

# **THERAPEUTIC DILEMMA: NONNUTRITIVE SWEETENERS (NNS) FOR GLYCEMIC CONTROL?**

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THE UNIVERSITY OF  
CHICAGO  
MEDICINE

# HISTORY OF THE PRESENT ILLNESS

63 year-old female presents, as new referral, with uncontrolled Type 2 Diabetes

Diagnosed ~age 46

No prior hospitalizations for diabetes; No known DKA or hypoglycemic events, though does not monitor home glucose

Therapeutic regimen:

Prior: Metformin – stopped 1.5 years ago during an unrelated hospitalization

Glipizide – stopped 1.5 years ago during an unrelated hospitalization

Actos – stopped by PCP when patient started on insulin

Current: Lantus 18 U (since mid-2012) – denies non-adherence

	7 8/12/1997 1021	6 1/28/1998 1003	5 8/21/2001 1003	4 2/5/2002 0848	3 1/2/2013 1649	2 11/25/2013 1132
DIABETIC SCREENING...						
Glucose, Fasting	103					
Glucose, Non-Fasting		105				
Glycosyl.Hemoglobin	6.6 *	5.7 *				
HbA1C			8.7 * !▲	8.3 * !▲	6.7 * !▲	11.6 * !▲

# PAST MEDICAL HISTORY

Type 2 Diabetes Mellitus: **Lantus 18 U**

Dyslipidemia: **atorvastatin 20 mg**

Hypertension: **lisinopril, hydrochlorothiazide, metoprolol**

Chronic Kidney Disease, Stage III

Primary Biliary Cirrhosis: **hydroxyzine, cholestyramine-aspartame**

Osteopenia: **Calcium + Vitamin D**

Asthma: **albuterol, Symbicort**

Depression

# SOCIAL AND FAMILY HISTORY

## SOCIAL

Unemployed

Lives Alone

1 daughter – very supportive

Tobacco 1 ppd

Previously heavy etoh use

No illicit drugs

## FAMILY

Diabetes – maternal aunt

Hypertension – sister

Father died in a car accident

1 Brother shot dead in 30's

1 brother diet of etoh liver  
disease in 40's

# REVIEW OF SYSTEMS

**Constitutional:** Positive for fatigue and unexpected weight change. Negative for fever, chills, diaphoresis, activity change and appetite change. **Gaining weight, increased thirst.**

**HENT:** Negative for trouble swallowing, neck pain, and voice change.

**Eyes:** **Blurriness of vision intermittently.**

**Respiratory:** Negative for apnea, cough, shortness of breath and wheezing.

**Cardiovascular:** Negative for chest pain, palpitations and leg swelling.

**Gastrointestinal:** Negative for nausea, vomiting, abdominal pain, diarrhea, constipation and abdominal distention.

**Genitourinary:** Positive for **frequency.** Negative for urgency.

**Musculoskeletal:** Positive for **myalgias and arthralgias.** Negative for back pain.

**Neurological:** Positive for **numbness in bilateral lower extremities.** Negative for dizziness, tremors, weakness, light-headedness and headaches.

**Hematological:** Negative.

**Psychiatric/Behavioral:** Positive for **dysphoric mood.** Negative for sleep disturbance. The patient is **nervous/anxious.**

# COMPREHENSIVE DIABETES EVALUATION - HISTORY

## Diabetes-Related Complications:

### Microvascular:

Retinopathy: optho last seen > 1 year ago. No known retinopathy

Neuropathy: Bilateral numbness, tingling LE. No autonomic symptoms. No history of foot wounds/infections.

Nephropathy: Suspected

### Macrovascular:

No known CHD, CVD, or PAD

+Hypertension, Dyslipidemia, and Overweight (BMI 28.3)

History of Diabetes Education: Remote

# COMPREHENSIVE DIABETES EVALUATION - HISTORY

## Nutrition and Physical Activity:

### Diet:

Breakfast: None

Lunch: Dinner leftovers (fried chicken or baked chicken), mashed potatoes

Dinner: Same as lunch

Snacks/Desserts: fruit 2 x per week, cake 2 x per week, chips

Sugary Beverages: 72 ounces of Pepsi per day = 248 g carb

Activity: None

Psychosocial: Depression which likely contributes to worsening of her diabetes.

# COMPREHENSIVE DIABETES EVALUATION: PHYSICAL EXAMINATION

BP 133/69 | Pulse 64 | Ht 170.2 cm (5' 7") | Wt 81.965 kg (180 lb 11.2 oz) | BMI 28.30 kg/m<sup>2</sup>

**Constitutional:** She appears well-developed and well-nourished. No distress.

**Head:** Normocephalic and atraumatic.

**Eyes:** Conjunctivae normal and EOM are normal. Pupils are equal, round, and reactive to light.

**Neck:** Normal range of motion. Neck supple. No thyromegaly present. No thyroid nodules appreciated. Acanthosis nigricans and skin tags are absent.

