at the bottom of each panel shows the distribution of BMI. The broken lines give a 95-percent point-wise confidence envelope around the fit.
Mechanisms By Which NNS May Stimulate Energy Intake

• Stimulate fat intake
• Informed use increases intake
• Loss of signal fidelity
• Water effects
• Activation of reward
• Training the palate
• Inherent liking
A. Change in preference after repeated exposure to orangeade with 0.42M sucrose and 0.02 M added citric acid
B. Change in preference after repeated exposure to orangeade with 0.42M sucrose
C. Change in preference after repeated exposure to orangeade with 0.42M sucrose and 0.043 M added citric acid
D. Change in preference after repeated exposure to orangeade with 0.42M sucrose

Fig. 2. Mean ranking number (±S.E.M.) for preference of sour and sweet orangeades at baseline and after repeated exposure (after exp) to these specific beverages, shown for children (A and B) and adults (C and D) divided by Sweet (●), Sour (○), and Control Groups (□)
Mechanisms By Which NNS May Stimulate *Energy Intake*

- Stimulate fat intake
- Informed use increases intake
- Loss of signal fidelity
- Water effects
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- Inherent liking
Summary

• A relatively small proportion of the population consumes high intensity sweeteners, but the prevalence of consumers is growing.

• In a non-energy yielding medium high intensity sweeteners may stimulate appetite.

• There is little evidence that high intensity sweeteners stimulate food intake or promote positive energy balance.

• Multiple mechanisms have been proposed implicating high intensity sweetener use with increased energy intake, but strong evidence is available for none. Still, several warrant further investigation:
  – Cognitive effects
  – Water effects
  – Gut signaling