Diabetes/ Insulin Resistance

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High Fructose/Sucrose Diets for inducing Hypertriglyceridemia and Insulin Resistance in Rodents

A Brief Scientific Literature Review- October 2008

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High Fructose Diets

Consumption of sucrose and more recently of High Fructose Corn Syrup (HFCS) has increased dramatically through processed foods such as beverages, jams, jellies, baked goods and dairy products. HFCS is inexpensive and sweeter than sucrose which increases its palatability and hence is rapidly replacing sucrose in processed foods; this has been suggested to induce overeating in humans (1, 2).

In the past few decades, we have learned that an increased intake of refined carbohydrates such as HFCS and the disaccharide sucrose (which is composed of fructose + glucose), is associated with hypertension, obesity, diabetes, kidney disease and cardiovascular diseases, both in humans and rodents (3-6, 7, 8-14). These detrimental effects of fructose on health can be attributed to how fructose is metabolized after its dietary intake. After absorption in the gastrointestinal tract, fructose is transported via the portal circulation to the liver, where it enters hepatocytes via the glucose transporter GLUT5-independently of insulin - and is rapidly metabolized (15, 16). Also, phosphofructokinase, a hepatic enzyme that governs glycolysis in liver, negatively regulates glucose breakdown while fructose can evade this rate-limiting control mechanism and is metabolized into glycerol- 3-phosphate and acetyl–coenzyme A. These two intermediate metabolites are then used as substrates for glyceride synthesis, contributing to very low-density lipoprotein (VLDL) triglyceride production in the liver (3, 7). Furthermore, due to the lack of GLUT5 expression in β-cells, fructose unlike glucose does not directly stimulate pancreatic insulin release (16). The exposure of the liver to such large quantities of fructose leads to rapid stimulation of lipogenesis and triglyceride accumulation, which in turn contributes to reduced insulin sensitivity and hepatic insulin resistance/glucose intolerance (3). A recent finding that dietary fructose fails to stimulate both insulin and leptin secretion and attenuates postprandial ghrelin suppression has led to suggestion that prolonged consumption of diets high in fructose could lead to increased caloric intake and contribute to weight gain and obesity (17).

Rat Models

Amongst rodents, high fructose diets induce hypertriglyceridemia, insulin resistance and hypertension in Sprague-Dawley (SD) rats (8-10), Wistar rats (11, 12) and hamsters (13, 14). The SD (18) and Wistar rat (19) are established models of sucrose-induced insulin resistance and hypertriglyceridemia. Both of these phenotypes can develop within two weeks when these animals are fed a diet containing 65% sucrose (by weight) relative to one with 65% corn

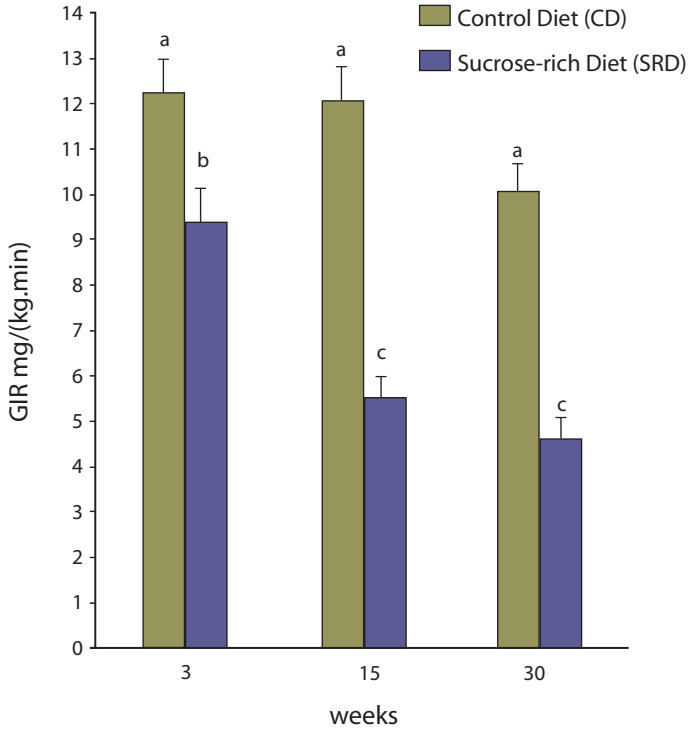

FIGURE 1. Glucose infusion rate (GIR) during the euglycemichyperinsulinemic clamp in rats fed control (CD) or sucrose-rich (SRD) diets for up to 30 wk. Values are means ± SEM, n = 6. Values that do not share a letter differ (P < 0.05). Graphic representation - for details see reference (11).