**Cardiovascular:** Normal rate, regular rhythm and normal heart sounds.

**Pulmonary/Chest:** Effort normal and breath sounds normal. She has no wheezes or rales.

**Abdominal:** Soft. She exhibits no distension. There is no tenderness.

**Musculoskeletal:** Normal range of motion. She exhibits no edema and no tenderness.

**Foot examination:** no visible wounds/ulcers. 2+ dorsalis pedis/posterior tibial pulses. Patellar and Achilles reflexes normal. Normal monofilament bilaterally and vibratory sensation and proprioception are intact.

**Skin:** Skin is warm and dry. Rash noted. She is not diaphoretic. No erythema.

There is a ~1 cm circumferential papular, crusted lesion on her lateral left shin which appears to be healing and is without surrounding erythema, edema, or warmth.

**Psychiatric:** Her behavior is normal. Judgment and thought content normal.

Mood is depressed, tearful when discussing her blood sugars. Appears motivated to change.



# COMPREHENSIVE DIABETES EVALUATION - LABS

Glucose	338
Sodium	138
Potassium	4.3
Chloride	102
CO2	26
Anion Gap	10
BUN	30
Creatinine	1.5
GFR	35
Calcium	9.5
Albumin	3.7
Total Protein	7.9
T bili	0.1
Alk Phos	287
AST	26
ALT	20

WBC	10.9
HGB	12.4
HCT	38.0
PLT	324

TSH	1.06

Hemoglobin A1c	11.6

Urine Albumin/Creatinine	632.0

Total Cholesterol	193
LDL	124
HDL	45
Triglycerides	120

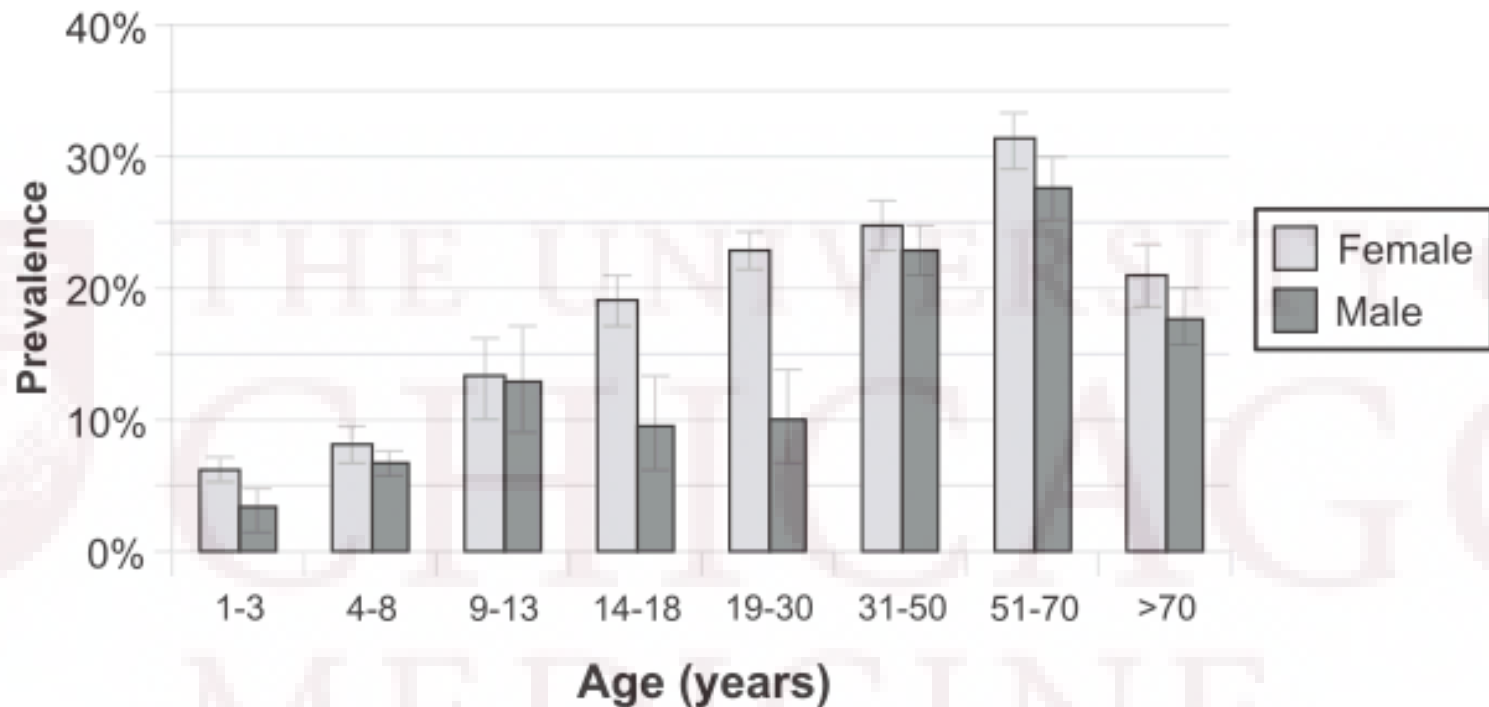
**WHAT THERAPEUTIC RECOMMENDATIONS DO  
YOU HAVE?**

