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FIELD OF VISION

Opposite fates of fructose in the development of metabolic syndrome

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Abstract

This short review comments on the recently published work of Ishimoto *et al* regarding the opposing effects of fructokinase C and A isoforms on fructose-induced metabolic syndrome in mice. The framework for the commentary is the preexisting background of epidemiological and experimental data regarding the association between ingestion of fructose, as present in sweetened beverages, and the development of metabolic syndrome. The work of Ishimoto *et al* clearly confirms the negative effect of fructose on lipid and glucose metabolism, independently from the amount of energy provided by the ingested sugar. It also confirms the absolute requirement of liver fructose metabolism, driven by fructokinase activity, in order to develop the full spectrum of metabolic syndrome alterations.

Key words: Lipid metabolism; Fatty liver; Obesity; Hyperglycemia; Dyslipidemia

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INVITED COMMENTARY ON HOT ARTICLES

Non-communicable diseases continue to place an enormous burden on humanity, and have recently surpassed infectious diseases as the primary concern for human health. Among the former, cardiovascular events derived from the development of atherosclerosis associated with chronic metabolic diseases (such as obesity, type 2 diabetes mellitus and metabolic syndrome) are increasing all over the world. Besides genetic predisposition, two lifestyles options that are deeply rooted in affluent Western societies are fuelling this vicious trend: a lack of physical activity and the consumption of hypercaloric diets which tip people's energy balance to an overwhelming excess of ingested, unused energy. Dietary changes favor the consumption of processed, palatable, high-calorie-density foodstuffs over traditional ones. Among the former are the whole spectrum of sweetened beverages (fruit juices, sodas, milk shakes, *etc.*) which are sweetened with High Fructose Corn Syrup or sucrose. In both cases, such beverages offer the ingestion of large amounts of two simple sugars, glucose and fructose, in similar proportions[1,2].

When ingesting calories in liquid form, as in the case of the consumption of sugar-sweetened beverages, there is a lack of an appropriate compensatory response and thus no corresponding adequate reduction in the ingestion of calories provided by solid food. Therefore, it favors an excessive daily intake of calories. However, besides the increase in ingested calories, the particularities of fructose metabolism also need to be considered. Fructose is the carbohydrate with the greatest ability to induce hypertriglyceridemia, in part due to a more marked increase in hepatic lipogenesis than that resulting from a similar intake of glucose[3,4].

After entering liver cells, fructose is rapidly metabolized by the enzyme fructokinase to fructose-1-phosphate. Fructose feeding induces its own metabolism by increasing fructokinase expression. The product of fructokinase (fructose 1-phosphate) is further metabolized by the enzyme aldolase to the triose phosphates glyceraldehyde 3-phosphate and dihydroxyacetone phosphate. The former enters directly into the glycolytic pathway producing pyruvate, which is converted to acetyl-CoA and citrate inside the mitochondria, providing the carbon moiety for de novo synthesis of long-chain fatty acids. Meanwhile, dihydroxyacetone phosphate is converted into glycerol 3-phosphate, which provides the glycerol backbone of triglycerides. Since hepatic fructose metabolism bypasses the main rate-controlling enzyme of glycolysis, phosphofructokinase, a high flux of this carbohydrate to the liver results in a marked increase in lipogenesis and in the production of very low density lipoproteins. In contrast, glucose is first phosphorylated in position 6 by glucokinase, followed by isomerization to fructose-6-phosphate, which is converted by phosphofructokinase into fructose 1, 6-diphosphate before entering the glycolytic pathway. The progression of glucose to complete glycolysis is under the control of phosphofructokinase activity, which is very tightly regulated by the products of the glycolytic pathway, citrate and ATP. Thus, when large amounts of glucose are consumed, there is a feedback inhibition of glycolysis and glucose uptake, limiting pyruvate production, and the lipogenic effect is not as intense as in the case of fructose[5]. Furthermore, research from our laboratory has shown that fructose, but not glucose at a similar energy intake, can down-regulate the liver peroxisome proliferator activated receptor (PPAR) system, impairing fatty acid oxidation, and thus helping the accumulation of fatty acids for triglyceride accretion[6]. At least in male rats, the effect of fructose on the PPARα system is related to the induction of a clear state of liver leptin-resistance[7].