starch (18, 19). It has been shown that, as in humans, the active ingredient from the high sucrose diet is fructose rather than glucose which results in the metabolic syndrome; whereas equivalent amounts of glucose or starch do not induce these indications (20-22). Unless fed for a prolonged period of time, these high fructose/sucrose diets do not appear to lead to excessive weight gain (11).

In addition to inducing the metabolic syndrome, administering a high fructose diet to SD rats results in the development of renal hypertrophy, afferent arteriolar thickening, glomerular hypertension, and cortical vasoconstriction (23). When SD rats were fed a 60% fructose diet for 10 weeks, it induced hypertriglyceridemia, hyperinsulinemia and more importantly hyperuricemia (20). Uric acid has been implicated to play a role in the metabolic syndrome by inhibiting nitric oxide bioavailability which is required by insulin to stimulate glucose uptake. Lowering uric acid in these high fructose fed animals was able to prevent or reverse features of metabolic syndrome such as hyperinsulinemia, systolic hypertension, hypertriglyceridemia and weight gain (20). Also, Shapiro et al have recently shown that chronic fructose consumption induces leptin resistance in SD rats and accelerates high fat induced obesity (24). Similar to SD rats, Wistar rats fed with a 66% fructose diet over

a period of 10 weeks had increased systolic and diastolic blood pressure and increased pulse pressure, an index of vascular stiffness (12). When the high fructose diet was supplemented with long-chain (n-3) polyunsaturated fatty acids the metabolic and vascular disorders were prevented (12).

Hamster Models

The Syrian Golden hamster (Mesocricetus auratus) is a widely used model for lipoprotein research since the main plasma cholesterol carrier in the hamster is LDL and unlike rats, its lipoprotein metabolism appears to closely resemble that of humans (25). Hamsters can be made hyperinsulinemic, hypertriglyceridemic, and insulin-resistant by feeding them with high fructose diets (13). Similar to rats, hamsters fed high fructose diets (~60% of energy) may develop insulin resistance and elevations in triglycerides after only two weeks compared to diets low in fructose (13, 14). The fructose fed hamster model is characterized by high plasma levels of VLDL and apolipoprotein B due to hepatic lipoprotein overproduction (14). Interestingly, hamsters fed high sucrose diets do not have elevated triglycerides levels and develop only mild insulin resistance relative to those fed diets high in fructose (13). Since sucrose is one-half fructose, it appears that the level of dietary fructose is quite important in the rapid development of insulin resistance and elevated triglycerides in hamsters.

Mouse Models

In contrast to rats and hamsters, the mouse is used less frequently as a model for sucrose/fructose- induced insulin resistance and hypertriglyceridemia. The response to high fructose/sucrose diets is very strain-dependent in the mouse (26) and commonly used strains like the C57Bl/6 mice either do not develop insulin resistance or develop slowly (27). When C57Bl/6 mice and Wistar rats were gavaged with high fructose for three weeks, C57Bl/6 mice in contrast to Wistar rats responded with lowered plasma triglycerides and total cholesterol thus presenting a biochemical profile that could be considered to be healthier for the cardiovascular system (28). On the other hand, when C57/Bl6 mice were fed a high fructose diet for eight weeks, they developed increased mean arterial pressure, reduced glucose tolerance and increased plasma cholesterol which was attributed to the activation of the sympathetic and angiotensin systems (29). Also, Cunha et al showed that twelve weeks of high fructose feeding of C57/Bl6 mice resulted in impairment of renal function documented by increase in urinary protein excretion and increase in urinary volume (30). However, the mouse genome is easier to manipulate than that of the rat and several knockout models (that are prone to develop atherosclerosis) also show elevated triglyceride responses to high dietary fructose (31).

Thus, depending on the rodent model chosen, high fructose/sucrose diets can replicate several aspects of the human metabolic syndrome such as hypertriglyceridemia, hypertension and hyperinsulinemia.

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