Sugar Substitutes & Metabolic Syndrome: The Sweet Addiction
ACP: September 22, 2019

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Disclosures

None

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Objectives

- Epidemiology of Obesity
- The Evolution of Artificial & Natural Alternative Sweeteners
- The Effects of Sugar Substitutes on Energy Consumption
- The Effects of Sugar Substitutes on the Neuronal, Hormonal Response & Glucose Homeostasis
- The Effects of Sugar Substitutes on the Microbiome

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Epidemiology of Obesity

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The Obesity Epidemic

Global Health Crisis

Exhibits no boundaries

All ages, ethnicities, races

1980-2000

Prevalence Obesity in Adults: 35%

Prevalence Obesity <20 yo: 20%

Obesity prevalence remained stable since 2000

Increase in obesity among women & extreme obesity

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Ogden, C.L., et al, JAMA, 2016

Flegal, K.M., et al., JAMA, 2016

The Cost of Obesity

Greater healthcare costs vs Drug/Alcohol Use

Americans spend $38 billion/year trying to lose weight

NIH spends <1% of its budget on obesity research

The Healthcare Costs of Obesity

Obesity is one of the biggest drivers of preventable chronic diseases and healthcare costs in the United States. Currently, estimates for these costs range from $147 billion to nearly $210 billion per year.[1] In addition, obesity is associated with job absenteeism, costing approximately $4.3 billion annually[2] and with lower productivity while at work, costing employers $506 per obese worker per year.[3]

[1] Cawley J and Meyerhoefer C. The Medical Care Costs of Obesity: An Instrumental Variables Approach. *Journal of Health Economics*, 31(1): 219-230, 2012; And Finkelstein, Trogdon, Cohen, et al. Annual Medical Spending Attributable to Obesity. Health Affairs, 2009.
[2] Cawley J, Rizzo JA, Haas K. Occupation-specific Absenteeism Costs Associated with Obesity and Morbid Obesity. *Journal of Occupational and Environmental Medicine*, 49(12):1317?24, 2007.
[3] Gates D, Succop P, Brehm B, et al. Obesity and presenteeism: The impact of body mass index on workplace productivity. *J Occ Envir Med*, 50(1):39-45, 2008.

OBESITY AND WEIGHT LOSS = NOT THIS SIMPLE…

Energy IN > Energy OUT ≠ Obesity

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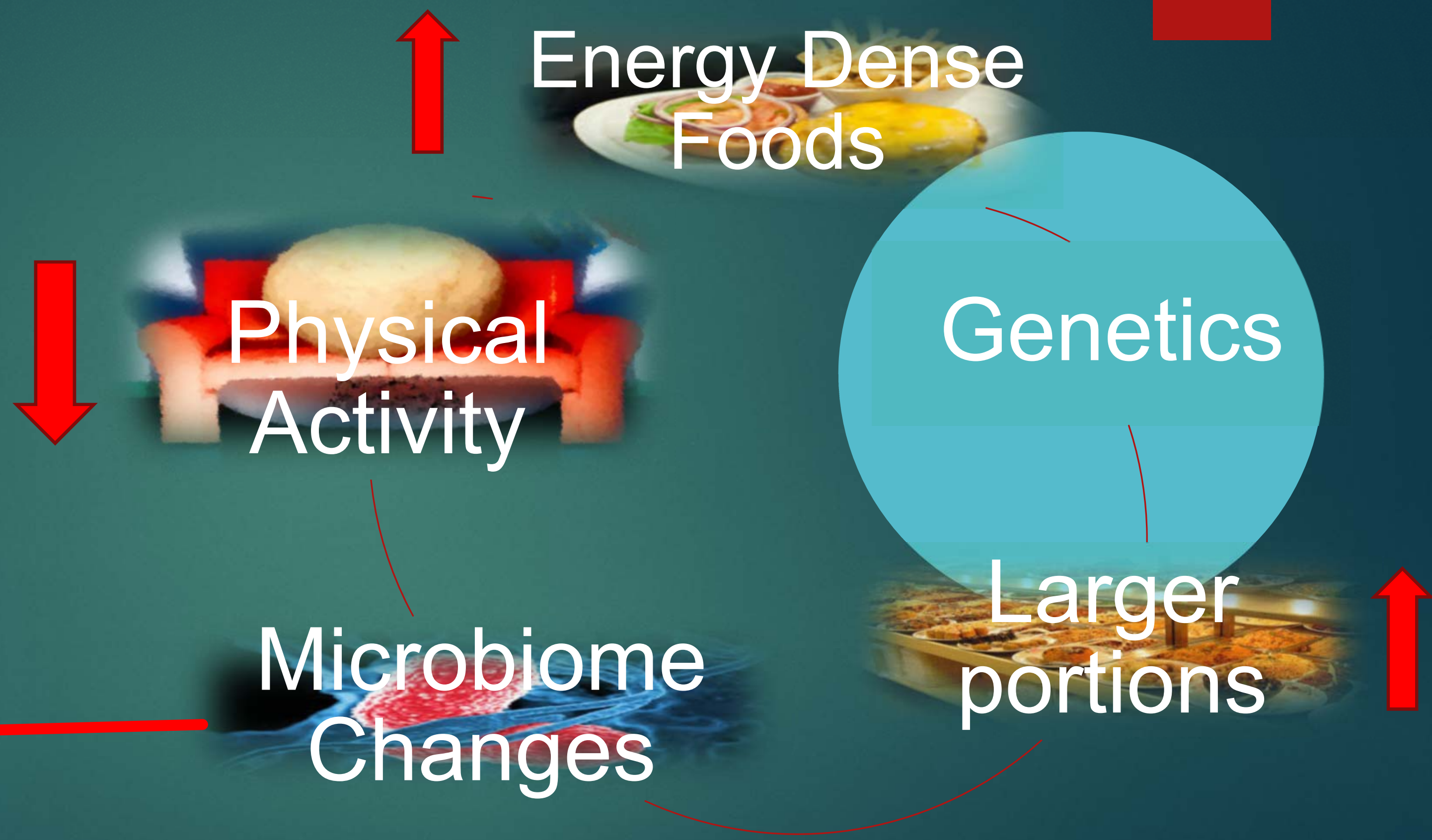
Obesity is Multifactorial



