

Calorie Control Council Response to Nagai *et al*

“The role of peroxisome proliferator-activated receptor γ coactivator-1 β in the pathogenesis of fructose-induced insulin resistance”

Nagai Y, Yonemitsu S, Erion DM, et al. The role of peroxisome proliferator-activated receptor γ coactivator-1 β in the pathogenesis of fructose-induced insulin resistance. *Cell Metab* 2009;9:252-64.

Background

This article is a collaboration from several departments within Yale University School of Medicine (New Haven, CT) and ISIS Pharmaceuticals (Carlsbad, CA). Gerald Shulman is the senior and corresponding author, with a history of studying the effects on fructose on intermediary (especially glycogen) metabolism. Peroxisome proliferator-activated receptor γ coactivator-1 β PGC-1 β is a transcriptional coactivator¹ for sterol regulatory element-binding protein (SREBP), the master regulator of hepatic lipogenesis².

Author Justification

Metabolic syndrome and diabetes, both characterized by insulin resistance, have both reached epidemic proportions worldwide with the adoption of westernized diets and increased consumption of fructose, stemming from the wide and increasing use of high-fructose corn syrup (HFCS) sweeteners (1, 2). It is well established that fructose is more lipogenic than glucose and high-fructose diets have been linked to hypertriglyceridemia, nonalcoholic fatty liver disease and insulin resistance (3-6). Despite a clear relationship between fructose and increased hepatic lipogenesis, the mechanisms responsible for this association remain poorly defined.

Hypothesis

PGC-1 β mediates fructose-induced lipogenesis via upregulation³ of SREBP. Therefore, knockdown⁴ of PGC-1 β would prevent this from occurring.

Experimental Design

The authors evaluated the role of PGC-1 β in the pathogenesis of fructose-induced insulin resistance by using an antisense oligonucleotide⁵ (ASO) to knockdown PGC-1 β in liver and adipose tissue of chronically (4 weeks) fructose-fed rats. Rats received either regular chow, which provided 60% of calories from carbohydrates (predominantly starch), or a high-fructose diet that provided 66.8% of calories from pure fructose.

Results

¹ Protein that interacts with additional factor(s) to activate gene transcription (copying of DNA into messenger RNA).

² Lipid synthesis in the liver.

³ Process by which a cell increases the quantity of a cellular component, such as RNA or protein, in response to an external variable.

⁴ Technique by which the expression of one or more host genes is reduced by treatment with a short DNA or RNA oligonucleotide with a sequence complementary to an mRNA transcript. The change in gene expression caused by the binding of this oligonucleotide to its transcripts causes decreased gene expression via blocking of mRNA translation (production of protein from RNA).

⁵ Single strand of DNA or RNA that is complementary to a chosen sequence. In the case of antisense RNA, it prevents protein translation of certain messenger RNA strands by binding to it. Antisense DNA can be used to target a specific, complementary RNA.

- PGC-1 β ASO improved the normal consequences of fructose overfeeding by reducing expression of SREBP and downstream lipogenic genes in liver.
- It reversed fructose-induced hepatic (liver) insulin resistance in basal and insulin-stimulated states.
- And PGC-1 β ASO also increased insulin-stimulated whole-body glucose disposal due to a threefold increase in glucose uptake in white adipose tissue.

Author Conclusions

1. PGC-1 β plays an important role in the pathogenesis of fructose-induced insulin resistance.
2. PGC-1 β knockdown prevents fructose-induced hypertriglyceridemia and hepatic and peripheral insulin resistance.
3. PGC-1 β inhibition may, thus, be a therapeutic target for treatment of diabetes, hypertriglyceridemia, and insulin resistance associated with increased [fructose-induced] *de novo*⁶ lipogenesis.

Critique

- The thrust of this specific work is clearly the development of drug interventions in treating and preventing obesity; namely, a PGC-1 β inhibitor. Hence the involvement of ISIS Pharmaceuticals.
- The primary critique of this paper lies in the presumption that fructose overexposure in the diet is an important cause of obesity. Consumption of fructose—as a component of nutritive sweeteners like sucrose, HFCS, honey and fruit juice concentrates—has increased at roughly the same rate as total calorie and other macronutrient intakes over the past three decades (7). And the ratio of fructose-to-glucose in the diet has remained largely unchanged over that same time period (8). We're not just eating more fructose than we were 30 years ago; we're eating more of *everything*.
- The focus on HFCS rather than sucrose, honey or fruit juice concentrates appears arbitrary. All are compositionally equivalent (half fructose and half glucose), and HFCS and sucrose are consumed in equal amounts in the US. It may be the authors have confused pure fructose with HFCS; they tested fructose, but did not test HFCS. HFCS and fructose are quite obviously not the same product.
- The authors' false presumption of fructose overexposure justifies their use of excessive fructose levels (66.8% of calories) in experimental diets. Human fructose exposure is typically 10% of calories (9); the authors thereby exposed rats to nearly seven times this amount for four weeks in order to induce metabolic abnormalities. Humans taking in this level of fructose would need to consume *all* of their calories as added nutritive sweetener (half fructose and half glucose) and still would not reach this level of exposure.
- While these experiments will be useful in drug development, their basic design clearly represents an extreme distortion of the human diet. The authors' results clearly cannot be reliably used to predict typical human metabolic outcomes.

References

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⁶ New

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