Carbohydrates and artificial sweeteners in human nutrition

Effects of sugar and artificial sweeteners on cardiometabolic risk factors: role of energy fluxes
Luc Tappy, M.D. Lausanne, Switzerland

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• In what is sugar different from other carbohydrates?

• Why do we suspect that sugar is responsible for metabolic diseases?

• Is sugar always bad? Functional perspectives
All cells can use glucose as an energy substrate
Most cells can use fatty acids
Fructose is metabolized in a 2-step process: it has first to be converted into lactate, glucose, or fatty acids in the liver. Fructose conversion into glucose and fatty acids comes with some energy loss.
Fructose-metabolizing cells
liver, gut, kidney tubules

Fructolysis

Gluconeogenesis
Glycogenesis

Lactic ac. production

De novo Lipogenesis
Effects of Short-Term Fructose Overfeeding on Whole-Body Insulin Sensitivity

Fructose overfeeding decreases hepatic insulin sensitivity

Hyperinsulinemic-euglycemic clamps at ca 30 mU/L insulin

Effects of a 6-days fructose overfeeding (+ 3g/kg/day)

Faeh et al, Diabetes 2005
Fructose overfeeding does not decrease whole-body (muscle) insulin sensitivity

Hyperinsulinemic-euglycemic clamps at ca 100 mU/L insulin

Hypercaloric (+15% energy)
High fructose (+1.5g/kg/d)

Lê et al, AJCN 2006
Fructose increases fasting TG

Effects of a 1 and 4 weeks overfeeding with 1.5g fructose/kg/day (ca + 15% energy) on fasting triglycerides in healthy males

Lê K et al. Am J Clin Nutr 2006;84:1374-1379
Effects of excess fructose, not excess energy

F Theytaz et al, 2013; Sobrecases et al, 2010; Egli et al, 2014
Fructose ingestion increases fasting and post-prandial TG

Teff et al, JCEM 2004
Fructose overfeeding increases intrahepatic fat

Intrahepatic fat content (% control)

HISI (% control)

Lecoultre et al, Obesity 2013
Effects of excess fructose or excess energy?

Intrahepatic fat (% Control)

Lecoultre et al, 2013
Fructose promotes fat deposition from VLDL

Fructose → Dietary fats → Chylo-TG → VLDL-TG
Effects of high Fructose vs Glucose diets on abdominal body fat

Stanhope et al, J Clin Invest 2009
Excess sugar intake

Splanchnic de novo Lipogenesis

TG, cholesterol

Intrahepatocellular lipids

Intramyocellular lipids

Résistance à l'insuline, diabète

Foie normal

Foie cirrhotique
Effects of a REDUced Consumption of Sweetened Beverages

REDUCS Study

Preliminary results March 2015 (EB meeting Boston)

• 27 overweight males and females consuming > two 33cl sugar-sweetened beverages per day

• Randomized to artificially sweetened beverages (ASB) or sweetened beverages (SSB) during 12 weeks as sole intervention

• Measurement of intrahepatic fat (MRS), visceral adipose tissue (MRI), and fasting metabolic markers after
  • - 4-week run-in
  • - 12 week ASB or SSB

VC Campos et al, Obesity 2016
REDUCS Study

Invited to inclusion visit: n=75
Signed Consent: n=34
Did not attend baseline/MR n=3

Allocated to SSB: n=13
Allocated to ASB: n=18

Drop-out:
Pregnancy (n=2)
Medical Condition (n=2)

SSB group attending 16 week of the study: (n=13)
ASB group attending 16 week of the study: (n=14)

Phone and emails Screens: n=128

Study plan
- Week 0:
  - Inclusion distribution of beverages
  - Monitoring of physical activity
  - 24-hour urine collection
  - Basic clinical assessment
  - Magnetic Resonance Spectroscopy

Randomization:
sugar-sweetened beverages (SSB) or artificially sweetened beverages (ASB)

- Week 2 and 4:
  - Basic clinical assessment
distribution of beverages

- Week 6:
  - 3-day diet record
  - Monitoring of physical activity
  - 24-hour urine collection
  - Basic clinical assessment

- Week 8 and 10:
  - Basic clinical assessment
distribution of beverages

- Week 12:
  - 3-day diet record
  - Monitoring of physical activity
  - 24-hour urine collection
  - Basic clinical assessment
  - Magnetic Resonance Spectroscopy
REDUCS Study: replacement of sugar-sweetened beverages (SSB) by artificially sweetened beverages ASB decreases intra-hepatic fat.
Effects of ASB on subjects with and without hepatic steatosis
Does physical activity modulate the effects of a high fructose diet?

- 8 M, aged 21.50±0.96, BMI 22.09±0.67 studied during
  - 4-day sedentary conditions-isocaloric-low fructose
  - 4-day sedentary conditions-isocaloric-high fructose (3g/kg/d)
  - 4-day moderate physical activity (2 times 30min cycling sessions at 125 kW)-isocaloric-high fructose

Fructose  Starch  Lipids  Protein

S-LF  S-HF  PA-HF

Léonie EGLI et al, Diabetes 2013
Effects of fructose and exercise on triglyceride-rich lipoproteins

**TRL-TG (mmol/L)**

Oral $^{13}$C-labelled fructose

Ctrl vs Fru: $P<0.001$

Fru vs FruEx: $P<0.001$
Effects of fructose and exercise on $^{13}$C palmitate synthesis

Ctrl vs FruEx: $P<0.001$

Fru vs FruEx: $P<0.001$
How is fructose metabolized during exercise?

Net CHO ox
Glucose production and oxidation
Lactate production and oxidation

Virgile LECOULTRE
AJCN 2010
How is fructose metabolized during exercise?

Glucose production = 76 umol/kg/min

Lactate production = 94 umol/kg/min
Lactate oxidation 97 umol/kg/min
How is fructose metabolized during exercise?

Glucose production = 84 umol/kg/min
+10% vs Glu 2.0g/min

Lactate production = 120 umol/kg/min
Lactate oxidation 121 umol/kg/min
+30% vs Glu 2.0g/min

Net CHO ox
+30% vs Glu 2.0g/min
Low fructose input

Fructose → Heat loss → Glucose → Lactate → Liver, gut, kidney

Low energy output

VLDL-TG → CO₂

Muscle

+ → ATP
High fructose input

Liver, gut, kidney

Fructose

Glucose

Heat loss

Lactate

VLDL-TG

Muscle

Low energy output

CO₂

+ ATP
High fructose input

Fructose

Liver, gut, kidney

Heat loss

Glucose

Lactate

VLDL-TG

High energy output

Muscle

CO₂ + ATP
Conclusions

Sugar has unique properties due to the hepatocentric metabolism of its fructose component:

Fast absorption, temporary splanchnic storage, and «controlled» release of energy substrate.

With high energy intake-low energy output: splanchnic anabolism and energy storage → hepatic insulin resistance, NAFLD.

With high energy intake-high energy output: splanchnic lactate/ glucose release for peripheral oxidation → support skeletal muscle work.