Artificial Sweeteners and Obesity: More than an Association?

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Disclosure: No conflicts of interest
Artificial Sweeteners and Obesity

Outline

1) Brief overview of commonly used artificial sweeteners and how they convey sweetness

2) Studies reporting an association between artificial sweetener use and obesity

3) Data & concepts refuting or supporting a causal role
FDA Regulates 6 Artificial Sweeteners

- **Sucrose**
- **Saccharin** 300x ADI ~ 3 sodas
- **Aspartame** 200x ADI ~ 18 sodas
- **Acesulfame-K** 200x ADI ~ 30 sodas
- **Sucralose** 600x ADI ~ 6 sodas
- **Neotame & Advantame** 10,000-20,000x ADI
FDA Regulates 6 Artificial Sweeteners

- **Sucrose**: Accepted Daily Intake (ADI)
- **Saccharin**: ADI ~ 3 sodas
- **Aspartame**: ADI ~ 18 sodas
- **Acesulfame-K**: ADI ~ 30 sodas
- **Sucralose**: ADI ~ 5 sodas
- **Neotame**: ADI ~ 30 sodas
Stevia (and sugar alcohols) not included in this presentation

Sucrose

Acesulfame K
ADI ~ 30 sodas

Saccharin
ADI ~ 3 sodas

Aspartame
ADI ~ 18 sodas

Aspartic Acid

Methanol

Sucralose
ADI ~ 5 sodas

Neotame
ADI ~ 30 sodas

Rebaudioside A
300x
ADI ~ 3 sodas

Stevia (and sugar alcohols) not included in this presentation
Saccharin

Constantine Fahlberg

Saccharin

Ira Remsen
Saccharin

Constantine Fahlberg

Ira Remsen

Johns Hopkins University in 1877
Saccharin

Constantine Fahlberg

Saccharin

Ira Remsen

Russian  caxap (sakar)
Latin  succarum
German  Zucker
Arabic  شکر (súkkar)
Persian  شکر (šakar)
Sanskrit  शर्करा (śárkarā)
How Non-Nutritive Sweeteners Signal

Taste Papillae
How do artificial sweeteners work?

How Non-Nutritive Sweeteners Signal

Chandrashekar et al., Nature, 2006
How Non-Nutritive Sweeteners Signal

Taste Bud

Taste Papillae

7-TMD GPCRs

salt: ENaC
sour: PCKD channels
sweet: T1R2+T1R3
bitter: T2Rs
umami: T1R1+T1R3
How Non-Nutritive Sweeteners Signal

How do artificial sweeteners work?

Chandrashekar et al., Nature, 2006

Taste Bud
Taste Papillae

VPM
Operculum
Insula

Central tegmental tract

Parabrachial nucleus
Nucleus tractus solitarius

VII Facial
IX Glossopharyngeal
X Vagus

salt
sour
sweet
bitter
umami

ENaC
PCKD channels
T1R2+T1R3
T2Rs
T1R1+T1R3

7-TMD GPCRs
Taste Receptor Expression

Ehrenberg R,
ScienceNews 2010, Vol 177
Taste Receptor Expression

Intestine

Glucose or artificial sweeteners

SGLT-1 GLUT2

Glucose or artificial sweeteners

SGLT-1
GLUT2

Glucagon Like Peptide 1 (GLP1)

↓ Gastric Emptying
↓ Appetite
↓ Glucagon
↑ Insulin

Ehrenberg R,
ScienceNews 2010, Vol 177
Artificial Sweeteners and Obesity

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Obesity and Artificial Sweetener Use

Secular Trend between 1960 and 2010

% Population


14.3% 15.8% 16.4% 26.2% 34.9%

% obese (BMI > 30 kg/m²)

JAMA – Feb 2014

34.9%
Obesity and Artificial Sweetener Use

% Obese (BMI > 30 kg/m²)

% Consuming artificial sweeteners

Fueling the Obesity Epidemic?
Artificially Sweetened Beverage Use and Long-term Weight Gain

San Antonio Heart Study

Change of BMI after 7-8 yr follow-up according to diet soda consumption

Example

Change of BMI after 7-8 yr follow-up according to diet soda consumption

Female
5’6”, 155 lb, BMI 25.0

7-8 years later............

