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Editorial

Exploring Fructose Metabolism in Hepatic Lipogenesis

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Editorial

Fructose, also known as fruit sugar, is a monosaccharide that was discovered in 1894 by the chemist Augustin-Pierre Dubrunfaut [1]. It is naturally found in fruits and vegetables, but is found in higher abundance in sugar cane, maize, granulated sugar, and sugar beets. In recent decades, maize has been used to produce High Fructose Corn Syrup (HFCS), a concentrated glucose-fructose mix, which is used as a sweetener for many processed foods and soft drinks. Due to the increased availability and consumption of HFCS in the modern diet, it has become paramount to understand the effects of fructose on human metabolism.

Fructose consumption triggers de novo lipogenesis, a metabolic pathway in which excess carbohydrates are converted into fatty acids. This pathway is regulated by the ATP Citrate Lyase (ACLY), an enzyme that links carbohydrate metabolism with lipogenesis. ACLY converts citrate (fructose metabolite derived from conversion of F1P) into acetyl-CoA, which can be readily used in lipogenesis. Overconsumption of fructose leads to altered metabolism, accumulation of fatty acids, and contributes to the pathogenesis of diseases like diabetes, obesity, heart disease, and Nonalcoholic Fatty Liver Disease (NAFLD) [2,3]. However, the pathways in which fructose exacerbates these diseases is yet to be fully understood. An article published by Zhao et al. attempts to further elucidate the fructose pathway by determining the roles of ACLY and the stomach microbiota in relation to hepatic lipogenesis [4]. Zhao finds that a two pronged mechanism is required to induce hepatic lipogenesis, in which the gut microbiota supplies fructose carbons to the liver in a ACLY-independent manner and the lipogenic pathway is activated by fructolysis in hepatocytes, which is independent from both ACLY and the microbiota [4].

Targeting ACLY is a promising therapeutic target as it converts citrate, a metabolic product from fructose, into acetyl-coA for use in lipogenesis. ACLY inhibition has been previously pursued and the FDA approved inhibitor, ETC-1002/bempedoic acid, is shown to reduce LDL-C levels up to 27% alone and higher in combination therapies [5]. However, Zhao et al. [4] has found that liver specific ACLY KO (LAKO) mice fed with fructose did not significantly affect global levels of hepatic metabolites or inhibit triglyceride accumulation. This finding is significant because it challenges existing models of fructose metabolism as it suggests that fructose is implicated in multiple pathways that can contribute to lipogenesis.

To identify alternate fructose pathways, Zhao et al. [4] identified differentially regulated genes in fructose fed LAKO mice compared to the fructose fed Wildtype (WT) control. The use of LAKO mice in fructose feeding is important as it allows for discovery of ACLY-independent fructose-dependent lipogenic pathways. While WT mice upregulated ACLY, LAKO mice upregulated ACLY-CoA synthetase short chain family member 2 (ACSS2) [4]. This is consistent with pervious data showing that ACLY KO results in increased ACSS2 expression [6]. ACSS2 is an enzyme that can convert acetate into acetyl-coA and is known to be regulated by the lipogenic transcription factor SREBP, which is activated in response to fructose consumption [7,8]. This intimately links ACSS2 and acetate production to fructose metabolism.

There are multiple pathways that generate acetate and Zhao et al was able to identify the gut microbiome as a source of acetate. Fructose is normally absorbed by the small intestine; however excess fructose can enter the colon and be processed into acetate by the gut microbiota [9]. Zhao et al. used antibiotic treatment and isotope tracing to find that mice with a depleted microbiome derived less lipogenic products from fructose and had overall reduced lipogenesis [4]. This suggests that targeting the gut microbiota can be used as a potential therapy for lipogenic diseases. While fructose can contribute to hepatic acetate pools, other sources of acetate were able contribute as well. Additionally, Zhao et al. also found that fructose consumption can upregulate lipogenic genes independently of ACLY and the microbiota. This result, implies that inhibition of the microbiota may not be sufficient to prevent hepatic lipogenesis on its own.

The fructose pathway is a complex relationship between diet, metabolism, and the gut microbiome, all of which can be potential targets for lipogenic diseases. Further research, however, is required to fully elucidate all aspects of fructose metabolism and develop therapies. It will be important to identify the contribution of other sources of acetate (acetogenic fibers, acetate solution/vinegar), as acetate can freely feed into hepatic lipogenesis. By identifying sources of acetate, it may be possible to develop a diet (reduced fructose/acetate) that can reduce lipogenesis.

Many antibiotics currently available affect the gut microbiota and can potentially be used for therapy. However, targeting the gut microbiota may be detrimental as it is implicated in multiple pathways such as digestion, nutrition, host immune system maturation, and disease mediation [10]. Previous studies have shown disruption of the gut microbiota can lead to microbial dysbiosis and prolonged/repeated use of antibiotics contributes to antibiotic resistance [11]. Thus, it will be essential to identify and target the specific sub-populations of the microbiota that generate acetate to develop therapies that disrupt the microbiome the least.

In cancer, studies have shown that HFCS consumption can result in increased intestinal tumor growth through increased uptake of fructose [12]. In respects to the findings of Zhao it et. it may be possible that non-intestinal tumors can still benefit from HFCS consumption

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through the microbiota. These findings propose an interesting therapy for cancer, as depletion of the microbiota may disrupt tumors that are dependent on acetate for survival. Thus, it may be necessary to develop screening methods that can identify tumors that are sensitive to acetate depletion. While these proposed treatments may be promising, further elucidation of fructose metabolism is required to develop more effective therapies for lipogenic diseases and cancer.

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