Uric Acid and Fructose: Potential Biological Mechanisms

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Summary: Excessive fructose consumption is associated with the development of metabolic syndrome and type II diabetes. Both conditions are well-known risk factors for cardiovascular and renal diseases. Uric acid synthesis is linked biochemically to fructose metabolism, thus the widespread consumption of this monosaccharide has been related to steady increasing levels of serum uric acid during the past few decades. Recent evidence has suggested that uric acid may act as a cardiorenal toxin. In this regard, experimental studies have suggested that the primary noxious effect of uric acid occurs inside the cell and is likely the stimulation of oxidative stress. More studies to disclose the harmful mechanisms associated with increasing intracellular uric acid levels after a fructose load are warranted.

Semin Nephrol 31:426-432

Keywords: Hyperuricemia, fructose, metabolic syndrome, renal damage, oxidative stress

Fructose consumption has increased markedly in the United State during the past 30 years, in part because of the introduction and generalized use of high fructose corn syrup (HFCS) by the food industry.[1] Sucrose, which is a disaccharide formed by one molecule of fructose and one molecule of glucose, also is consumed worldwide and is a major source of fructose. Other sources of fructose consist of that present in fruits and honey.

Epidemiologic studies have shown a parallel increase in fructose ingestion with the presence of metabolic syndrome traits. For example, in the National Health and Nutrition Examination Survey (2003-2006) a high frequency of increased blood pressure was observed in those ingesting more than 74 g/d of fructose from added sugars and fruit juices compared with those ingesting less than 74 g/d even after adjusting for other known risk factors.[2] In addition, because of its unique hepatic metabolism, fructose consumption is associated with the risk of developing dyslipidemia, fatty liver, and hyperuricemia,[3] all of which are associated with metabolic syndrome and are well-known risk factors for the development of cardiovascular and renal damage.

This article reviews recent concepts on the potential deleterious mechanisms exerted by fructose with the primary focus being on the damaging effects induced by the increased intracellular concentrations of uric acid (UA) that occur secondary to fructose ingestion.

FRUCTOSE METABOLISM

The metabolism of fructose is different in many ways from that of glucose. First, the rate of the body's use of fructose is fast and exceeds that of glucose; second, the uptake of fructose lacks a negative feedback mechanism, which explains its excessive catabolism when high doses are consumed.[3] The liver is the primary site of dietary fructose metabolism after intestinal absorption in the jejunum. Fructose uptake is mediated by the fructose-specific transporter GLUT5 and glucose-fructose transporter GLUT2,[4] and is transported via the portal vein, gaining access to hepatocytes via GLUT2. Fructose also is metabolized by the kidney and intestines because these organs strongly express GLUT5 and ketohexokinase.[5,6]

Fructose-accelerated metabolism in the liver is caused by both high expression and high affinity of ketohexokinase C (KHK-C, the first enzyme in fructose metabolism, Km = 0.80 mmol/L of D-fructose[7]) for its substrate. Fructokinase-mediated phosphorylation of fructose to fructose-1 phosphate will continue as long as fructose is available and as a consequence can result in transient intracellular adenosine triphosphate (ATP) depletion. This is in contrast to glucose metabolism, which is tightly controlled at the level of glucokinase because in this setting a feedback mechanism prevents excessive glucose phosphorylation and ATP depletion.

Consumption of large amounts of fructose alone can exceed the capacity of intestinal fructose absorption, resulting in diarrhea. However, consumption of glucose along with fructose, a combination usually consumed in

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Presented in part and published in abstract form at the 40th Annual Meeting of the American Society of Nephrology, October 31-November 5, 2007, San Francisco, CA (J Am Soc Nephrol 2007;18:184A [abstract F-PO376]).

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0270-9295/ - see front matter

doi:10.1016/j.semnephrol.2011.08.006

beverages and meals, enhances fructose absorption; this effect likely is mediated by the translocation of the glucose-fructose transporter GLUT-2 to the enterocyte apical membrane domain.[8] In addition, fructose absorption increases during long-term fructose consumption because this sugar up-regulates the intestinal fructose transporter, Glut 5, as well as hepatic and intestinal KHK-C in response to fructose exposure.[9]

Although KHK-C is the enzyme responsible for the metabolism of fructose in liver, kidney, and small intestine, there is a different splice variant called KHK-A that is present in many other organs.[7] The physiologic function of KHK-A isoform still is unknown because its Km is too high (7.0 mmol/L[7]) to be relevant for plasma fructose levels (31 μmol/L to 2.0 mmol/L[10]).

