Physiological and Pathological effects of Sugars

Sugar in the Diet: Is There a Sweet Spot?
Sydney, October 30, 2015

Masaccio: Cacciata dal paradisio (Adam and Eve banished from Paradise)
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Conflicts of interest
- Research support: Nestec AG, Switzerland; Ajinomoto Co Inc, Japan
- Conference fees: Ferrero, Italy

Nutritional recommendations for sugars

- EFSA 2010: no adverse effect up to 20-25% total energy; no sufficient evidence for an upper limit
- IOM 2002: no more than 25% total energy as added sugars (for 2000 kcal/d, ca 125g sugar/j, of which ca 62 g fructose)
- AHA 2013: added sugar intake <36 g/j (men), or <29 g/j (women)
- WHO 2015: limit free sugar intake to max 10% total energy intake (better 5%)
- SACN 2015: limit free sugar intake to max 5%

What is special about sugar?
Why suspect that sugar is responsible for metabolic diseases?
Does dietary sugar make you fat?, how?
Does sugar specifically favour abdominal obesity?
Does sugar cause insulin resistance?
Does sugar increase blood lipids?
Does sugar cause NAFLD?
What are the effects of exercise
What is special about sugar?

Sugar cane cutting in Haiti

Sugar is composed of glucose and fructose

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Substrates</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>sucrase</td>
<td>sucrose</td>
<td>maltose, isomaltose</td>
</tr>
<tr>
<td>maltase</td>
<td>maltose, isomaltose</td>
<td>glucose, glycerol</td>
</tr>
<tr>
<td>glucoamylase</td>
<td>starch</td>
<td>glucose</td>
</tr>
</tbody>
</table>

- HFCS
- Fruits
- Honey

Sugar is composed of glucose and fructose.

All cells can use glucose as an energy substrate.
Most cells can use fatty acids.

Most cells cannot use fructose as an energy substrate.
Fructose 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.

Ca. 5% energy loss
Ca. 25% energy loss

Fruits
Honey

All cells can use glucose as an energy substrate.
Most cells can use fatty acids.

Fructose has first to be converted into lactate, glucose, or fatty acids in the liver.

Ca. 5% energy loss
Ca. 25% energy loss

Fructose conversion into glucose and fatty acids comes with some energy loss.
### Metabolic fate of oral fructose

13C-fructose studies

<table>
<thead>
<tr>
<th>13C-Glucose prod.</th>
<th>13CO2</th>
<th>lactate prod.</th>
<th>Hep. de novo lipogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 g oral fructose(^1)</td>
<td>50%</td>
<td>50%</td>
<td>25% ?</td>
</tr>
<tr>
<td>Mixed meal with 25 g fructose(^2)</td>
<td>30%</td>
<td>42%</td>
<td>?</td>
</tr>
<tr>
<td>Mixed meal with 25 g fructose + 25 g glucose(^2)</td>
<td>21%</td>
<td>37%</td>
<td>?</td>
</tr>
</tbody>
</table>


\(^2\) Theytaz et Nutrients 2014, 6(7), 2632-2649; doi:10.3390/nu6072632

### Effects of fructose ingested with or without glucose on postprandial TG responses and de novo lipogenesis

![Diagram of fructose metabolism and effects on lipogenesis](image-url)
Why suspect that sugar is responsible for metabolic diseases?

F. Botero

High Sucrose/High Fructose diets in rodents

- Obesity
- Dyslipidemia
- NAFLD/NASH
- Insulin resistance / diabetes mellitus

High fructose diet as animal model of metabolic diseases
Not designed to compare fructose/sucrose to other substrate
Not designed to assess substrate vs energy intake

Epidemiological studies: added sugar or sweetened beverages and body weight (far from exhaustive!!)

**Positive association with body weight**
- ...

**No positive association with body weight**
- Maillard G et al. Macronutrient energy intake and adiposity ... JIO. 2000 24(12):1608-17
- ...

