Small Intestine Safeguards Against Fructose-Driven Fatty Liver in Mice

Researchers found that overconsumption of fructose overburdened the small intestine, leading to fatty liver disease.

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When mice ingest fructose-containing food or drink, the small intestine helps process the sugar and diverts it from the liver, according to a study published in Nature Metabolism. The researchers reported that overconsumption of fructose—especially over a short time span or in a beverage—can cause the sugar to sidestep the gut and head for the liver, leading to the accumulation of fat.

“What we discovered and show here is that, after you eat or drink fructose, the gut actually consumes the fructose first—helping to protect the liver from fructose-induced damage,” study coauthor Zoltan Arany, MD, PhD, a professor of medicine at the University of Pennsylvania in Philadelphia, said in a press release. But consuming too much fructose can overwhelm this process.

Over the last century, fructose (fruit sugar) consumption has soared. Excessive intake of fructose, especially in drinks, has been linked to diabetes and non-alcoholic fatty liver disease (NAFLD). Prior studies have shown that surplus fructose ingestion can lead to an accumulation of fat in the liver through a process called lipogenesis. This storage of fat can develop into NAFLD, which over time can lead to cirrhosis and liver cancer.

The enzyme ketohexokinase breaks down fructose, which is found in fruits, honey and table sugar. The enzyme is present in the liver as well as in the small intestine, where fructose is metabolized into breakdown products and absorbed before it gets to the liver. Previously, it was unknown whether fructose metabolism in the small intestine contributed to or took away from lipogenesis in the liver.

In the multicenter study, researchers deleted the gene for the enzyme in the gut of the mice. The resulting overflow of fructose headed to the liver, making the mice more susceptible to hyperlipidemia (elevated blood fat levels) and hepatic steatosis (fat buildup).

On the other hand, when the team ramped up the amount of ketohexokinase in the gut, less of the fructose found its way into the liver, reducing lipogenesis. So the rate of fructose clearance in the

small intestine determines the point at which overconsumption of the sugar would lead to fatty liver development.

Moreover, imbibing fructose via a sweet drink (as opposed to eating it) or taking it all rapidly instead of over a 45-minute period increased the likelihood of lipogenesis. “Importantly, we also show that consuming the food or beverage slowly over a long meal, rather than in one gulp, can mitigate the adverse consequences,” said Arany.

When the rate of fructose intake surpassed the rate of intestinal metabolism, the sugar drove fat formation in the liver. Whether these results hold true for humans remains to be ascertained.

“Collectively, our findings show fructose induces lipogenesis when the intake rate exceeds the gut’s capacity to process fructose and protect the liver,” said Arany.

Click here to read the study abstract in Nature Metabolism.

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