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# IMPROVING GLYCEMIC CONTROL IN OUR PATIENT



# PREVALENCE OF NNS BEVERAGE INTAKE



**Figure 3**—Prevalence (% SE) of nonnutritive sweetened beverage intake among U.S. children and adults as determined by one 24-hour recall (National Health and Nutrition Examination Survey 2007–2008) according to age group. The sample size of participation by age group for females was ages 1 to 3 (n = 575), 4 to 8 (n = 435), 9 to 13 (n = 418), 14 to 18 (n = 353), 19 to 30 (n = 513), 31 to 50 (n = 950), 51 to 70 (n = 873), and >70 (n = 484). The sample size of participation by age group for males was ages 1 to 3 (n = 617), 4 to 8 (n = 502), 9 to 13 (n = 412), 14 to 18 (n = 380), 19 to 30 (n = 518), 31 to 50 (n = 889), 51 to 70 (n = 869), and >70 (n = 466).



# ACC.14

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## Prevention

### DIET DRINK CONSUMPTION AND THE RISK OF CARDIOVASCULAR EVENTS: A REPORT FROM THE WOMEN'S HEALTH INITIATIVE

59,614 women (mean age 62.8) from Women's Health Initiative Observational Cohort:  
No preexisting CVD  
Only women with diet drink intake data were included

Primary outcome:

Composite of incident CHD, CHF, MI, PCI, ischemic CVA, PAD, CVD death

Results:

After adjustment for CVD risk factors (demographics, BMI, smoking, hormone therapy, physical activity, energy intake, salt intake diabetes, hypertension, high cholesterol, and sugar sweetened beverage intake), women who consumed  $\geq 2$  diet drinks per day had higher risk of CVD events (HR 1.3, 95% CI 1.1-1.5) and overall mortality (HR 1.3, 95% CI 1.04-1.5) compared to women who consumed  $\leq 3$  diet drinks per month.

# CARDIOVASCULAR OUTCOMES STUDIES

Fung TT, et al. Sweetened [NNS] beverage consumption and risk of coronary heart disease in women. Am J Clin Nutr. 2009;89:1037-42.

Lin J, Curhan GC. Associations of sugar and artificially sweetened soda with albuminuria and kidney function decline in women. Clin J Am Soc Nephrol. 2011;6:160-166.

Lutsey, et al. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. Circulation. 2008; 117:754-61.

Duffey KJ, et al. Dietary patterns matter: diet beverages and cardiometabolic risks in the longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) study. Am J Clin Nutr. 2012;95:909-15.

# CHALLENGES OF STUDYING NNS EFFECTS

Epidemiologic studies may be limited by methodological dilemmas...

## Observational studies

- Allow for long-term assessment of changes in health outcomes

- Can only identify associations and not causality

- Confounding due to many dietary and health variables correlating with NNS intake

- Poor dietary recall

- Changes in beverage habits overtime

- Reverse causality - overweight/obese individuals more likely to consume diet drinks

## Intervention studies/Randomized control trials tend to be short-term

Metabolic effects seen in vitro and in animal models have often not translated to humans. Yet emerging data shows that NNS are not as metabolically inert as previously believed.