Relationships between Changes in Food Consumption and Weight Changes Every 4 Years

Study participants included 50,422 women in the Nurses’ Health Study (NHS), followed for 20 years (1986 to 2006); 47,898 women in the Nurses’ Health Study II (NHS II), followed for 12 years (1991 to 2003); and 22,557 men in the Health Professionals Follow-up Study (HPFS), followed for 20 years (1986 to 2006).

Does dietary sugar make you fat? How?

Body weight gain always corresponds to a positive energy balance

If sugar does promote weight gain, it must cause energy balance to become positive by either

- Decreasing energy expenditure
- Increasing energy intake
Effects of fructose on energy expenditure

Fructose increases post-prandial thermogenesis in lean and obese subjects

D Simonsen et al, AJP 1990

Effects of high fructose or high glucose diets on BMR

Table 2: effects of high fructose- or high glucose diets on basal metabolic rate

<table>
<thead>
<tr>
<th>Study</th>
<th>dietary intervention</th>
<th>Participants</th>
<th>% change in BMR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox et al, 2011</td>
<td>25% total E as fruct for 12 weeks</td>
<td>16 overweight subjects (9M, 7F)</td>
<td>-7.56</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>25% total E as gluc for 12 weeks</td>
<td>15 overweight subjects (7M, 8F)</td>
<td>-1.71</td>
<td>NS</td>
</tr>
<tr>
<td>McDewitt et al, 2000</td>
<td>50% excess energy as fruct during 4d</td>
<td>8 normal weight F</td>
<td>2.60</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 overweight F</td>
<td>0.69</td>
<td>NS</td>
</tr>
<tr>
<td>Abdel-Sayed, 2008</td>
<td>3 g fructose/kg/day during 7 days</td>
<td>6 normal weight M</td>
<td>0.00</td>
<td>NS</td>
</tr>
<tr>
<td>Ngo-Sock et al, 2010</td>
<td>3 g fructose/kg/day during 7 days</td>
<td>11 normal weight M</td>
<td>0.97</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 g glucose/kg/day during 7 days</td>
<td>2.17</td>
<td>NS</td>
</tr>
<tr>
<td>Lô et al, 2006</td>
<td>1.5 g fructose/day for 4 week</td>
<td>8 normal weight M</td>
<td>-3.92</td>
<td>NS</td>
</tr>
<tr>
<td>Lô et al, 2009</td>
<td>3.0 g fructose/day for 7 days</td>
<td>8 normal weight M</td>
<td>0.00</td>
<td>NS</td>
</tr>
</tbody>
</table>

Thermic effect of fructose vs glucose

Table 1: Studies having compared the thermic effect of oral fructose and glucose

<table>
<thead>
<tr>
<th>Study</th>
<th>Test meals</th>
<th>Participants</th>
<th>TE fruct [%TE glus]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharief et al, 1982</td>
<td>5 g suc or gluc/kg ideal body wt</td>
<td>6 normal weight M</td>
<td>153.8</td>
</tr>
<tr>
<td>Tappy et al, 1986</td>
<td>75 g pure fructose or glucose (6M,4F)</td>
<td>10 young, normal weight subjects</td>
<td>156.9</td>
</tr>
<tr>
<td>Simonsen et al, 1988</td>
<td>75 g pure fructose or glucose</td>
<td>5y, nw M, 4 y, nw f</td>
<td>156.7</td>
</tr>
<tr>
<td>Schwarz et al, 1989</td>
<td>75 g fruct or gluc in a test meal</td>
<td>20 normal weight subjects (10M, 10F)</td>
<td>115.9</td>
</tr>
<tr>
<td>Schwarz et al, 1992</td>
<td>75 g fruct or gluc in a test meal</td>
<td>23 normal weight and overweight F</td>
<td>121.4</td>
</tr>
<tr>
<td>Martines et al, 1994</td>
<td>1g fruct or gluc/kg body wt</td>
<td>6 normal weight M</td>
<td>104.7</td>
</tr>
<tr>
<td>Fukagawa et al, 1995</td>
<td>75 g pure fructose or glucose</td>
<td>8 young (19-29 y.) normal weight subjects (6M,2F)</td>
<td>116.0</td>
</tr>
<tr>
<td>Blaak et al, 1996</td>
<td>75 g pure fructose</td>
<td>10 young normal weight M</td>
<td>138.8</td>
</tr>
<tr>
<td>Van Gaal et al, 1999</td>
<td>100 g pure fructose</td>
<td>13 obese F</td>
<td>151.7</td>
</tr>
</tbody>
</table>