Artificial sweeteners
High omega 6:3 FA
Immunizations
Abx

De Filippo, C., et al., Proc Natl Acad Sci U S A, 2010   Mbakwa, C.A., et al., J Pediatr, 2016   Segata, N., Curr Biol, 2015

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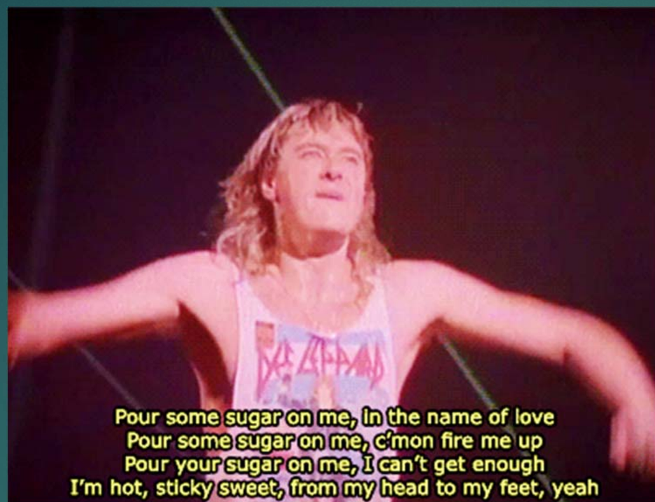
Sugar

The Sugar Addiction: The Gut-Brain axis



Sugar ingestion → Dopamine, opioid receptor binding, Ach release in nucleus accumbens → Reward → Excessive sugar intake

Pseudo-Sugar: What defines an artificial sweetener/non-nutritive sweetener?

Low calorie

Not metabolized by host

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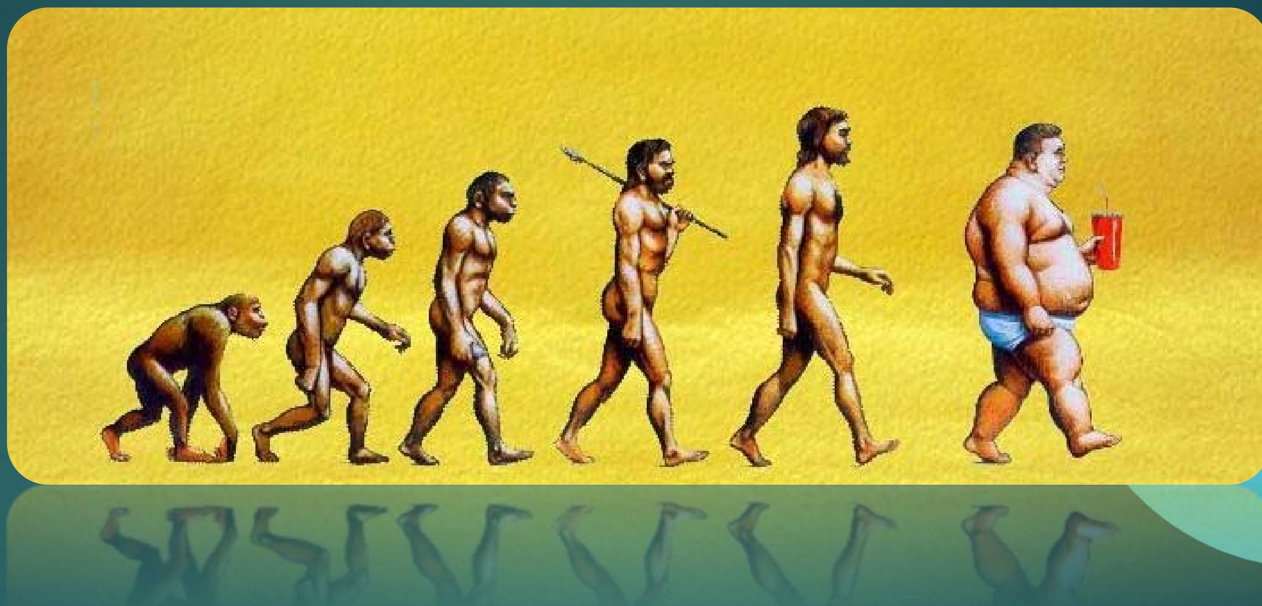
The Evolution of Sugar Substitutes



Sugar-laden diets are ubiquitous
Humans & animals display preferences for sweet taste- starts early in life
AS has grown in popularity as awareness of obesity epidemic increases
Over 6000 products on the market in the US alone

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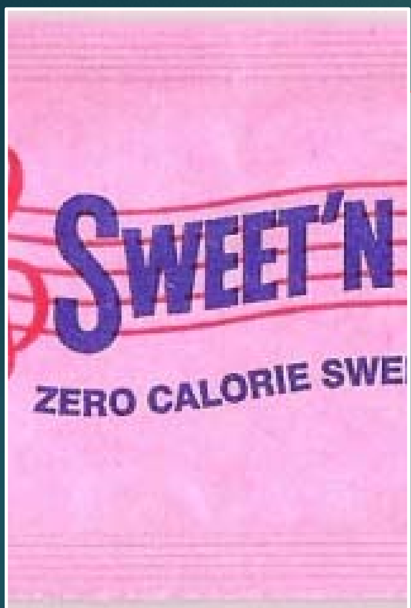

Saccharin

- Increased WWI sugar shortages
- Use increased 1960s low-calorie foods
- Developed to combat obesity epidemic & insulin resistance

