Sucrose and fructose: Is sugar really like cocaine?

Ian Macdonald
Nottingham
UK
Outline

• Recent claims regarding sugar and addiction
• Theoretical problems with fructose re: fat deposition and obesity/insulin resistance
• Dopaminergic activation: sweet taste, high GI foods
• Brain glucose requirements
• Fructose feeding and muscle/liver fat – specific or energy overfeeding?
Negative claims about sucrose/fructose
(summarised by Ferris Jabr, Scientific American 2013)

• ‘By consuming so much sugar we are not just demonstrating weak willpower and indulging our sweet tooth—we are in fact poisoning ourselves according to a group of doctors, nutritionists and biologists, one of the most prominent members of which is Robert Lustig’

• Journalists, Taubes & Bittman: ‘argue that sugar poses far greater dangers ... it is a toxin that harms our organs and disrupts the body’s usual hormonal cycles. Excessive consumption of sugar, they say, is one of the primary causes of the obesity epidemic and metabolic disorders like diabetes, as well as a culprit of cardiovascular disease.’
Recent statements refuting claims that sugar is toxic/addictive

• In a series of meta-analyses examining dozens of human studies, Sievenpiper and colleagues found no harmful effects of typical fructose consumption on body weight, blood pressure or uric acid production.

• Tappy: There is no evidence ... that fructose is the sole, or even the main factor in the development of these diseases, nor that it is deleterious to everybody.

• Ferris Jabr, Scientific American 2013:
  – the available evidence to date suggests that, for most people, typical amounts of dietary fructose are not toxic.
  – Even if Lustig is wrong to call fructose poisonous and saddle it with all the blame for obesity and diabetes, his most fundamental directive is sound: eat less sugar. Why? Because super sugary, energy-dense foods with little nutritional value are one of the main ways we consume more calories than we need, albeit not the only way.
Recent findings—Although some studies hint towards some potential adverse effects of excessive fructose consumption especially when combined with excess energy intake, the results from clinical trials do not support a significant detrimental effect of fructose on metabolic health when consumed as part of a weight maintaining diet in amounts consistent with the average estimated fructose consumption in Western countries. However, definitive studies are missing.

Summary and conclusion—Public health policies to eliminate or limit fructose in the diet should be considered premature. Instead, efforts should be made to promote a healthy lifestyle that includes physical activity and nutritious foods while avoiding intake of excess calories until solid evidence to support action against fructose is available. Public health is almost certainly to benefit more from policies that are aimed at promoting what is known to be good than from policies that are prohibiting what is not (yet) known to be bad.
Theoretical aspects regarding potential problems caused by Fructose/Sucrose

• SSB (and other energy containing drinks) – poorly recognised by appetite / satiety systems.
  – Leads to passive overconsumption of energy?
• Metabolic effects of fructose (how does it differ from glucose?)
  – Does not stimulate insulin secretion
  – Stimulates hepatic de novo lipogenesis (? Increases liver fat, increases serum TG) – glucose may do the same?
  – Depletes hepatic ATP
• Oral health – cariogenic effects of fermentation of fructose/sucrose in the mouth. Timing wrt meals, frequency, quantity, oral hygiene (tooth brushing etc)

• Also speculated that Fructose activates brain ‘reward’ (dopaminergic) pathways, leading to craving for sweet foods and even ‘addiction’
Dopaminergic activation

- Dopamine D1 and D2 receptors in the amygdala appear to be involved in the acquisition and expression of fructose-conditioned flavour preferences in rats.
- Dopamine signalling in the medial prefrontal cortex and amygdala is required for the acquisition of fructose-conditioned flavour preferences in rats.
Bernal et al - 2009

Given the role of dopamine in the amygdala (AMY) in the processing and learning of food reward, the present study examined whether dopamine D1-like or D2-like antagonists in this site altered acquisition and/or expression of a fructose-CFP.

D1-like and D2-like receptor antagonism in the AMY and NAcS resulted in similar reductions in, but not elimination of the expression of a fructose-CFP,

and D1 receptor antagonism in the AMY and NAcS during training hastened the extinction of the fructose-CFP.

These data suggest that dopamine-responsive neurons within the two sites are part of a regional network of brain sites that mediate flavor-flavor conditioning in a manner similar to proposed regional networks of interacting brain sites for other aspects of feeding behavior.
Malkusz et al - 2012
administration of dopamine antagonists blocks acquisition and expression of
fructose-conditioned flavour preferences

So not as clear-cut as first proposed. Some aspects affected, others not.
Intense Sweetness Surpasses Cocaine Reward (Lenoir et al, 2007)

Overconsumption of sugar-dense foods or beverages is initially motivated by the pleasure of sweet taste and is often compared to drug addiction. Though there are many biological commonalities between sweetened diets and drugs of abuse, the addictive potential of the former relative to the latter is currently unknown.

Rats were allowed to choose mutually-exclusively between water sweetened with saccharin and intravenous cocaine. The large majority of animals (94%) preferred the sweet taste of saccharin.

The preference for saccharin was not attributable to its unnatural ability to induce sweetness without calories because the same preference was also observed with sucrose, a natural sugar.

The preference for saccharin was not surmountable by increasing doses of cocaine and was observed despite either cocaine intoxication, sensitization or intake escalation—the latter being a hallmark of drug addiction.
Lenoir et al conclusions

• ... sweet receptors evolved in ancestral environments poor in sugars and are thus not adapted to high concentrations of sweet tastants.