Fructose does not stimulate post-prandial satiety factors in blood

Teff et al, JCEM 2004
Effects of sugar preloads on food intake

- 50 g glucose, 50 g fructose, aspartame or water drink
- Buffet lunch with food intake monitoring 2.25h later
- 6 non-obese male subjects

Rodin et al, AJCN 1990

Does sugar specifically favour abdominal obesity?

Effects of high Fructose vs Glucose diets on body fat in overweight subjects

Stanhope et al, J Clin Invest 2009
Does sugar cause insulin resistance?

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

Fructose overfeeding decreases hepatic insulin sensitivity

% inhibition of Hepatic Glucose Output

Hyperinsulinemic-euglycemic clamps at ca 30 mU/L insulin

Effects of a 6-days fructose overfeeding (+ 3g/kg/day)
Fructose overfeeding does not decrease whole-body (muscle) insulin sensitivity

Hyperinsulinemic-euglycemic clamps at ca 100 mU/L insulin
Hypercarnolic (+15% energy)
High fructose (+1.5g/kg/d)

Lê et al, AJCN 2006

### Does Fructose increase blood lipids?

Annibale Carracci: the butcher shop. Ca 1580

<table>
<thead>
<tr>
<th>Study</th>
<th>subjects</th>
<th>Intervention</th>
<th>procedure</th>
<th>hepatic insulin sensitivity</th>
<th>whole body (muscle) insulin-mediated glucose uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lê et al, AJCN 2006</td>
<td>7 non-obese young subjects (7M)</td>
<td>1.5g fructose/kg/day during 4 weeks hyperinsulinemic clamps</td>
<td>2-step</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td>Feen et al, Diabetes 2005</td>
<td>7 non-obese young subjects (7M)</td>
<td>3g fructose/kg/day for 6 days hyperinsulinemic clamps</td>
<td>2-step</td>
<td>decreased</td>
<td>unchanged</td>
</tr>
<tr>
<td>Lê et al, AJCN 2009</td>
<td>24 non-obese young subjects (9M)</td>
<td>3.5 g/kg lean body mass hyperinsulinemic clamps</td>
<td>2-step</td>
<td>decreased</td>
<td>unchanged</td>
</tr>
<tr>
<td>Lê et al, Diabetes Care 2012</td>
<td>8 non-obese M and 8 non-obese F</td>
<td>3 g fructose/kg/day 2-step clamp hyperinsulinemic clamp (2 doses) in decreased in M, but not in F</td>
<td>unchanged</td>
<td>unchanged</td>
<td></td>
</tr>
<tr>
<td>Thoroum et al, Metabolism 2009</td>
<td>6 subjects weight maintenance diet containing 10% fructose for 3 months hyperinsulinemic clamp</td>
<td>13% fructose substituted for sucrlose during 3 months</td>
<td>unchanged</td>
<td>unchanged</td>
<td></td>
</tr>
<tr>
<td>Blak et al., Diabetes Care 2010</td>
<td>13 non-obese younger 25% sucrlose during 6 weeks two-step hyperinsulinemic clamp</td>
<td>13% non-obese young 25% sucrlose</td>
<td>unchanged</td>
<td>unchanged</td>
<td></td>
</tr>
<tr>
<td>Avignon A et al, Diabetes Care 2013</td>
<td>38 middle-aged subjects with type 2 diabetes 3 h fructose/kg/day for 6 days with and without a polyphenol deuterated glucose</td>
<td>2-step hyperinsulinemic clamp (without glucose)</td>
<td>NM</td>
<td>decreased</td>
<td></td>
</tr>
</tbody>
</table>

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
Fructose ingestion increases post-prandial TG and impairs TG clearance after a meal

What is the amount of fructose required to increase fasting plasma TG?