Sharma A et al., Indian J Pharmacol. 2016
Swithers SE., Behav Anal. 2015
Sylvetsky AC et al., Am J Clin Nutr. 2012

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Artificial sweetener use in agriculture

Artificial sweeteners have been used since the 1950's

- Promote feeding & weight gain in agricultural animals
- Cheaper alternative to sugar

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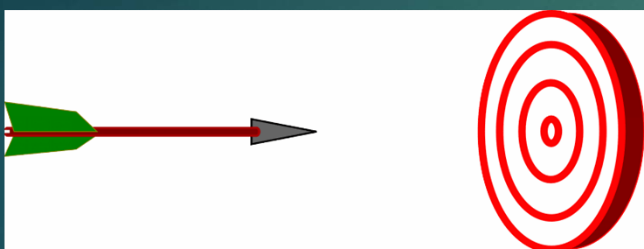
Types of Sugar Substitutes

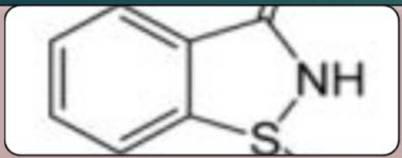


- AKA Non-nutritive sweeteners (NNS)
  - Artificial Sweeteners
    - Aspartame, saccharin, sucralose
  - Natural Alternative Sweeteners
    - Stevia, rare sugars, sugar alcohols, monk fruit

Common FDA Approved Sugar Substitutes

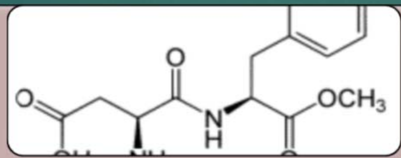
Sweetener	Trade Names	FDA Approved	# X sweetness of sucrose	Common Uses
Saccharin	Sweet 'N Low, Sugar Twin Necta Sweet	1879	200-700	Soft drinks, candy, medicine, toothpaste, lip gloss, baked goods, dressing
Aspartame	NutraSweet, Equal	1981	200	Gum, diet soda, instant tea/coffee, yogurt, pudding
Acesulfame-K	Sweet One, Sweet and Safe, Sunette, Swiss Sweet	1967	200	Soft drinks, baked goods, gum, gelatin
Sucralose	Splenda	1998	600	Baked goods
Stevia/Erythritol	Truvia, PureVia	1955	300	Baked goods, soft drinks
Sugar alcohols	**Sorbitol, Mannitol, Xylitol**	**Naturally occurring**	**0.5-1**	**Candy, gum, naturally in fruits/vegetables**

Artificial sweeteners: the details



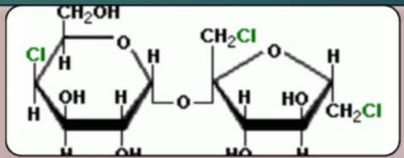
Saccharin

- Drinks, candy, medicine, toothpaste
- Not in baking products (unstable w/ heat)



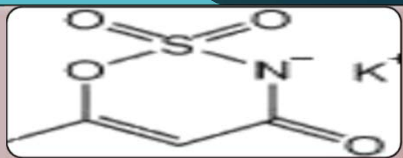
Aspartame

- Dipeptide (aspartic acid + PHA)
- Gum, drinks, desserts, candy
- Not used for baking (loses sweetness)



Sucralose

- Stable hot & cold temp
- Baking



Acesulfame potassium

- Bitter taste in large amounts

Natural Alternative Sweeteners

Studies in healthy & DM pts

Stevia (stevioside and rebaudioside A metabolites)

- Native plant South America
- Studies show reduction in blood glucose, less calorie consumption

Rare sugars (i.e. D-sorbose, Allulose, Tagatose)

- Monosaccharaides found in nature
- Studies show reduction in BW vs HFCS

Sugar alcohols (polyols i.e. sorbitol)

- Hydrogenated mono and disaccharides, some alter gastric emptying
- Less post-prandial glucose response vs sucrose/glucose, no change in satiety

Monk fruit (luo han guo)

- Native fruit in China, plant
- Improvement in glucose tolerance testing

Major limitations: human studies

- Majority of large studies are based on dietary recall
  - Poor awareness of foods/beverages that contain artificial sweeteners
    - Toothpaste, mouthwash, frozen dinners, sauces
- Small human sample sizes
- Short study durations (<3 months)

CONSUMPTION OF ARTIFICIAL SWEETENERS

NHANES database

1999-2007 increased from 6.1 → 12.5% children

18.7% → 24.1% adults

Nurses Health Study (NHS)

Prevalence 56%

Health Professionals Follow-up study (HDFS)