# Sucralose Affects Glycemic and Hormonal Responses to an Oral Glucose Load

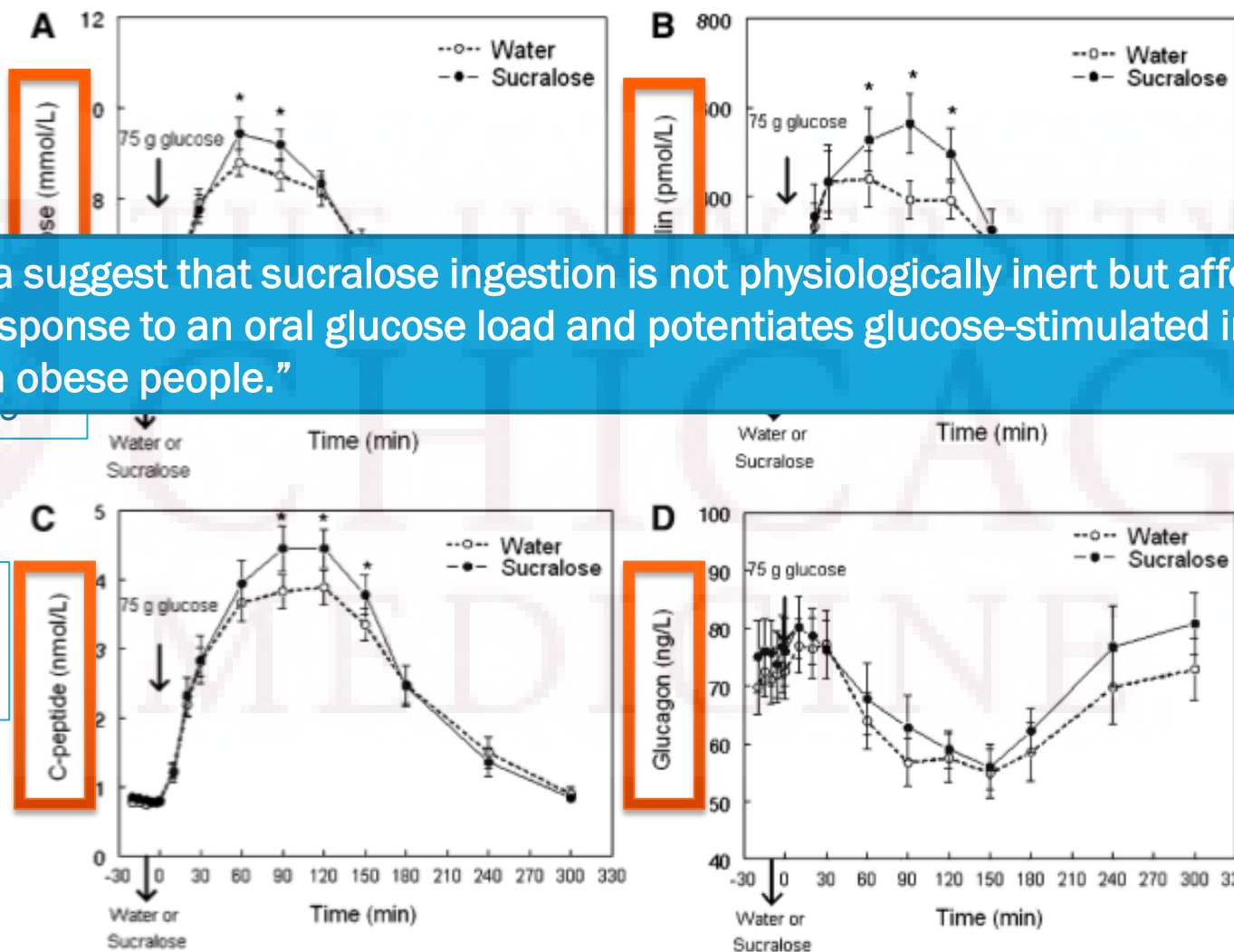
17 obese patients (BMI 42.3 +/- 1.6 kg/m<sup>2</sup>) who were insulin-sensitive and did not use NNS prior to the study.

After a 12 hour overnight fast, patients had the following plasma measurements at 20, 15, 10, 6, and 2 minutes before and at 10, 20, 30, 40, 60, 90, 120, 150, 180, 240, and 300 minutes after 75 g glucose load:

plasma glucose, insulin, C-peptide, glucagon, glucose-dependent insulinotropic polypeptide (GIP), and active GLP-1

Subjects drank 48 mg sucralose or equivalent volume of water before glucose ingestion





“These data suggest that sucralose ingestion is not physiologically inert but affects the glycemic response to an oral glucose load and potentiates glucose-stimulated insulin secretion in obese people.”

P = 0.03  
AUC  
P = 0.13

AUC  
P = 0.45

**Figure 1**—Mean plasma glucose (A), insulin (B), C-peptide (C), and glucagon (D) concentrations in obese subjects after drinking either sucralose or water 10 min before ingestion of a 75-g glucose load (given at time = 0 min). \*Value significantly different from corresponding water condition value, P < 0.004.

