Nature Reviews Endocrinology | Published online 3 Nov 2016; doi:10.1038/nrendo.2016.181

METABOLISM

Diabetes mellitus promotes hepatic fructose uptake

> ...the diabetic state leads to more ingested fructose getting absorbed...

The rise in fructose in our diet has been associated with the increasing incidence of metabolic disorders, but we need a greater understanding of the mechanisms associated with this effect. Now, in new data published in *eLife*, investigators have identified an insulin-sensitive mechanism that regulates fructose uptake in the small intestine, which might shed light on this problem.

In the small intestine, fructose is absorbed via glucose transporter 2 (GLUT2) and glucose transporter 5 (GLUT5), which are present on enterocytes. Building on previous work in which thioredoxin-interacting protein (TXNIP) was shown to regulate glucose uptake by interacting with another glucose transporter, GLUT1, Richard Lee and his team at Harvard University, Boston, Massachusetts, USA, investigated whether TXNIP can regulate fructose absorption via GLUT2 and GLUT5.

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The team first found that TXNIP can physically bind to both GLUT2 and GLUT5, which in turn regulates fructose absorption. In a human cell line, overexpression of *GLUT2* and/or *GLUT5* did not increase fructose uptake as measured with radiolabelled fructose. However, uptake was increased with the coexpression of *TXNIP*. Similarly, in embryonic fibroblasts from *Txnip* knockout mice, ~50% less fructose was retained in these cells than in cells from wild-type mice, an effect rescued by expression of human *TXNIP*. Radiolabelled fructose was also decreased in livers from *Txnip* knockout mice compared with wild-type controls.

Importantly, the team found that, like glucose, fructose can itself increase the expression of *Txnip* in the small intestine and that the interaction between GLUT2 and GLUT5 with TXNIP is dependent on the levels of fructose intake.

Finally, as *TXNIP* expression is elevated in conditions of impaired glucose tolerance, the investigators used streptozotocin to induce a type 1 diabetes mellitus-like phenotype in mice. In streptozotocin-injected mice, intestinal expression of *Txnip* was increased, which in turn increased fructose absorption. Radiolabelled fructose was also found to be increased in blood from the hepatic portal vein. This effect was reduced in streptozotocin-injected *Txnip* knockout mice.

"The central finding of our study is that the diabetic state leads to more ingested fructose getting absorbed from the intestine and sent to the liver," explains Lee. "In the liver, fructose can then promote insulin resistance." In addition to setting up collaborations to investigate this mechanism in humans, Lee and colleagues are investigating whether different types of diabetes mellitus all cause increased fructose absorption.

Tim Geach

ORIGINAL ARTICLE Dotimas, J. R. *et al.* Diabetes regulates fructose absorption through thioredoxin-interacting protein. *eLife* **5**, e18313 (2016)