Prevalence 54%

San Antonio Heart Study

Prevalence 48%

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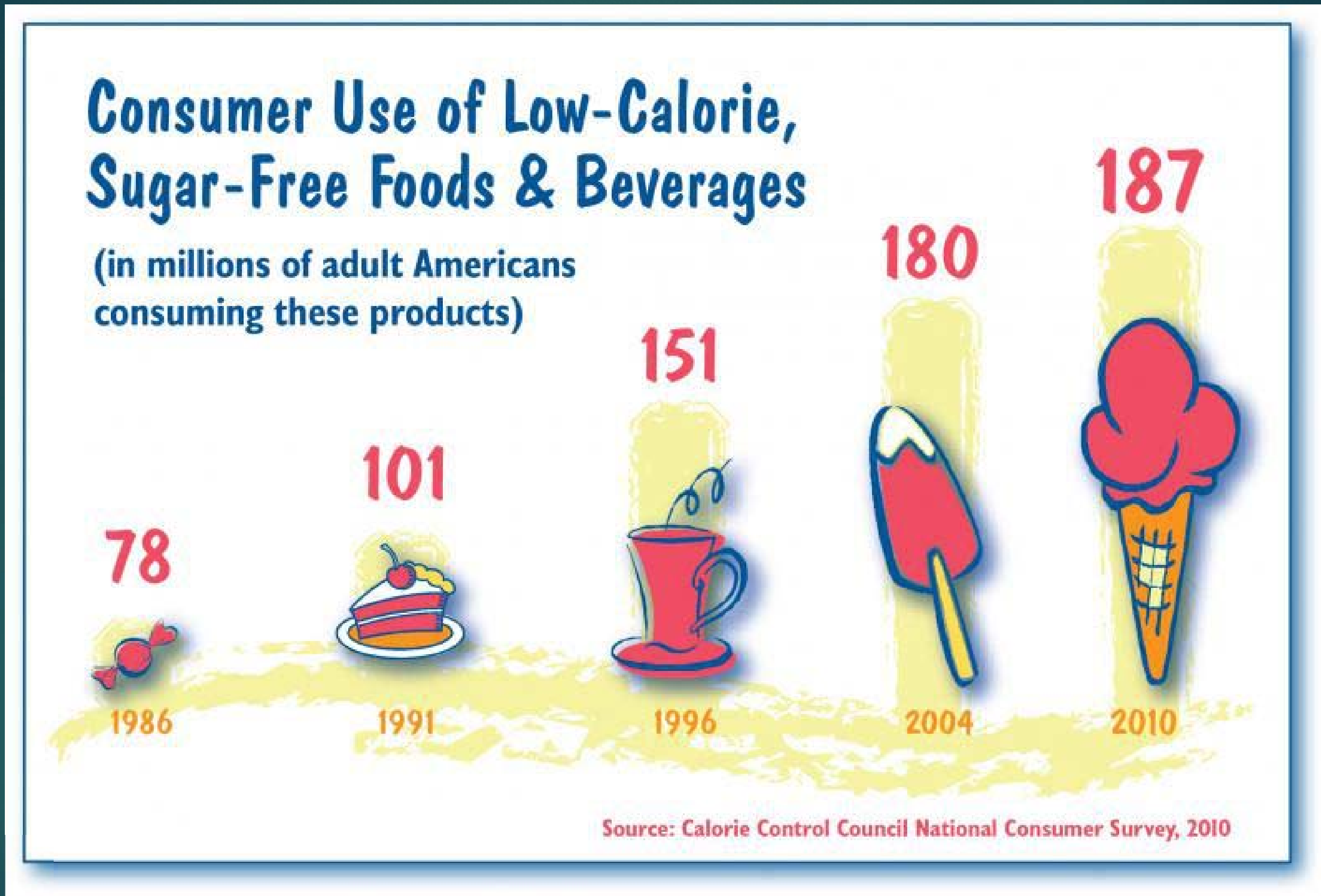

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Dietary Trends

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Why are we discussing artificial sweeteners in an obesity talk, aren't they supposed to help people lose weight?

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What a Conundrum

Despite increased use of artificial sweeteners:

- Prevalence of obesity has stayed stable over the past decade
- Suggests NOT good weight loss tool

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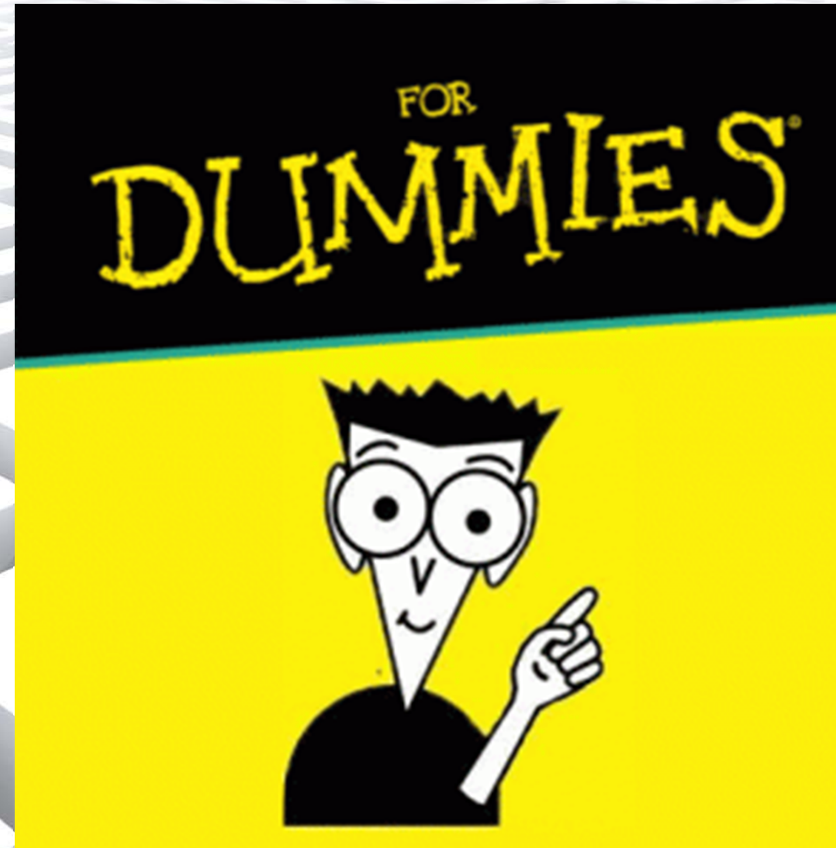
Artificial sweeteners vs sugar = similar risk

- HTN
- CAD
- Insulin Resistance
- Obesity

Bernstein AM, et al.,Am J Clin Nutr. 2012
Gardener H et al., J Gen Intern Med. 2012

O'Connor L et al., Diabetologia. 2015 Duffey KJ et al., Am J Clin Nutr. 2012 Sakurai M et al., Eur J Nutr. 2014
Fowler SP et al.,Obesity. 2008

