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Fructose-induced alterations of glucose and lipid homeostasis: progressive organ dysfunction leading to metabolic diseases or mere adaptive changes?

Luc Tappy

Physiology Department, Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland

In the 1970s and 1980s, the monosaccharide fructose, because of its low glycemic effect, attracted much interest as a potential sweetener for patients with diabetes mellitus (1). Many decades later, its widespread use in the food supply, both as a component of sucrose as well as in high-fructose corn syrup, has become a major suspect in the current epidemic of obesity, type 2 diabetes mellitus, nonalcoholic fatty liver disease, and cardiovascular diseases (2).

Assigning such a pathogenic role to dietary fructose rests on a large body of scientific evidence: many animal and human intervention studies have documented potential mechanisms linking fructose intake with metabolic diseases (3). Alterations in circulating satiety gut hormones by fructose (4), and/or fructose-induced central leptin resistance (5) have been proposed to be responsible for energy overconsumption and obesity. The prominent first-pass hepatic fructose uptake, and the high lipogenic potential of fructose in liver cells, have been hypothesized to be instrumental in initiating increased secretion of atherogenic triglyceride-rich lipoproteins, and in initiating hepatic steatosis (3). In addition, a high-fructose diet has been shown to impair insulin-induced suppression of endogenous glucose output, corresponding to some degree of hepatic insulin resistance (6). These metabolic alterations, all induced by a high-fructose diet, may be the first steps toward the development of insulin resistance and diabetes, dyslipidemia and cardiovascular diseases, and nonalcoholic fatty liver disease. In addition, positive correlations between total fructose or sugar intake, added sugar intake, and/or sugar-sweetened beverage intake and risk of cardiometabolic diseases have been observed in many prospective cohort studies (7). As a result of these and other studies, several health agencies and national guidelines have issued recommendations to drastically reduce the consumption of added sugars, including fructose.

In this issue of *The American Journal of Clinical Nutrition*, Smajis et al. (8) report the results of an elegant study in which a group of healthy subjects consumed 100 g fructose/d in addition to their usual diet for 8 wk. They did not, however, observe the expected metabolic effects of fructose. First, participants did not increase their body weight during the study, but significantly reduced energy intake from other foods (mainly from added sugars). Similar observations were recently reported in overweight subjects supplemented with fructose drinks (9). These results clearly argue against fructose failing to elicit satiety signals. Second, no significant ectopic lipid deposition (as measured by MRI) was detected in the liver, cardiac muscle, or skeletal muscle, nor was there evidence of organ dysfunction, among subjects who ingested added fructose.

This is not the first time that a fructose intervention trial in healthy subjects has failed to produce metabolic dysfunction. One may argue that the duration of the intervention was too short to see important effects. Eight weeks, however, is a reasonably long period for a nutritional intervention, and it would be expected that any adverse metabolic effects associated with fructose exposure would be detectable by then. The study of Smajis et al. is similar to another study (10) in which healthy subjects were asked to consume 1.5 g fructose/kg body weight daily for 4 wk. This study documented an increase in fasting blood triglyceride after 1 wk, without any progression during the next 3 wk. It also documented a modest alteration of hepatic insulin sensitivity. In the Smajis et al. study, neither blood triglyceride concentration nor hepatic insulin sensitivity was altered with fructose intake.

The rapid, modest alterations of blood triglycerides and hepatic insulin sensitivity observed immediately after switching from a low- to a high-fructose diet in short-term interventions such as the study of Lê et al. (10) may therefore represent adaptive changes, i.e., the reflection of a new metabolic steady state, rather than early markers of cardiometabolic diseases. The occurrence of such a new steady state implies that energy balance is maintained and body fat does not change over time, as appears to be the case in the Smajis et al. study. In contrast, association of a high fructose intake together with positive energy balance is likely to lead to more progressive, potentially deleterious effects over time. In this regard, it is of interest that fructose-induced increases in intrahepatic fat concentrations were observed with high fructose (or high glucose) intake associated with a positive energy balance, but not associated with a weight-maintaining diet

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Address correspondence to LT (e-mail: luc.tappy@unil.ch).

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(11). Similarly, fructose-induced hypertriglyceridemia appears more important with hypercaloric than with isocaloric diets (12). This points to the well-known adverse metabolic effects of excess energy consumption, and to a still unsolved question: is an excess energy intake from fructose associated with more damageable effects than are excess energy intakes from other nutrients?

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