On the other hand, it is well known that fructose-rich diets increase plasma triglyceride levels. This effect recently was shown to be mediated by complex mechanisms that promote glycogen accumulation, increase hepatic de novo fatty acid synthesis, and decrease β-oxidation in the mitochondria.[11] In brief, fructose is phosphorylated by KHK-C to fructose 1-phosphate, and then metabolized to triose phosphates, glyceraldehyde, and dihydroxyacetone phosphate via aldolase B.[3] The glyceraldehyde that undergoes phosphorylation to glyceraldehydes 3-phosphate drives the gluconeogenic pathway toward glucose and glycogen synthesis (Fig. 1). Once liver glycogen is restocked, the intermediates of fructose metabolism are directed toward triglyceride synthesis.[3] Because fructose is commonly ingested along with glucose, fructose intermediates rapidly diverge to this last pathway. Thus, carbons derived from dietary fructose can be found in both free fatty acids and plasma triglycerides. The latter are incorporated into very-low-density lipoproteins and released from the liver where they are stored in fat and muscle.[3] Fructose intermediates also may be metabolized further to pyruvate via pyruvate dehydrogenase to acetyl-CoA and citrate in mitochondria, providing substrates for de novo lipogenesis.[11] In addition, excessive citrate production induces the synthesis of malonyl CoA, which is an inhibitor of the β-oxidation rate-limiting enzyme carnitine *O* palmitoyltransferase-1.[12] Therefore, de novo lipogenesis and defective β-oxidation are coupled processes that finally result in intrahepatic lipid accumulation. Interestingly, patients with hereditary fructose intolerance have a deficiency in aldolase-B and cannot metabolize fructose to triglycerides, yet develop fatty liver.[13,14] This phenomenon suggests that other mediators derived from fructose metabolism may converge in pathways that result in the increased synthesis and/or decreased oxidation of fatty acids.

A unique characteristic of fructose metabolism is the synthesis of UA as a byproduct[3] (Fig. 1). The metabolic pathway involved in this effect starts when fructose is first phosphorylated by KHK-C to fructose 1–phosphate. Because this enzyme is not regulated by the intracellular negative feedback mechanisms, when a large load of fructose is ingested, the ATP necessary to accomplish this reaction is rapidly exhausted. The fast production of adenosine monophosphate (AMP) is either deaminaded to inosine monophosphate (IMP) or dephosphorylated to adenosine, both being ultimately degraded to hypoxanthine and UA by the enzyme xanthine oxidase.[3] In addition, the depletion of phosphate, which is sequestered in fructose 1–phosphate, stimulates the activity of AMP deaminase and then promotes further AMP breakdown to IMP and eventually UA.[3] The observation that the concentration of fructose may be an important risk factor for ATP depletion suggests that the manner in which fructose is consumed may have important consequences. Thus, gulping a soft drink would be potentially more harmful than sipping it because higher concentrations would be obtained. For the same reason, drinking fructose would in general be more deleterious than consuming fructose contained within a food matrix (such as in fruits).

CLASSIC DELETERIOUS MECHANISMS ASSOCIATED WITH FRUCTOSE CONSUMPTION

Several mechanisms have been proposed by which high loads of fructose have damaging effects. For example, dyslipidemia secondary to fructose consumption is asso-

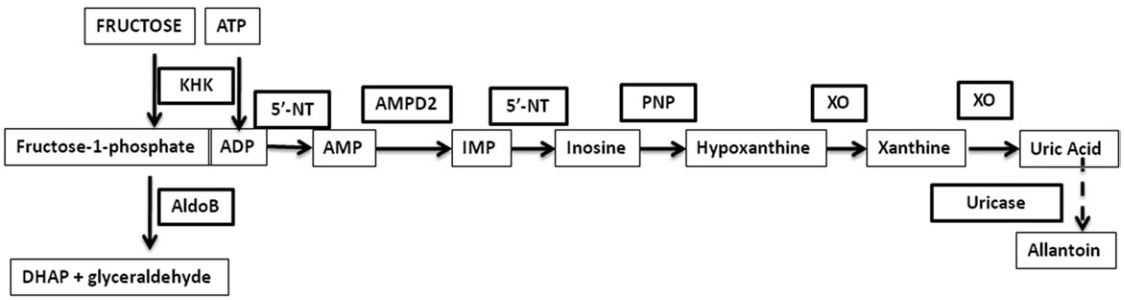

Figure 1. Esquematic of purine metabolism after fructose phosphorilation. Fructose is rapidly phosphorilated by fructokinase (KHK) as it enters into the cells. Phosphorylated fructose is then converted by aldolase B (AldoB) to dihydroxiacetone phosphate (DHAP) and glyceraldehyde for further metabolism. ATP depletion from fructose phosphorilation results in increased AMP levels by 5'-nucleotidase (5'-NT) which are then metabolized to IMP by AMPD2. IMP metabolism results in further uric acid generation in birds, humans, and some mammals due to defective urate oxidase (uricase) activity. Most mammals have efficient uricase, thus converting uric acid to allantoin (dashed arrow). PNP, purine nucleoside phosphorilase; XO, xanthine oxidase. ADP, adenosine monophosphate; AMP, adenosine monophosphate; IMP, inosine monophosphate.