# RELATIVE SWEETNESS OF NNS TO SUCROSE – POTENT STIMULATORS OF SWEET TASTE RECEPTORS



Sucrose

1x

Aspartame

200x

Saccharin

450x

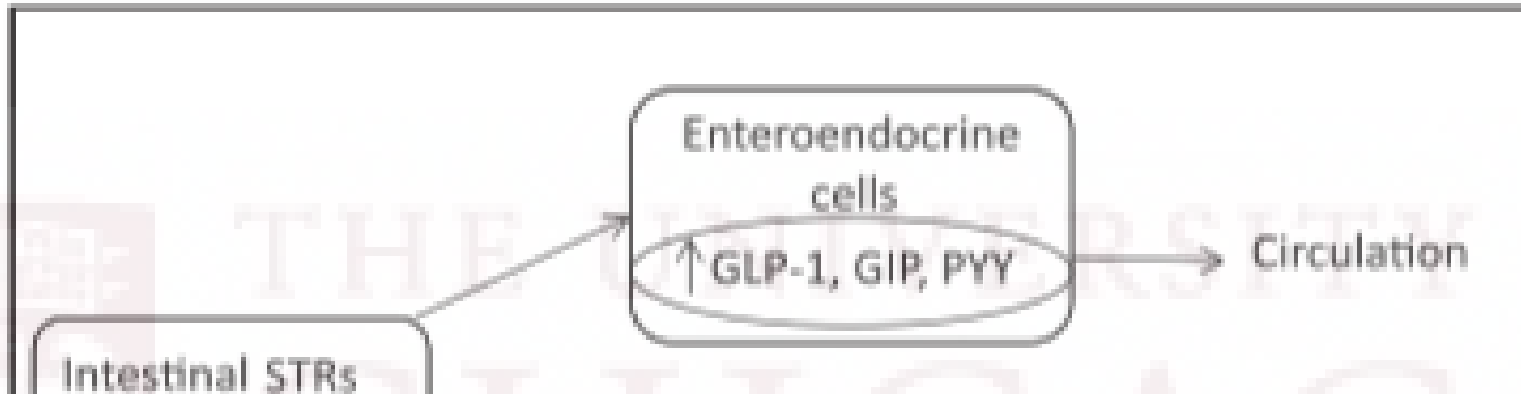
Sucralose

600 x

Stevia

Up to 300x

# SWEET TASTE RECEPTORS



“Could non-nutritive sweeteners be accentuating postprandial glycemia via effects on sweet taste receptors, thereby contributing to the progression of glucose intolerance.”

**FIG. 1. Putative relationships between intestinal STRs, SGLT1 and GLUT2, glucose absorption, and incretin hormones GLP-1, GIP, and PYY.**

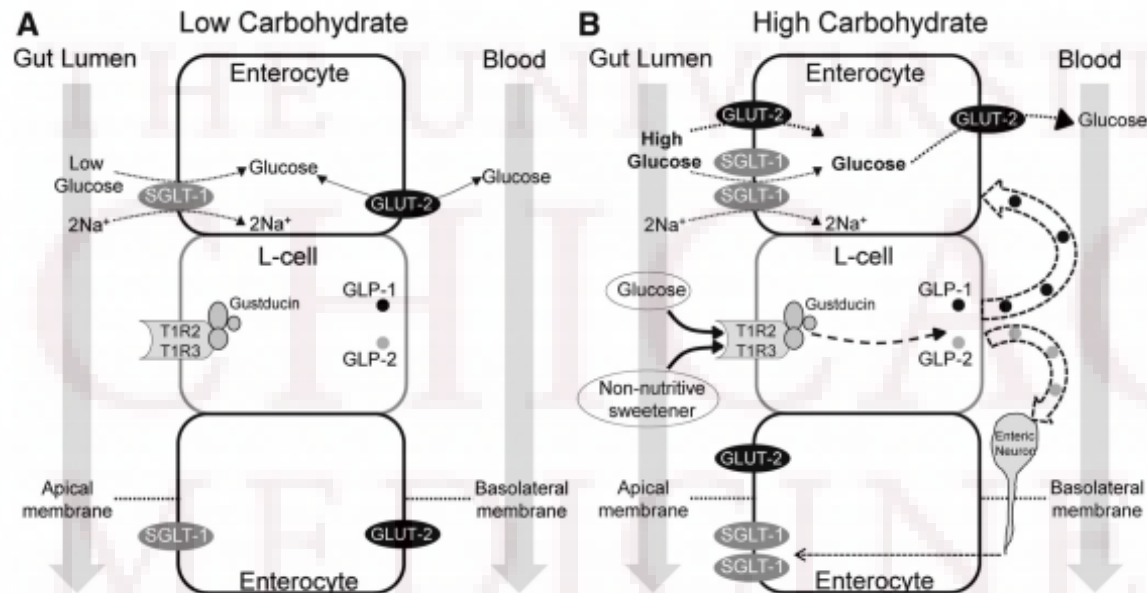
Young RL, et al. Disordered control of intestinal sweet taste receptor expression and glucose absorption in type 2 diabetes. *Diabetes*. 2013;62:3532-41.

Greenfield JR, Chisholm DJ. How sweet it is: intestinal sweet taste receptors in type 2 diabetes. *Diabetes*. 2013;62:3336-37.