Energy balance



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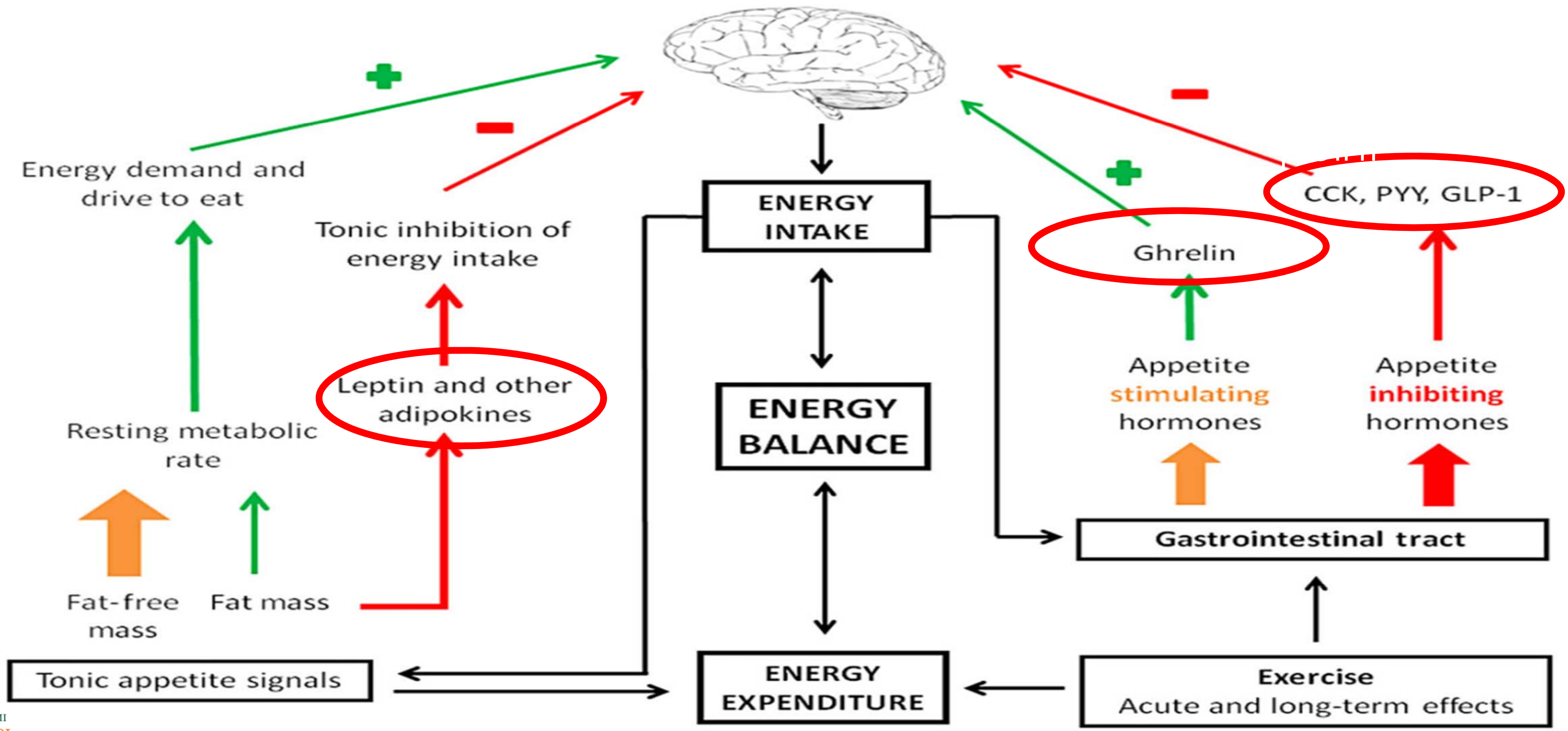
Energy Balance



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obesity reviews (2015) 16 (Suppl. 1), 6

Key peripheral hormones → hypothalamus

Appetite stimulants (hunger)

- Ghrelin

Appetite suppressants (satiety)

- Cholecystokinin (CCK)
- Polypeptide Y (PYY)
- Glucagon-like-peptide 1 (GLP-1)

What happens after sugar ingestion: In a

Sugar ingestion → Increase blood glucose → Upregulation GLP-1, GIP, PYY → Pancreatic beta cell stimulation → Insulin secretion → Cellular uptake of glucose for energy

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The Effects of Artificial Sweeteners on the Hormonal Response and Glucose Homeostasis:

GLP-1

- Incretin hormone & neuropeptide (gut hormone)
- Primary source is intestinal L cell in ileum
- GLP-1 secretion dependent on presence of nutrients in small intestine
- (+) pancreatic beta cells → release insulin in response to rising blood sugar
- (-) glucagon secretion

Glucose ingestion (+) GLP-1 and GIP at greater levels vs sucralose → more delayed gastric emptying & increased satiety

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Skibicka KP., Front Neurosci. 2013

Food reward: INVOLVES TWO PATHWAYS

Sensory Pathway

- Sweet taste receptors in oropharynx (G protein receptors)
- Send signals to hypothalamus & amygdala (reward centers)

Post- Ingestion Pathway

- Depends on energy content of food/beverage

Yang Q.,Yale J Biol Med. 2010 Stice E et al., J Abnorm Psychol. 2008 Avena NM et al.,Neurosci Biobehav Rev. 2008
Smeets PA et al., Am J Clin Nutr. 2005

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Normal physiology after 

consumption

Anticipatory/Cephalic Phase

- Flavor and taste cues
  - Food ingestion (+) sweet taste receptors oral cavity prior to nutrient absorption in anticipation of sugar
  - (+) physiologic responses & hormone release
    - Insulin secretion
    - Heat production
    - Satiety hormones i.e. GLP-1

Teff KL., Physiol Behav. 2011

Swithers SE., Behav Anal. 2015

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Altered physiology after  ingestion

- Artificial sweetener ingestion

- Dampened hormonal response (no sugar load)
  - No insulin release
  - No heat production
  - No satiety hormone release (GLP-1)→ less satiety (more hunger)

