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# Fructose surges damage hepatic adenosyl-monophosphate-dependent kinase and lead to increased lipogenesis and hepatic insulin resistance

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ABSTRACT

Fructose may be a key contributor to the biochemical alterations which promote the metabolic syndrome (MetS), non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2DM): (a) its consumption in all forms but especially in liquid form has much increased alongside with incidence of MetS conditions; (b) it is metabolized almost exclusively in the liver, where it stimulates de novo lipogenesis to drive hepatic triglyceride (TG) synthesis which (c) contributes to hepatic insulin resistance and NAFLD (Lustig et al., 2015; Weiss et al., 2013; Lim et al., 2010; Schwarzet al., 2015; Stanhope et al., 2009, 2013) [1–6]. The specifics of fructose metabolism and its main location in the liver serve to explain many of the possible mechanisms involved. It also opens questions, as the consequences of large increases in fructose flux to the liver may wreak havoc with the regulation of metabolism and would produce two opposite effects (inhibition and activation of AMP dependent kinase-AMPK) that would tend to cancel each other. We posit that (1) surges of fructose in the portal vein lead to increased unregulated flux to trioses accompanied by unavoidable methylglyoxal (MG) production, (2) the new, sudden flux exerts carbonyl stress on the three arginines on the γ subunits AMP binding site of AMPK, irreversible blocking some of the enzyme molecules to allosteric modulation, (3) this explains why, even when fructose quick phosphorylation increases AMP and should therefore activate AMPK, the effects of fructose are compatible with inactivation of AMPK, which then solves the apparent metabolic paradox. We put forward the hypothesis that fructose loads, via the increase in MG flux worsens the fructose-driven metabolic disturbances that lead to unrestricted de novo lipogenesis, fatty liver and hepatic insulin resistance. It does so via the silencing of AMPK. Our hypothesis is testable and if proven correct will shed some further light on fructose metabolism in the liver. It will also open new roads in glycation research, as modulation of MG catabolism may be a way to dampen the damage. Research on this area may have important therapeutic potential, e.g., more momentum to find new and improved carbonyl quenchers, new insights on the action of metformin, more evidence for the role of GAPDH inactivation due to mitochondrial overload in diabetes complications. AMPK plays a central role in metabolism, and its function varies in different tissues. For that reason, synthetic activators will always stumble with unwanted or unpredictable effects. Preventing MG damage on the protein could be a safer therapeutic avenue.



## Fructose as an initiator of hepatic insulin resistance, MetS and diabetes

It has become apparent that changes in dietary composition associated with the Western Diet may be at the root of the biochemical alterations which promote the metabolic syndrome (MetS), non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2DM) [3,7,8]. Fructose is a chief candidate since: (a) its consumption in all forms but especially in liquid form has much increased alongside with incidence of MetS conditions; (b) it is metabolized almost exclusively in the liver, where it stimulates de novo lipogenesis to drive hepatic triglyceride (TG) synthesis which (c) contributes to NAFLD, hepatic insulin resistance and dyslipidemia [1–6,9–11]. On the other hand, fructose increases uric acid production, which, via quenching of NO and effects on eNOS, has been associated with hypertension, another key co-morbidity in MetS patients [12–16]. The specifics of fructose metabolism and its main location in the liver serve to explain many of the possible mechanisms involved. It also opens questions, as some of the consequences of large increases in fructose flux to the liver (it is not rare to achieve a bolus dose of 40 g of fructose in liquid form- as found in 24 ounces of soda or juice- [1,3]), for which we are not prepared by evolution, may wreak havoc with the

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regulation of metabolism and would produce two opposite effects that would tend to cancel each other. We posit a new metabolic explanation that would solve the paradox. We will first briefly review fructose metabolism, then frame the paradox, next propose an alternate metabolic hypothesis, and finally indicate how to test it and make predictions.

## Hepatic fructose metabolism stimulates de novo lipogenesis as well as AMP and uric acid production

Fructose is almost exclusively metabolized in the liver. As shown in Fig. 1, fructose is taken up by hepatocytes via Glut2 and Glut8 transporters (1). Of note, this fructose is almost always accompanied by an equal amount of glucose (not represented here) [8,17]. Glucose will help replenish glycogen stores and stimulate insulin secretion, which fructose does not. The key difference with glucose is that fructose enters glycolysis more directly and in an unregulated fashion (it leaps regulated steps in glycolysis-glucokinase and phosphofructokinase) [8,17]. Phosphorylation by fructokinase (2) followed by an aldolase B splitting (3) leads quickly and directly to trioses (4). When there is a concurrent glucose flux, much of the trioses pool can be converted into triglycerides (TG) in de novo lipogenesis (5). These TG are packed with apoB100 as VLDL (6) or may accumulate in the liver and initiate NAFLD (7). What has been overlooked is the fact that an increased, unregulated triose flux would, by necessity, increase methylglyoxal (MG) production [18,19] (8). *MG fate will be one of the main actors in our hypothesis.*

The other edge of the sword is the consequences of quick ATP depletion by fructokinase. Due to the unregulated activity of this enzyme (evolutionary determined for low fluxes of fructose), a large fructose load would quickly deplete cytosolic ATP, especially when catalyzed by fructokinase C (2) [15,16]. This is partially remedied by adenylate-kinase (9) with production of AMP (10). AMP is catabolized to uric acid (11). Indeed this is a reaction sequence that occurs in animals and data from humans are in agreement, as fructose consumption is associated with hyperuricemia and hypertension [12,15,16,20]. There is another (unexplored as yet) key consequence of raising AMP concentrations or rather lowering ATP/AMP ratios: activation of the master allosteric energy regulator: AMP-dependent kinase (AMPK). *AMPK is the other main actor in our hypothesis.*

In fact, it has recently been shown that inhibition of Glut 8 by trehalose reduces fat deposition in hepatocytes and overexpression of Glut 8 increases it via a pathway mediated precisely by AMPK [21–23].