# SWEET TASTE RECEPTORS, HYPERINSULINISM, AND WEIGHT GAIN?

2602 Brown and Rother Non-Nutritive Sweeteners and the Gut

J Clin Endocrinol Metab, August 2012, 97(8):2597–2605



**FIG. 1.** A model of intestinal glucose absorption in the fasting or low luminal carbohydrate state (A) or after a high-carbohydrate meal, with or without non-nutritive sweeteners (B). In the low luminal carbohydrate state, glucose is largely transported from the gut lumen into the enterocyte via SGLT-1. Glucose may pass in a bidirectional manner between the enterocyte and the bloodstream via GLUT2 located on the basolateral membrane, depending on the plasma glucose concentration and the metabolic needs of the enterocyte. In the presence of high luminal carbohydrate, glucose binds to sweet-taste receptors on enteroendocrine L cells, initiating a signal transduction cascade that results in GLP-1 and GLP-2 release. GLP-2 may cause up-regulation of SGLT-1 via enteric neurons. GLP-1 may act in a paracrine manner on nearby enterocytes to up-regulate apical GLUT2. Non-nutritive sweeteners can also bind to enteroendocrine sweet-taste receptors, causing GLP-1 release (*in vitro*) and increased intestinal glucose uptake (*in rodents*).

# ADIPOGENESIS?

## Artificial Sweeteners Stimulate Adipogenesis and Suppress Lipolysis Independent of Sweet Taste Receptors

**Becky R. Simon<sup>1</sup>, Sebastian D. Parlee<sup>2</sup>, Brian S. Learman<sup>2</sup>, Hiroyuki Mori<sup>2</sup>, Erica L. Scheller<sup>2</sup>, William P. Cawthorn<sup>2,3</sup>, Xiaomin Ning<sup>2</sup>, Katherine Gallagher<sup>4</sup>, Björn Tyrberg<sup>5</sup>, Fariba M. Assadi-Porter<sup>6</sup>, Charles R. Evans<sup>2</sup>, and Ormond A. MacDougald<sup>1,2,7,8</sup>**

*\*Running Title: Artificial Sweeteners Regulate Adipocyte Differentiation and Metabolism*

Sweet taste receptor ligands stimulate adipogenesis and suppress lipolysis; however, these effects do not require T1R2 and T1R3 (G-protein coupled sweet taste receptors found in taste buds, gut, and pancreas), despite their expression in adipose tissue.

Some artificial sweeteners regulate adipocyte differentiation and metabolism through a sweet taste receptor-independent mechanism.



# Sweet Taste Receptor Deficient Mice Have Decreased Adiposity and Increased Bone Mass

Becky R. Simon<sup>1</sup>, Brian S. Learman<sup>2</sup>, Sebastian D. Parlee<sup>2</sup>, Erica L. Scheller<sup>2</sup>, Hiroyuki Mori<sup>2</sup>, William P. Cawthorn<sup>2,4</sup>, Xiaomin Ning<sup>2</sup>, Venkatesh Krishnan<sup>4</sup>, Yanfei L. Ma<sup>4</sup>, Björn Tyrberg<sup>5,6</sup>, Ormond A. MacDougald<sup>1,2,3\*</sup>

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## Abstract

Functional expression of sweet taste receptors (T1R2 and T1R3) has been reported in numerous metabolic tissues, including the gut, pancreas, and, more recently, in adipose tissue. It has been suggested that sweet taste receptors in these non-gustatory tissues may play a role in systemic energy balance and metabolism. Smaller adipose depots have been reported in T1R3 knockout mice on a high carbohydrate diet, and sweet taste receptors have been reported to regulate adipogenesis *in vitro*. To assess the potential contribution of sweet taste receptors to adipose tissue biology, we investigated the adipose tissue phenotypes of T1R2 and T1R3 knockout mice. Here we provide data to demonstrate that when fed an obesogenic diet, both T1R2 and T1R3 knockout mice have reduced adiposity and smaller adipocytes. Although a mild glucose intolerance was observed with T1R3 deficiency, other metabolic variables analyzed were similar between genotypes. In addition, food intake, respiratory quotient, oxygen consumption, and physical activity were unchanged in T1R2 knockout mice. Although T1R2 deficiency did not affect adipocyte number in peripheral adipose depots, the number of bone marrow adipocytes is significantly reduced in these knockout animals. Finally, we present data demonstrating that T1R2 and T1R3 knockout mice have increased cortical bone mass and trabecular remodeling. This report identifies novel functions for sweet taste receptors in the regulation of adipose and bone biology, and suggests that in these contexts, T1R2 and T1R3 are either dependent on each other for activity or have common independent effects *in vivo*.