- Future sugar exposure
  - Abnormal response persists→ insulin resistance, increased caloric intake

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In a 

- THE BODY DEVELOPS A DAMPENED HORMONAL RESPONSE BECAUSE THE INTAKE OF SWEETS IS NO LONGER PREDICTABLY FOLLOWED BY A SUGAR LOAD
- ARTIFICIAL SWEETENERS INTERFERE WITH BASIC LEARNED, PREDICTIVE RELATIONS BETWEEN SWEET TASTES (SENSORY) & POST-INGESTION PATHWAYS
  - (-) anticipatory responses that normally serve to maintain physiological homeostasis

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The Effects of Artificial Sweeteners on Energy Consumption

Improved palatability promotes feeding (rodent & human models)

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Overcompensation Phenomenon

- •8 obese patients

When patients were aware they were consuming aspartame containing products, caloric intake was maintained or slightly increased vs caloric intake from conventional diet w/o AS

When diet covertly changed to aspartame containing products, patients had 25% reduction in caloric intake vs conventional diet

Suggests part of increased caloric consumption attributed to AS is conscious decision to overcompensate

Porikos KP, The American Journal of Clinical Nutrition, 1977

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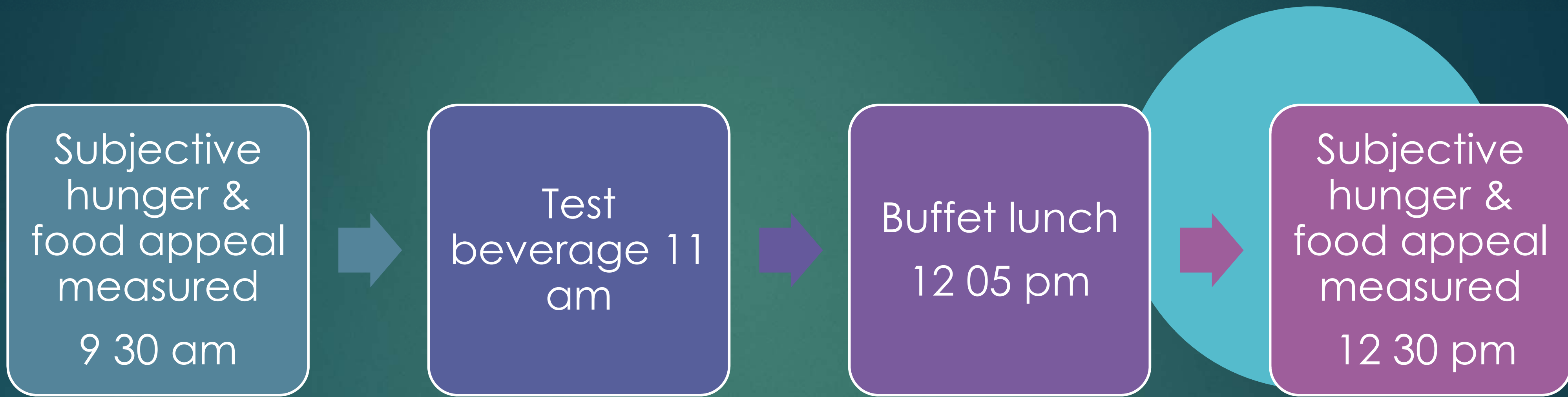
Effects of Artificial Sweeteners on subjective appetite & food appeal

Consuming aspartame with and without taste: Differential effects on appetite and food intake of young adult males

Richard M. Black *, Lawrence A. Leiter*,†, G.Harvey Anderson*

18 normal weight males: Each wk received beverage @ 11 am

- 280 ml carbonated mineral water (CMW) (control)
- 560 ml CMW
- 280 ml CMW w/ APM powder
- 280 ml CMW w/ encapsulated APM
- 560 ml APM soft drink



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Conclusions

560 ml CMW & 560 ml APM soft drink

- Suppressed appetite
  - Volume not APM content

280 ml CMW w/ APM powder

- Increased subjective appetite vs 280 CMW control (improved palatability)

280 ml CMW w/ encapsulated APM

- No effect on appetite
  - Importance of activating taste oral taste receptors (Sensory pathway in reward)

The Effects of Artificial Sweeteners on the Neuronal, Hormonal Response & Glucose Homeostasis

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Int J Obes (Lond). 2017 Jan 10. doi: 10.1038/ijo.2016.225. [Epub ahead of print]