Fructokinase, and its capacity to respond to fructose increasing its expression[8-10] thereby facilitating the incorporation of fructose into liver metabolism, is of paramount importance in the manifestation of metabolic disturbances induced by fructose ingestion. For example, Ouyang *et al*[11] have shown that patients with non alcoholic fatty liver disease consume nearly approximately 2-fold to 3-fold more fructose than controls, primarily in the form of sweetened beverages, and present higher liver expression of fructokinase. In an experimental model of male rats supplemented with 10 % w/v fructose solution, we found that atorvastatin, a hypocholesterolemic drug, counteracts fatty liver and inflammation by reducing the fructose-related liver fructokinase induction[12].

All this background information is capital to clearly appreciate the real importance of the information provided by Ishimoto *et al*[13] in their paper published recently in Proceedings of the National Academy of Sciences. Fructokinase exists in two isoforms, fructokinase A and fructokinase C, with differentiated patterns of tissue expression. Fructokinase C is primarily expressed in liver, kidney and intestines, while the A isoform is expressed ubiquitously[14]. Due to the lower K_m of fructokinase C, this isoform is held to be mainly responsible for fructose metabolism[15]. By cleverly using the knock-out mice that developed themselves for both isoforms (KO-A/C) or only for isoform A (KO-A) and two patterns of fructose supplementation (15% and 30% w/v solutions of fructose in drinking water for 25 wk), Ishimoto *et al*[13] clearly delineated the roles of fructokinase A and fructokinase C in the induction of the manifestations of metabolic syndrome by fructose.

While wild-type mice supplemented with 15% fructose presented almost the full panoply of metabolic syndrome manifestations (obesity, hyperglucemia, hyperinsulinemia, hyperleptinemia and fatty liver), KO-A/C mice supplemented with 30% fructose, despite ingesting equivalent amounts of fructose, presented no manifestations of metabolic syndrome at all. In contrast, KO-A mice supplemented with 30% fructose, although ingesting the same amount of fructose as their matching wild-type controls, presented a more severe manifestation of metabolic syndrome than their wild-type counterparts. Ishimoto *et al*[13] carefully confirmed, by using recombinant fructokinase A, that this isoform, although having a low affinity for fructose, is capable of metabolizing fructose at a range of physiological concentrations.

In our opinion, three clear facts can be derived from the results presented by Ishimoto *et al*[13]: (1) KO-A/C mice were protected from developing metabolic syndrome, despite having a similar fructose intake and energy balance as their wild-type counterparts, which did indeed, develop metabolic syndrome. This experiment clearly demonstrates that the induction of metabolic syndrome by fructose does not depend on the amount of energy ingested (similar in KO-AC and wild-type control mice), instead it depends on the metabolism of ingested fructose, which clearly depends on the presence of fructokinase activity in tissues; (2) The fructokinase A isoform plays a physiological role in the metabolic fate of fructose. Its absence increases fructose concentration in plasma, even in animals ingesting only tap water; and (3) Furthermore, the absence of fructokinase A activity, as in KO-A mice, which shifts the whole metabolism of fructose to the C isoform, worsens the metabolic alterations induced by fructose ingestion. As mentioned above, fruc-

tokinase C is mainly expressed in liver and kidney and, to a lesser extend, intestines. If we consider that, after fructose ingestion, the sugar is rapidly and almost completely extracted by the liver through the glucose transporter 2[16], these results clearly point to the liver as the main target organ of fructose, and the one whose metabolic alteration finally results in the manifestation of metabolic syndrome in the whole organism. It would be very interesting to generate KO-C mice and supplement them with fructose in order to definitely confirm this claim.

While recognizing the problems of directly transposing experimental results obtained from animal models to the everyday-life of human consumption of sweetened beverages, the work of Ishimoto *et al*[13] demonstrates that fructose especial metabolism clearly matters as a key factor in the development of pathologies associated with the metabolic syndrome.

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