**Citation:** Simon BR, Learman BS, Parlee SD, Scheller EL, Mori H, et al. (2014) Sweet Taste Receptor Deficient Mice Have Decreased Adiposity and Increased Bone Mass. PLoS ONE 9(1): e86454. doi:10.1371/journal.pone.0086454

# Nonnutritive Sweeteners: Current Use and Health Perspectives

“At this time, there are insufficient data to determine conclusively whether the use of NNS to displace caloric sweeteners in beverages and foods reduces added sugars or carbohydrate intakes, or benefits appetite, energy balance, body weight, or cardiometabolic risk factors.”

“...Paucity of data from well-designed human trials exploring the potential role of NNS in achieving and maintaining a healthy body weight and minimizing cardiometabolic risk factors.”

“There are some data to suggest that NNS may be used in a structured diet to replace sources of added sugars and that this substitution may result in modest energy intake reductions and weight loss.”

“The evidence reviewed suggests that when used judiciously, NNS could facilitate reductions in added sugars intake, thereby resulting in decreased total energy and weight loss/weight control, and promoting beneficial effects on related metabolic parameters. However, these potential benefits will not be fully realized if there is a compensatory increase in energy intake from other sources.”

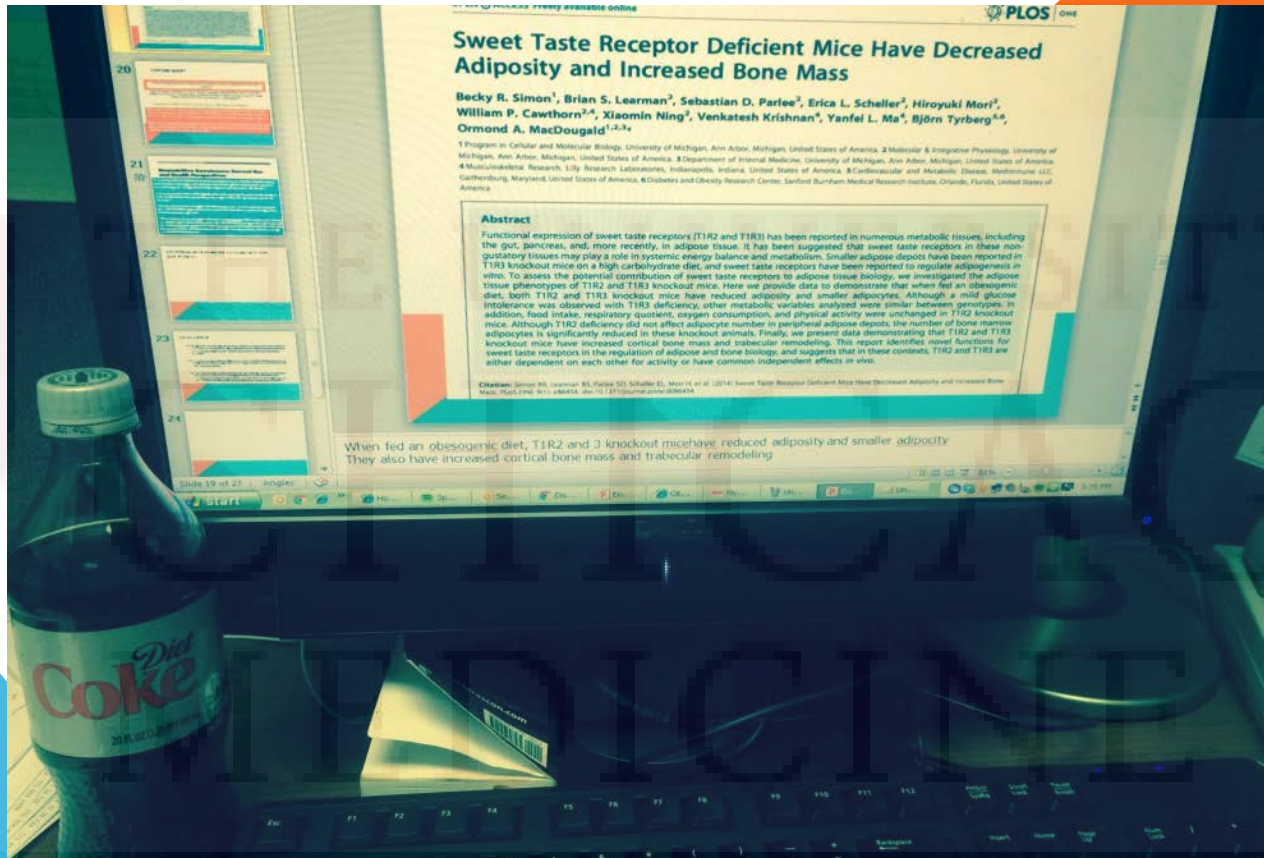
# CONCLUSIONS

Non-nutritive sweetened beverages continue to be recommended as alternatives to sugar-sweetened beverages, which have unequivocally been linked to obesity and metabolic syndrome.