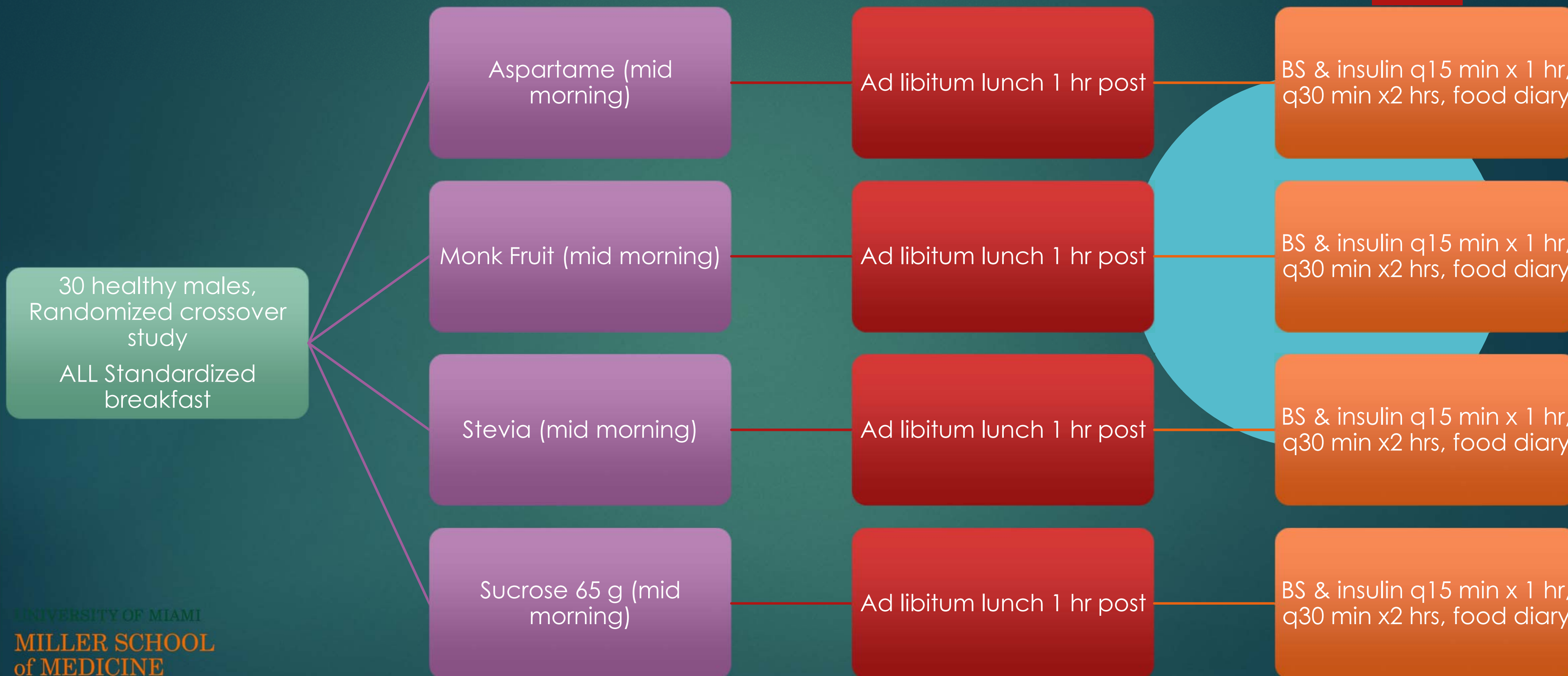
Effects of aspartame-, monk fruit-, stevia- and sucrose-sweetened beverages on postprandial glucose, insulin and energy intake.

Tey SL[1], Salleh NB[1], Henry J[1,2], Forde CG[1,3].

Goal: Compare effects of artificial sweeteners to sucrose:

- Energy intake
- Blood glucose
- Insulin response

Study design



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Study conclusions

Artificial sweetener groups: greater ad libitum lunch intake compared to sucrose group

Energy saved from replacing sucrose with artificial sweetener was fully compensated for at subsequent meals

No difference in daily energy intake between test groups

Sucrose group had larger spikes in BS and insulin w/in 1st hr of test beverage

Artificial sweetener groups had higher BS and insulin 2 hrs post lunch

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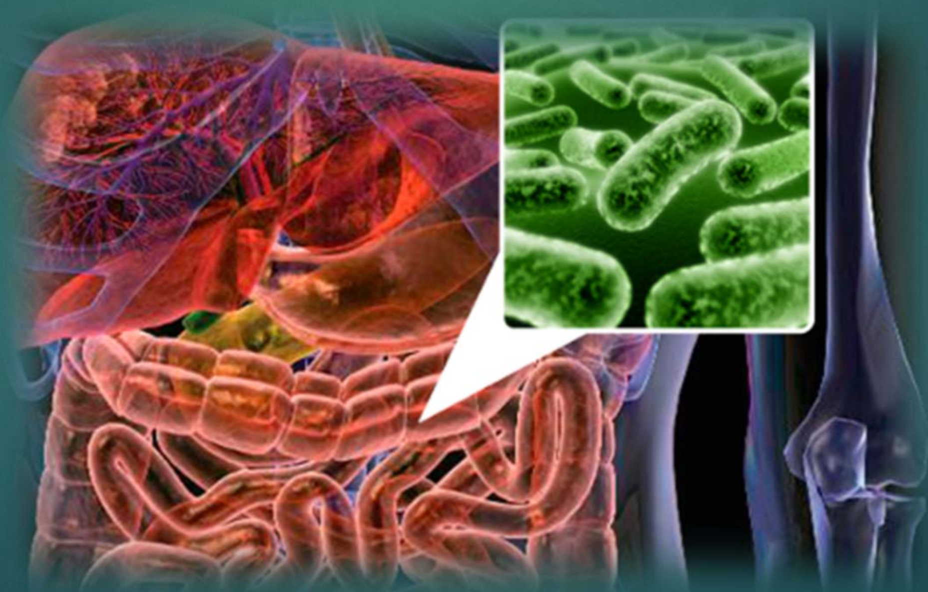
The Effects of Artificial Sweeteners: Microbiome



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Intestinal Microbiome

- Heterogenous population of bacteria
- Immense spatial distribution throughout GI tract
  - Surface area ~ 300 to 400 m^2
- Influenced by host internal and external environment
  - Dietary intake and physical activity
  - Host disease state

Xu J et al., Science. 2003
Turnbaugh PJ et al., Nature. 2006
Schloss PD et al., PLoS One. 2011
Backhed F et al., Proc Natl Acad Sci USA. 2004

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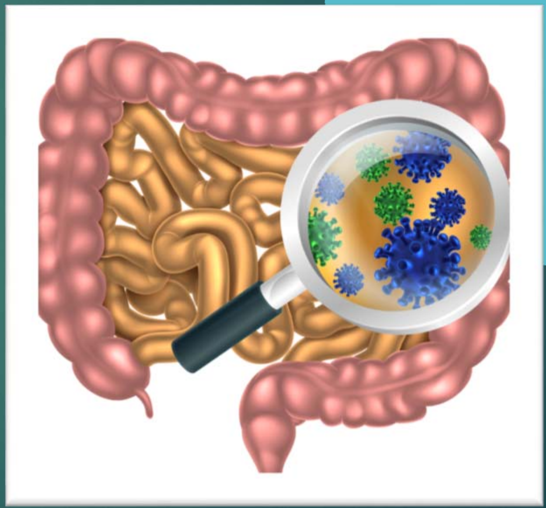
Microbiome: The basics

Majority are strict anaerobes

- *Bacteroidetes*
- *Firmicutes*

Facultative anaerobes

Aerobes



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Backhed F et al., Science. 2005
Ley RE et al., Proc Natl Acad Sci USA. 2005
Kleerebezem M et al., Annu Rev Microbiol. 2009
Qin J et al., Nature. 2010

Artificial sweeteners: effects on the microbiome

Low-dose aspartame consumption differentially affects gut microbiota-host metabolic interactions in the diet-induced obese rat.