1 diet soda a day
165 lb, BMI 26.5

161 lb, BMI 26.0

Obesity and Artificial Sweetener Use

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Artificial Sweeteners and Obesity
Artificial Sweeteners and Obesity

Ace-K, Saccharin & Sucralose

3T3-L1 cells: Adipogenesis
Mature adipocytes: Lipolysis
hMSCs:

Simon BR, et al. JBC 2013 **Sen (unpublished)

Sucralose and Saccharin

MIN6 cells & primary rodent pancreatic beta-cells: Insulin secretion

Corkey, Diabetes 2012
Artificial Sweeteners and Obesity

Sucralose > Aspartame > Saccharin

bacteriostatic


Suppression of intestinal microflora

Abou Donia, et al 2008 (Splenda)

ARTICLE

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez², Tal Korem², David Zeevi², Gili Zilberman-Schapira¹, Christoph A. Thaiss¹, Ori Maza¹, David Israeli³, Niv Zmora⁴, Shlomot Gilad⁵, Adina Weinberger², Yael Kuperman⁸, Alon Harmelin⁸, Ilana Kolodkin-Gal⁹, Hagit Shapiro¹, Zamir Halpern⁵, Eran Segal² & Eran Elinav¹
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Artificial sweeteners induce glucose intolerance by altering the gut microbiota

381 non-diabetic individuals (44% male, age 43.3 yr)
Artificial Sweeteners and Obesity

Acesulfame-K

Lactating rats concentrate Ace-K 6-fold in breast milk

(IPCS Inchem 0.7967)

Our preliminary data

Higher Ace-K concentrations in human breast milk than in serum

Also frequently detectable: saccharin, sucralose
Artificial Sweeteners and Obesity

Clinical Implication?

Offspring exposed during pregnancy or lactation had higher preferences for sweetness, whether non-caloric (ace-K) or caloric (sucrose) compared to control animals.

Not studied in humans – yet.........
Artificial Sweeteners and Obesity

Randomized, acute interventions studies in humans

Which artificial sweetener(s)?
In which context?
In which cohort?
**Method:** Diet soda (Diet Rite™ with ace-K & sucralose) vs. carbonated water before OGTT

**Subjects:** 12-25 years

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GLP-1 in Healthy Volunteers (n=22)

- Water
- Diet Soda

AUC 34% higher (p = 0.029)

GLP-1 in Type 1 Diabetes (n=11)

AUC 43% higher (p = 0.020)

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Brown RJ, Walter M, Rother KI. Diabetes Care 2009 and 2012
**Taste Receptor Expression**

**Neutraceuticals**
- Glucose or artificial sweeteners
- SGLT-1
- GLUT2

**Glucagon Like Peptide 1 (GLP1)**
- Gastric Emptying
- Appetite
- Glucagon
- Insulin

Sucralose affects glycemic and hormonal responses to an OGTT. Pepino MY, Tiemann CD, Patterson BW, Wice BM, Klein S. Diabetes Care 2013

Glucose incremental peak (p=0.03)
Insulin AUC p=0.03
Insulin incremental peak p=0.06
Artificial Sweeteners and Obesity

Our own data:

31 healthy adult volunteers (BMI 26 kg/m²)

RESULTS

AUC (sweetener pre-treatment) – AUC (water pretreatment)

Insulin AUC p=0.03
Insulin incremental peak p=0.06

Prior to OGTT
Artificial Sweeteners and Obesity

Our own (unpublished) data

31 healthy adult volunteers

Change in Insulin AUC in comparison to Water Pretreatment

- Red: Diet Rite
- Green: Diet Mountain Dew
- Pink: Sweeteners

Prior to OGTT
Beyond acute sweetener exposure,

what do long-term studies show?
Artificial Sweeteners and Obesity


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Sugar-Sweetened Beverages and Adolescent Body Weight

Cara B. Ebbeling, Ph.D., Henry A. Feldman, Ph.D., Virginia R. Chomitz, Ph.D., Tracy A. Antonelli, M.P.H., Steven L. Gortmaker, Ph.D., Stavroula K. Osganian, M.D., Sc.D., and David S. Ludwig, M.D., Ph.D.

