

C. Chotiwat , C. Sharp, K. Teff and R.B.S. Harris. Feeding a high-fructose diet induces leptin resistance in rats. *Appetite*. 2007; 49: 284.

Background

- This research report will be more difficult to critique since we have only the abstract to review.
- This research was intended to test whether a high-fructose diet would induce leptin resistance in rats, justified by the following rationale:
 - There is a suggested association between increased consumption of high fructose corn syrup (HFCS) and the recent increase in the incidence of obesity — this is assuredly the correlative hypothesis of Bray, Nielsen & Popkin (1).
 - Leptin is a hormone released by fat cells that has been shown to inhibit food intake and increase energy expenditure. It has been reported that elevated triglyceride levels inhibit leptin transport to brain receptors (2, 3) and that a high fructose diet increases post-meal triglycerides (no reference provided).
- Experiment 1: Researchers fed rats either a high-fructose (60% of calories as fructose) or low-fructose diet (no fructose) for 3 weeks
 - Triglycerides increased by 75% in high-fructose rats vs. low-fructose rats.
 - The infusion of leptin interperitoneally (abdominally) for 2 weeks reduced body fat in the low-fructose rats by 25%
 - High-fructose rats had lower body fat than low-fructose rats (3% vs. 5%)
- Experiment 2: Researchers fed high- and low-fructose diets as above for 4 weeks, and then injected the rats interperitoneally with increasing doses of leptin.
 - All leptin doses inhibited 2h food intake of low-fructose rats, but had no effect on high-fructose rats.
- Conclusions:
 - Consumption of a high-fructose diet induces leptin resistance.
 - Resistance may be via inhibition of leptin transport across the blood brain barrier by elevated levels of circulating triglycerides.

Critique

- Justification

The basic Bray, et al hypothesis is that HFCS is uniquely (aside from caloric contribution) responsible for rising obesity rates in the U.S. over the past 30 years. The hypothesis is correlative in nature, based on the strong statistical association between HFCS availability and obesity incidence since 1970. While correlations are useful for hypothesis generating, they constitute the weakest form of scientific proof (see Forshee, et al).

- While it appears certain that leptin influences food intake and energy expenditure, it should be remembered that many appetite regulators have been discovered in the last five years and that their intricate interplay is

still being worked out.

The authors do not mention that Banks used a high-fat diet (31% fat) to disrupt leptin processing in the brain (3). So leptin function is influenced by many more factors than dietary fructose levels.

The tacit reference for high fructose diets increasing post-meal triglycerides is likely the authors' contemporaneous work at Monell Chemical Senses Center, Philadelphia (4). Teff, et al fed 30% of calories as fructose vs. glucose. As has been mentioned in other critiques, such a diet is prejudicial in two ways: 1) this represents a 4-5 fold excess in dietary fructose vs. typical intake levels; and 2) fructose is never consumed alone in the foods we eat — it is always accompanied by an equal or greater amount of glucose from a sweetener, cereal grain, maltodextrin, corn syrup or glucose.

- Experiments
 - While the justification is based on increasing HFCS in the diet, the authors fail to acknowledge that:
 - § HFCS use increased at the expense of sucrose, so that the overall increase in dietary fructose exposure mirrors the increase in total calories over the past 30 years – less than 20%;
 - § Pure fructose is a poor model for HFCS; sucrose – untested – would be a far better model due to composition similarities.
 - It is hard to imagine how rats could tolerate 60% of calories as fructose. Elevated levels in humans with no compensating glucose causes bloating, gas and osmotic diarrhea (5). This represents a 7.5-fold excess in fructose vs. typical intake levels. Though metabolic anomalies can be observed at this exposure level, extrapolation to the typical human diet is meaningless for reasons mentioned above:
 - § Test levels of fructose are highly prejudicial;
 - § Fructose is always consumed with glucose, a moderating metabolic influence.
- Conclusions
 - The authors demonstrated that grossly-excessive levels of fructose elevate triglycerides and impair leptin metabolism, however, they did not demonstrate this in a physiologically relevant experimental system. The dietary construct was highly prejudicial and guaranteed to produce an untoward metabolic effect.
 - They did not demonstrate that HFCS impairs leptin metabolism.

References

1. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr* 2004;79:537-43.

2. Banks WA, Coon AB, Robinson SM, et al. Triglycerides induce leptin resistance at the blood-brain barrier. *Diabetes* 2004;53:1253-60.
3. Levin BE, Dunn-Meynell AA, Banks WA. Obesity-prone rats have normal blood-brain barrier transport but defective central leptin signaling before obesity onset. *Am J Physiol Regul Integr Comp Physiol* 2004;286:R143-50.
4. Teff KL, Elliott SS, Tschop M, et al. Dietary fructose reduces circulating insulin and leptin, attenuates postprandial suppression of ghrelin, and increases triglycerides in women. *J Clin Endocrinol Metab* 2004;89:2963-72.
5. Riby JE, Fujisawa T, Kretchmer N. Fructose absorption. *Am J Clin Nutr* 1993;58:748S-753S.