Although there is conflicting and insufficient data on the precise metabolic effects of non-nutritive sweeteners, a growing body of recent evidence supports that they are not physiologically inert, and that they may have deleterious metabolic effects.

These recommendations should make clear that although they may be used as a substitute, non-nutritive beverages should be consumed modestly and infrequently, and that unprocessed, unsweetened natural beverages such as water, milk, decaffeinated unsweetened tea, etc. should be consumed first







EXTRA SLIDES

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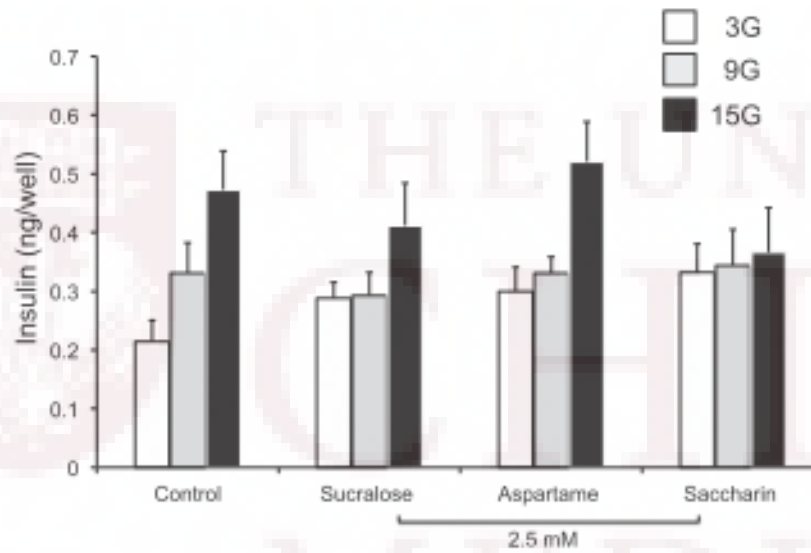
# POTENTIAL MECHANISMS OF EFFECTS OF NNS ON COMPENSATORY APPETITE AND FOOD INTAKE

Potential mechanisms	Description
Cephalic phase stimulation	Refers to a phase of early gastric secretions when food is in the mouth but has not yet reached the stomach; NNS might affect hunger and appetite at this phase.
Nutritive and osmotic effects	Refers to the possibility that the lower energy density and lower osmotic load of NNS versus caloric sweeteners could alter the rate of gastric emptying or other factors of digestion and absorption that might affect sensations of satiety.
Gut peptide response	Refers to the effect dietary macronutrients have on gut peptides that signal satiety; if NNS were to diminish the release of these peptides relative to caloric sweeteners, it could theoretically result in lower satiety and increased energy intake.
Palatability	NNS are typically added to increase palatability, and palatability is assumed to stimulate hunger and/or reduce satiation/satiety, thus increasing intake.
Informed use leading to overcompensation	Expected energy savings attributed to the substitution of an NNS-containing product could lead to subsequent indulgence rationalized by the previous energy savings and then overcompensation.
Loss of signal fidelity	Sensory properties signal information about the metabolic response required by consumption of the product. If the sensory cue of sweetness leads to inaccurate or inconsistent predictive power, energy regulation may be disrupted and could lead to positive energy balance from overconsumption triggered by this signaling.
Activation of reward systems	Refers to the possibility that the enhanced palatability conferred by NNS could play a role in reward-motivated feeding, thus added caloric intake when a nonfood reward could be provided.
Training the palate/learning to like the familiar	Refers to the possibility that repeated exposure to NNS may perpetuate a preference for sweet items in the diet, including items sweetened with caloric sweeteners.

A review by Mattes and Popkin (3) concluded that the available evidence either refuted or was insufficient to refute or support each of these potential mechanisms or hypotheses for NNS increasing appetite, hunger, or energy intake. NNS indicates nonnutritive sweeteners.

# METABOLIC STUDIES: WHAT DO NNS DO WITH INSULIN?

C



**FIG. 4. Insulin secretion.** *A:* Effect of 18-h exposure to 100  $\mu\text{mol/L}$  fatty acid (FA) on insulin secretion from isolated rat islets (73). *B:* Concentration dependence of MOG-stimulated insulin secretion from dissociated rat islets at basal 3 mmol/L glucose (73). *C:* Effect of artificial sweeteners on insulin secretion in dissociated rat islets (74). Effect of iron exposure in INS-1 (832/13) cells (Deeney et al., unpublished data). Data shown are means  $\pm$  SEM for at least three experiments.

Corkey B. Banting Lecture 2011. Hyperinsulinemia: Cause or Consequence? Diabetes. 2012;61:4-13.