ORIGINAL ARTICLE

A Trial of Sugar-free or Sugar-Sweetened Beverages and Body Weight in Children

Janne C. de Ruyter, M.Sc., Margreet R. Olothof, Ph.D., Jacob C. Seidell, Ph.D., and Martijn B. Katan, Ph.D.
Overweight & obese adolescents (n=224) who habitually consumed SSB randomized to:

- Home delivery of non-caloric drinks (intervention) or
- Supermarket gift cards but no instructions of what to purchase (control)

- Intervention lasted 1 year with 1 additional year follow-up
Elementary school children (n=641) who habitually consumed sugar sweetened beverages randomized to:

- 1 can (8 oz.) of 0 kcal artificially sweetened drink
- 1 identical can (8 oz.) of 104 kcal sugar-containing drink

Drinks were consumed in school (5 days per week) and at home on weekends for 18 months.
If a child stays on the same percentiles for height and weight

BMI-z score = 0
A Trial of Sugar-free or Sugar-Sweetened Beverages and Body Weight in Children

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A  BMI z Score as a Function of Time

- Artificial Sweetener group
- Sugar group
Caveat: Lack of control group

Interpretation: Kids who continue to drink regular soda in school gain more weight.
Artificial Sweeteners and Obesity

Key Concept: Reward

The brain cannot be 'fooled' in to thinking zero-calorie sweeteners are providing us with energy, warn researchers.

Food Navigator.com
24-Sep-2013
Both sucrose and sucralose activate the bilateral primary taste cortex (frontal operculum, anterior insula).

Artificial Sweeteners and Obesity

So far, no convincing evidence that artificial sweeteners prevent or alleviate obesity
Artificial Sweeteners and Obesity

So far, no convincing evidence that artificial sweeteners prevent or alleviate obesity

IN CONTRAST:

More adipogenesis and less lipolysis \((in\ vitro)\)
More insulin secretion \((in\ vitro/in\ vivo)\)
Less reward \((in\ vivo)\)
Thank You

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Nursing Staff 5SWS
Study Participants

Extramural Collaborators:
Claire Fraser, PhD (University of MD)
Steven Munger, PhD (University of MD)
Susan Schiffman, PhD (NC State University)
Non-Nutritive Sweeteners FDA regulated as GRAS

Stevia
Made from the leaves of a shrub that grows in South and Central America.
There are no long-term studies of health effects (but long-term use).

Sugar alcohols
Examples: Erythritol, xylitol, mannitol, maltitol
used for decades to sweeten chewing gum, candy, fruit spreads, toothpaste, cough syrup, and other products.

Newer, cheaper technologies (producing sugar alcohols from corn, wood, and other plant materials) explain their increased use.
Artificial sweeteners induce glucose intolerance by altering the gut microbiota
381 non-diabetic individuals (44% male, age 43.3 yr)

<table>
<thead>
<tr>
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<th>Spearman correlation to NAS consumption</th>
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<tr>
<td></td>
<td>R</td>
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<tr>
<td>BPSys</td>
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<td>Bpdia</td>
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<td>Waist-hip Ratio</td>
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<td>HbA1c%</td>
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<td>Fasting glucose</td>
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<td>ALT</td>
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Main Learning Objectives

- Distinguish between different artificial sweeteners
- Describe their mechanism of action
- Recognize the difficulties in establishing causality for obesity promoting effects
Artificial sweeteners induce glucose intolerance by altering the gut microbiota

7 individuals (5 male, age 28-36 yr) get saccharin at max ADI and daily (!!!) OGGTts