![Graph showing fructose intake vs fasting plasma TG](image)

Egli et al, in prep

Effects of excess fructose or excess energy?

![Bar chart comparing fasting plasma TG with different diets](image)

Theytaz et al, in prep; Sobrecases et al, 2010

Does sugar cause liver disease?
What are the effects of fructose overfeeding on Intra-Hepatic Lipid (IHCL)?

![Graph showing IHCL levels with increasing fructose intake as a percentage of daily energy requirements.]

Lecoultre et al, Obesity 2013 (In Press)

Effects of excess fructose or excess energy?

![Graph comparing IHCL levels with different fructose intakes as a percentage of daily energy requirements.]

Lecoultre et al, 2013

What are the effects of exercise?

Physical Activity

Le tour de France

W. Saris et al, 1989

- Tour de France 1988
- 22 cycling days + 1 resting day
- 4000 km
- 30 mountain passes
Food/drinks Consumed

<table>
<thead>
<tr>
<th></th>
<th>% energy</th>
<th>% carbohydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cookies</td>
<td>13.7</td>
<td>14.9</td>
</tr>
<tr>
<td>Maltodextrines</td>
<td>9.8</td>
<td>15.8</td>
</tr>
<tr>
<td>Sugar</td>
<td>5.9</td>
<td>9.4</td>
</tr>
<tr>
<td>Liquid Formulas</td>
<td>5.5</td>
<td>4.2</td>
</tr>
<tr>
<td>Soft Drinks</td>
<td>4.1</td>
<td>6.6</td>
</tr>
<tr>
<td>Energy Drinks</td>
<td>3.5</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Does physical activity modulate fructose’s effects?

- 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

Effects of fructose and exercise on triglyceride-rich lipoproteins

Oral $^{13}$C-labelled fructose

$^{13}$C-TRL-TG

Ctrl vs Fru: P<0.001
Fru vs FruEx: P<0.001

Effects of exercise on fructose metabolism

$^{3}$H$_2$-glucose

Blood + breath samples

NoEx

Additional blood + breath samples

ExFru

Additional blood + breath samples

FruEx

L Egli et al, Diabetes 2013
Estimated pathways for oral fructose disposal

<table>
<thead>
<tr>
<th></th>
<th>Period</th>
<th>NoEx</th>
<th>ExFru</th>
<th>FruEx</th>
<th>P (NoEx vs ExFru)</th>
<th>P (NoEx vs FruEx)</th>
<th>P (ExFru vs FruEx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fructose oxidation</td>
<td>120-540</td>
<td>26.6 ±1.0</td>
<td>24.4 ±1.0</td>
<td>43.5 ±1.9</td>
<td>0.053</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(g over 7h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fructose storage</td>
<td>120-540</td>
<td>27.3 ±0.6</td>
<td>28.9 ±0.8</td>
<td>10.7 ±1.4</td>
<td>0.25</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(g over 7 hours)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net glycogen storage</td>
<td>120-540</td>
<td>13.5 ±2.9</td>
<td>22.3 ±2.7</td>
<td>-116.7 ±5.8</td>
<td>0.24</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(g over 7h)</td>
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</tr>
</tbody>
</table>

- What is special about sugar? **Fructose**
- Why suspect that sugar is responsible for metabolic diseases? Epidemiological studies and common sense
- Does dietary sugar make you fat?, Yes, like any other substrate eaten in excess.
- Does sugar specifically favour abdominal obesity? Awaits confirmation by additional studies
- Does sugar cause insulin resistance? Does not cause muscle insulin resistance independently of body weight gain
- Does sugar increase blood lipids? Increases fasting and postprandial lipoproteins
- Does sugar cause NAFLD? Likely to contribute by increasing intrahepatic fat; proinflammatory?
- Effects markedly blunted by exercise

Egli et al, AJCN in press