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Dichotomous effects of glucose versus fructose on hepatic lipogenesis, mitochondrial function and insulin signaling

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Non-alcoholic fatty liver disease (NAFLD) is a liver manifestation of obesity and insulin resistance. Overconsumption of high-fat diet and sugar-sweetened beverages are risk-factors for development of NAFLD. The relative effects of different monosaccharides on pathogenesis of NAFLD are not clearly established. We studied metabolic outcomes of mice fed chow or high-fat diet (HFD) consuming either regular water or water sweetened with 30% fructose or glucose, monosaccharide components of table sugar. Mice on HFD supplemented with fructose developed more significant obesity, glucose intolerance and hepatomegaly, as compared to glucose supplemented mice. Fructose supplemented mice had higher levels of SREBP1c and de novo lipogenesis, while glucose enhanced ChREBP transcription factor and fatty acid oxidation. Liver metabolomics profile confirmed that fructose enriched endogenously synthesized fatty acid pools, while RNA-sequence analysis identified lipogenesis and insulin signaling pathways as uniquely regulated by fructose versus glucose metabolism. The most striking difference was observed in mitochondrial structure and function. On HFD, fructose intake was associated with larger number, but smaller mitochondrial size, while ATP and NADH levels were decreased with acute fructose injection. Ketohexokinase C (KHK), the first enzyme of fructose metabolism, was increased in mice with fructose supplementation and in obese adolescents with nonalcoholic steatohepatitis. Knockdown of fructose metabolism specifically in the liver resulted in decreased hepatic steatosis, enhanced mitochondrial function and improved glucose tolerance. Our data show that fructose confers poor metabolic outcomes associated with sugar intake, while glucose metabolism may even be protective.

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