• The supranormal stimulation of these receptors by sugar-rich diets, such as those now widely available in modern societies, would generate a supra-normal reward signal in the brain, with the potential to override self-control mechanisms and thus to lead to addiction
Human studies

- Impact of high GI foods on brain activation
- Human brain perfusion responses to the stress of induced hypoglycaemia
Effects of Dietary Glycemic Index on Brain Regions Related to Reward and Craving in (obese) Men - Lennerz et al, AJCN 2013 & Macdonald et al, AJCN 2013

A high GI meal (decreased plasma glucose) increased hunger and selectively stimulated brain regions associated with reward and craving in the late postprandial period, a time with special significance to eating behavior at the next meal. Specifically, the high GI meal elicited greater brain activity (fMRI and ASL) centered in the right nucleus accumbens, spreading to other areas of the right striatum and to the olfactory area.

*Plasma glucose data not reliable,*
*no fasting brain values to compare postprandial responses to,*
*is not an effect of sucrose/fructose but of high GI v low GI.*
*Only measurements made 4hr post meal.*

The higher GI meal led to greater brain activity centered in the right nucleus accumbens, other areas of the right striatum, and the olfactory area. These observations add to a growing literature on the effect of different foods and food ingredients on brain activation and are linked to a possible neuropsychological basis to food cravings. To more fully understand the fMRI responses, future studies should include concurrent behavioral measures of craving, food preference, and intake.
Brain activation, DA and cravings

Macdonald et al, AJCN 2013

• It is often assumed that dopamine plays a central role in hedonics, craving, and reward; however, this is most likely an oversimplification.

• A body of evidence instead supports a role for dopamine in nonhedonic components of motivation and instrumental learning.

• Specifically, interference with nucleus accumbens dopamine transmission has a negligible effect on food intake in animals.

• Human tyrosine depletion studies (which reduce DA levels) provide little evidence that dopamine mediates subjective craving for drug stimuli. Similarly, a recent study found that tyrosine depletion reduced subjective hunger ratings. This is contrary to the notion that people overeat to compensate for low dopaminergic activity.
Human brain perfusion (PET) responses to the stress of induced hypoglycemia – Teh et al, 2010

fMRI studies in hypoglycaemia have shown similar activation of DA regions to those seen in appetite/satiety studies.
Carbohydrate and human metabolism

an overnight fast

(a high CHO breakfast

Thus the brain requires approx 6 g. glucose per hour

(values approx. mg/min glucose equivalents for 65kg person)

(Frayn 1996)
Brain glucose requirements

- Approximately 6 g glucose per hour
- Increases with increased cognitive load
- Alternative substrates (e.g., ketones, lactate) can only supply up to 50% of fuel and take hours – days to adapt
- Continuous supply of glucose is essential, otherwise get hypoglycaemic counter-regulatory responses.
- Illustrates the physiological basis of an appetite system focussed on achieving an adequate carbohydrate intake
Fructose feeding and muscle/liver fat – specific or energy overfeeding?

Abstract: ……In trials of adults with ad libitum diets (that is, with no strict control of food intake), reduced intake of dietary sugars was associated with a decrease in body weight (0.80 kg, 95% confidence interval 0.39 to 1.21; P<0.001); increased sugars intake was associated with a comparable weight increase (0.75 kg, 0.30 to 1.19; P=0.001). Isoenergetic exchange of dietary sugars with other carbohydrates showed no change in body weight (0.04 kg, –0.04 to 0.13).

So the issue is overconsumption of energy not a problem with Sucrose/Fructose
Johnston et al, Gastroenterology, 2013

Effects of fructose/glucose on liver and muscle fat content – $^1$H MRS

32 overweight men with large waist (>94cm) – studied for two separate 2wk periods

1$^{st}$ energy balance - 75% from food (all supplied)
   - 25% from glucose / fructose powder added to water

2$^{nd}$ overfed - 100% from food (own habitual intake)
   - 25% additional from glucose / fructose powder in water
Subjects – overweight, large waist, otherwise healthy men

<table>
<thead>
<tr>
<th></th>
<th>Fructose n=15</th>
<th>Glucose n=17</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>35±11</td>
<td>33±9</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>96.8±7.4</td>
<td>93.9±8.7</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>30.0±1.4</td>
<td>28.9±1.7</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Body fat (%)</strong></td>
<td>34.5±4.6</td>
<td>33.9±4.2</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Waist (cm)</strong></td>
<td>103.8±4.9</td>
<td>103.3±5.2</td>
<td>0.77</td>
</tr>
</tbody>
</table>
MR Spectroscopy

liver fat content
isocaloric hypercaloric

weight (kg)

fructose pre, fructose post, glucose pre, glucose post
Serum Triglyceride (mmol/L)

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>G</th>
<th></th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>isocaloric</td>
<td><img src="isocaloric_graph.png" alt="Graph" /></td>
<td><img src="isocaloric_graph.png" alt="Graph" /></td>
<td>hypercaloric</td>
<td><img src="hypercaloric_graph.png" alt="Graph" /></td>
<td><img src="hypercaloric_graph.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

** Indicates significant difference.
Liver fat

Muscle fat
Johnston et al

• Feeding 25% of Energy as Fructose or Glucose for two weeks has minor metabolic effects when part of a weight maintenance programme

• Overfeeding with Fructose and Glucose increases Serum TAG, liver fat and tends to increase muscle fat but does not have significant effects on insulin resistance *(duration too short?)*
Summary/Conclusions

• Strong opinions have been expressed regarding toxic effects of sucrose and fructose and the potential for addiction to foods containing these carbohydrates
• Overwhelming scientific opinion based on an assessment of the literature is that these claims are not correct
• Craving for foods is likely to involve brain DA pathways which are also involved in ‘reward’ but it is not justified in using this as evidence that this illustrates addictive properties of such foods
• Experimental studies do not show potentially harmful metabolic consequences of high intakes of fructose when energy intake meets requirements (ie in a state of energy balance)