

Boosting liver mRNAs curbs appetite, body weight in obese mice

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Scientists from The University of Texas Health Science Center at San Antonio (UT Health San Antonio) today reported that inhibiting a liver enzyme in obese mice decreased the rodents' appetite, increased energy

expenditure in adipose (fat) tissues and resulted in weight loss.

The finding, published in *Cell Metabolism*, provides a potentially desirable drug target to treat metabolic issues such as obesity and diabetes, the authors said.

"We first needed to discover this mechanism and, now that we have, we can develop drugs to improve [metabolic syndrome](#)," said senior author Masahiro Morita, Ph.D., assistant professor of molecular medicine in UT Health San Antonio's Sam and Ann Barshop Institute for Longevity and Aging Studies.

"We have an [enzyme inhibitor](#) that we want to make more specific to increase its effects," said first author Sakie Katsumura, DDS, Ph.D., postdoctoral fellow in the Morita laboratory.

The [liver enzyme](#), called CNOT6L deadenylase, turns off messenger ribonucleic acids (mRNAs) that ordinarily carry genetic instructions from the nucleus to sites in the cell where two liver proteins are made.

One of the proteins, growth differentiation factor 15 (GDF15), sends signals to two regions of the hindbrain to control food intake. The other, fibroblast growth factor 21 (FGF21), sends signals to brown and white adipose tissues to increase [energy expenditure](#). CNOT6L deadenylase impedes mRNA code-carrying for both GDF15 and FGF21, which reduces these benefits.

The researchers' first-in-class CNOT6L inhibitor, dubbed iD1, stabilized liver GDF15 and FGF21 mRNAs in obese mice, increasing levels of the two proteins in the blood. After 12 weeks, treated rodents ate 40% less food and exhibited 30% reduced body weight. Energy expenditures in the adipose tissues increased by about 15%. Liver fat decreased 30%.

Mice treated with iD1 showed improved [insulin sensitivity](#) and lower blood glucose levels.

"In the treatment of metabolic disease, targeting mRNA is a fairly novel concept," said coauthor Nicolas Musi, MD, professor of medicine at UT Health San Antonio and director of the Sam and Ann Barshop Institute. "It is a new platform for thinking about how to treat this group of diseases."

In Texas and the U.S., obesity, type 2 diabetes, [fatty liver disease](#) and related metabolic disorders are at epidemic proportions.

According to the U.S. Centers for Disease Control and Prevention (CDC), more than 37 million Americans have diabetes. Type 2 diabetes represents at least 90% of the cases. In Texas, approximately 2.7 million people have diagnosed diabetes, and an additional 600,000 people in Texas have diabetes but don't know it. Another 7 million people in Texas have prediabetes.

Obesity prevalence in the U.S. is more than 40% and is climbing, according to the CDC. Obesity-related diseases include heart attack, stroke, type 2 diabetes and some cancers.

"These are very serious problems, and any intervention, including drugs, that can treat them are necessary," Dr. Musi said. "Dr. Morita and Dr. Katsumura have made a groundbreaking discovery by delineating this mechanism and the proof of concept that a drug that targets this pathway improves all these parameters including glucose levels, glucose tolerance and insulin resistance caused by a high-fat diet and fatty liver."

Their next step, Dr. Katsumura reiterated, is to refine this mechanism and identify new drugs that may be more specific and more potent.

"I want to congratulate Dr. Morita and Dr. Katsumura for this fantastic work," Dr. Musi said. "It is comprehensive, thorough and paradigm-changing."

More information: Masahiro Morita, Deadenylase-dependent mRNA decay of GDF15 and FGF21 orchestrates food intake and energy expenditure, *Cell Metabolism* (2022). DOI: [10.1016/j.cmet.2022.03.005](https://doi.org/10.1016/j.cmet.2022.03.005). [www.cell.com/cell-metabolism/f ... 1550-4131\(22\)00093-6](https://www.cell.com/cell-metabolism/fulltext/S1550-4131(22)00093-6)

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