Palmnäs MS[1], Cowan TE[2], Bomhof MR[2], Su J[3], Reimer RA[4], Vogel HJ[1], Hittel DS[4], Shearer J[4].

Goal of study:

- Evaluate effects of low dose aspartame x8 wks on fat composition in obese rats
  - Anthropometrics
  - Metabolic parameters
  - Changes in microbiome

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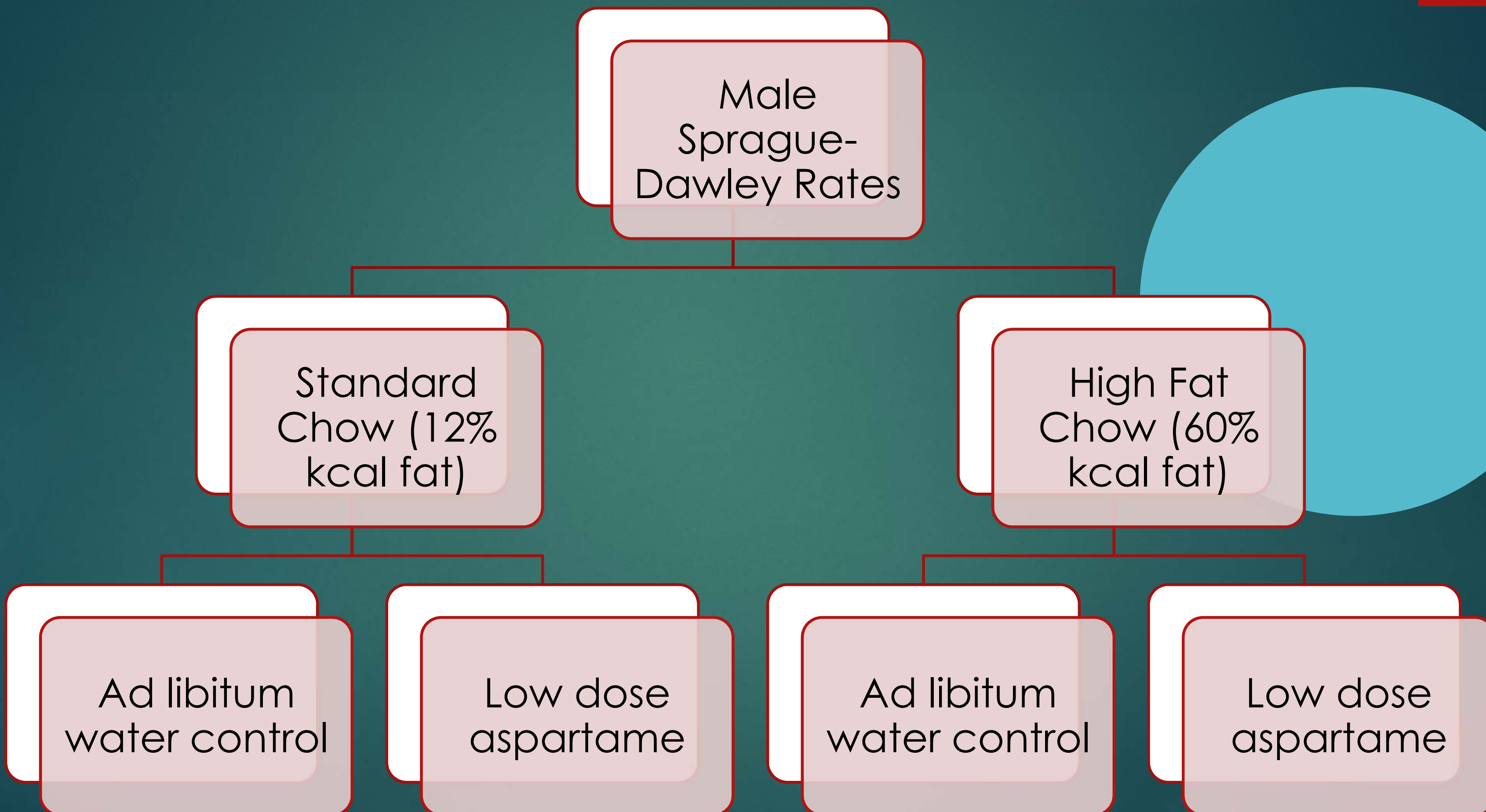
Study Design



Conclusions

HFD + ASP vs HFD + water: fewer calories, less weight gain

ASP groups in both standard chow & HFD: higher blood sugar, worse insulin tolerance test independent of body fat composition

Fecal analysis: ASP groups had increased total bacteria, greater abundance of Enterobacteriaceae & Clostridium leptum

HFD + ASP: increased Firmicutes: Bacteroidetes ratio which is typically seen in an obese host

Summary

- Artificial sweeteners are marketed as a healthy alternative to sugar & for weight loss
- Data suggests the intended effects do not correlate with evidence
- More promising data on natural alternative sweeteners
- Future research
  - Longer study durations to determine the long-term effects
  - Larger patient populations
    - Healthy individuals & DM

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That's a WRAP

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