Reversing key precursors to diabetes

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Yale researchers have found a way to disrupt the biological underpinnings of disorders that predispose a person to type 2 diabetes (T2D), raising the possibility of developing therapies to reverse these conditions. The study appears in the journal *Cell Metabolism.*

The Yale team examined whether targeting dinitrophenol (DNP)—a chemical that inhibits efficient energy production by cellular

mitochondria—to the liver could safely decrease high levels of triglycerides, non-alcoholic fatty liver disease (NAFLD), and insulin resistance, without dangerous toxicities. Researchers found that a DNP derivative reversed all these T2D precursor conditions in rats fed a high-fat diet. This drug also reversed hyperglycemia in two rodent models of T2D.

NAFLD affects one in three Americans, and is a major predisposing condition for the constellation of disorders—known as metabolic syndrome—that increase the risk of T2D and cardiovascular disease. NAFLD is also a key predisposing factor for severe liver inflammation that results in non-alcoholic steatohepatitis (NASH), cirrhosis, and liver cancer.

DNP was commonly used as a diet aid in the 1930s but was taken off the market by the FDA because it could cause fatally toxic hyperthermia. The Yale team, however, found a way to significantly reduce this dangerous toxicity by targeting DNP to the liver, where it led to reductions in liver triglycerides and improvements in both liver and muscle insulin sensitivity in animal models of NAFLD and T2D—without inducing hyperthermia.

"In this study we found that targeting DNP to the liver by a simple chemical modification could decrease liver fat content and reverse insulin resistance and diabetes in rodent models of NAFLD and T2D with a very large increase in the safety window compared to DNP," said senior author Dr. Gerald Shulman, the George R. Cowgill Professor of Physiological Chemistry, Medicine and Cellular & Molecular Physiology at Yale School of Medicine and an investigator of the Howard Hughes Medical Institute (HHMI).

The Yale team hopes the finding could lead to development of new therapies for hyperlipidemia, NAFLD/NASH, and type 2 diabetes, as

well as the cardiovascular disease that often follows these disorders.

"I am excited by these results since they demonstrate the potential feasibility of increasing hepatic mitochondrial uncoupling to safely treat the related epidemics of NAFLD, metabolic syndrome, and type 2 diabetes," Shulman explained. "These agents would represent a first in class set of therapeutics that would treat the root cause of type 2 diabetes."

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