## The paradox: fructose metabolism would activate AMPK via increased AMP which would block de novo lipogenesis

Changes in AMP/ADP ratio greatly increase the activity of AMPK [24,25]. It has been proven that fructose flux increases uric acid

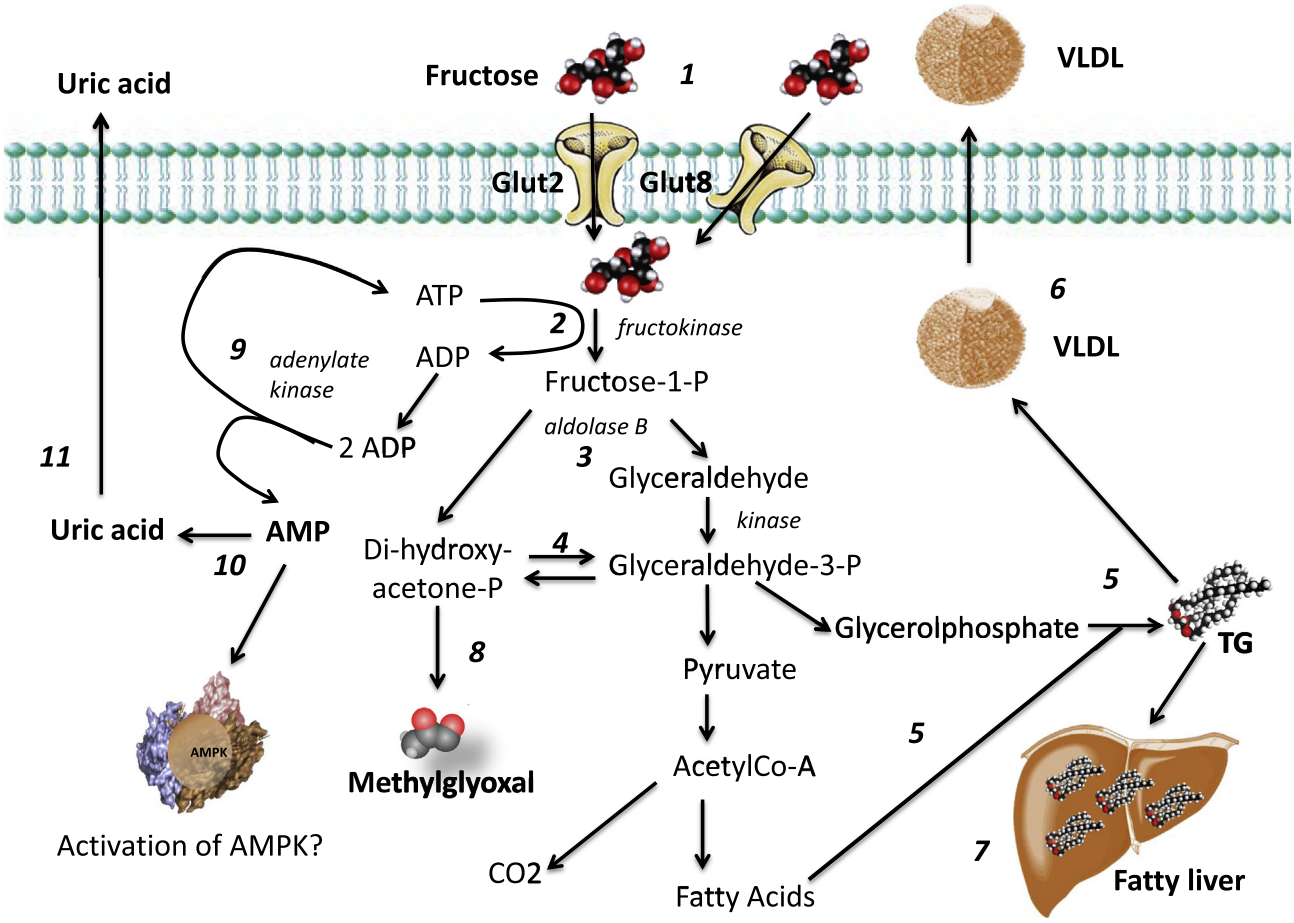


**Fig. 1.** Fructose metabolism in the liver. This diagram underlines the main steps in fructose metabolism. Key to our hypothesis is the production of AMP-which is the main activator of AMPK- and of methylglyoxal (MG). Fructose is taken up by hepatocytes via Glut2 and Glut8 transporters (1). Phosphorylation by fructokinase (2) followed by an aldolase B splitting (3) leads quickly and directly to trioses (4). When there is a concurrent glucose flux, much of the trioses pool can be converted into triglycerides (TG) in de novo lipogenesis (5). These TG are packed with apoB100 as VLDL (6) or may accumulate in the liver and initiate NAFLD (7). An increased, unregulated triose flux would, by necessity, increase methylglyoxal (MG) production (8). Adenylate-kinase (9) recycles ADP with production of AMP (10). AMP is catabolized to uric acid (11).