Health Effects of Sugars: In Search of Novel, Unsuspected Pathogenic Pathways 1,2

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There is currently intense debate regarding the role of sugars, and more specifically those containing fructose, in the pathogenesis of obesity, type 2 diabetes mellitus, and cardiovascular diseases. A lesser satiating effect from fructose from less stimulation of insulin, leptin, and other satiating gut hormones (1) and a high potential to stimulate de novo lipogenesis in the liver (2) were the major mechanisms suggested to account for the obesogenic effect of fructose.

In addition to hypotheses related to the specific metabolism of fructose, it was also proposed that the effects of liquid calories consumed as beverages may differ from those consumed as food (3). Energy intake in the form of sugar-sweetened beverages is, indeed, incompletely compensated for by reduction of solid calorie intake, but this possibly may be explained simply by the fact that consumption of fluids is triggered by thirst in response to body fluid depletion or hyperosmolarity, whereas consumption of solid food is mainly triggered by hunger in response to signals informing the organism of a lack of energy stores (i.e., low blood glucose and insulin indicating absence of food intake or low blood leptin indicating low adipose TG stores). It is no big surprise, therefore, that even without clear mechanisms explaining a decreased satiety with liquid calories, consumption of energy-rich drinks may cause excess energy intake.

It was also proposed that high fructose corn syrup (HFCS) may be more deleterious than sucrose, possibly because of more rapid gut absorption of free fructose and glucose from HFCS than of fructose and glucose from hydrolysis of sucrose during its digestion. However, postprandial blood glucose responses are very comparable after ingestion of HFCS or sucrose (4), and there is evidence that sucrose hydrolysis by the gut enzyme sucrase-isomaltase is very rapid and is not a rate-limiting process. Only a few studies reported different effects of HFCS and sucrose (5), and they failed to identify the mechanisms at hand.

In this context, the report by Ruff et al. in this issue of the Journal of Nutrition (6) that mice fed a diet containing a mixture of fructose and glucose as monosaccharides (F/G) over 40 wk postweaning did less well in later life than sucrose-fed mice comes as a surprise. The originality of this study was to focus not on metabolic diseases or blood risk markers, but on the way animals performed globally under close-to-wildlife conditions. This was done by releasing groups of male and female mice fed either F/G or sucrose together into so-called organismal performance assays, i.e., enclosures mimicking life in the wild, where animals had to compete for territories, access to food, and mates.

Mice fed F/G did not display obesity, dyslipidemia or insulin resistance when compared with sucrose-fed mice. However, females previously fed F/G lived less long and had lower reproductive performances than females fed sucrose. In contrast, longevity and ability to control territories in males were not affected by postweaning nutrition.

These observations differ from previous literature on fructose in several aspects. First, because of protocol constraints, all animals were fed the same F/G diet after being released into the organismal performance assays. Any differences observed between the mice fed F/G and those fed sucrose during the 40-wk postweaning period were therefore attributed to epigenetic, long-lasting effects of nutrition. Second, these effects were not directly related to classic metabolic markers such as increased body fat mass, visceral fat deposition, or insulin resistance, or to obvious dysfunctions of the gut, liver, or kidney, which are the organs that specifically express fructose-metabolizing enzymes. There is presently no hint regarding the possible underlying mechanisms. This is a riddle, because most organs in the body, including the reproductive organs and the nervous system, are not directly exposed to high blood fructose. If the preliminary observations reported in this provocative paper were to be confirmed in further experiments, one would therefore need to consider alternative pathways by which sugars may affect the functions of target organs and tissues. In sucrose-fed rats, insulin resistance develops as a result of intramyocellular lipid accumulation secondary to hepatic secretion of TG-rich lipoprotein. Similar distant lipotoxicity may possibly be exerted on other organs and tissues, including the female reproductive tract (7). It is also possible that metabolites released from the liver in response to sucrose, such as uric acid (8) or lactate (9), may exert regulatory effects on distant tissues. Recently, fructose ingestion was shown to stimulate the hepatic secretion of fibroblast growth factor 21 (10), a novel hormone that regulates lipid metabolism in the liver and adipose tissue. The role of alterations of fibroblast growth factor 21 secretion or its action on the long-term effects of fructose remain to be explored.

Finding possible mechanisms responsible for the long-term effects of sugar ingestion independent of changes in body composition and blood metabolic markers is already a challenge. In addition, the total amount of fructose and glucose absorbed, and their rate of absorption, are expected to be very similar with sucrose and F/G. How could F/G exert long-term effects different from those of sucrose? Here again, one can only make guesses. A continuously growing body of evidence points to a potential role of gut microbiota on host intermediary metabolism. Dietary sugars, and even artificial sweeteners, are...
known to substantially influence the composition of gut microbiota and may thus indirectly alter the host’s metabolism (11). Is it possible that F/G and sucrose differentially affect gut microbiota? Sugars may also indirectly affect gut microbiota by altering the glycosylation of glycans secreted by gut cells, with subsequent changes in gut barrier permeability (12).

In addition to pointing toward possible novel mechanisms by which sugars may affect health, the article by Ruff et al. (6) raises questions of immediate relevance to human nutrition. If feeding fructose and glucose as monosaccharides really leads to adverse long-term effects, and if similar adverse effects are not observed with sucrose, one may need to question the safety of the glucose-fructose syrups commonly used in North America, and which may become increasingly consumed in Europe as well because of pending changes in European Union regulations. These are important issues that may have important consequences on nutrition-related policies, public health, and the world economy. As such, it is urgent that these data be replicated, especially in other animal species, and that plausible mechanisms accounting for these effects of fructose-glucose mixtures be identified.

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