Researchers reverse type 2 diabetes and fatty liver disease in rats

26 February 2015

Yale researchers developed a controlled-release oral therapy that reversed type 2 diabetes and fatty liver disease in rats, according to a study published on Feb. 26 by *Science*.

Existing therapies for type 2 diabetes, and the closely associated conditions of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), have had limited success at treating the root causes of these diseases. Building on earlier research, the Yale team—led by Gerald I. Shulman, M.D., the George R. Cowgill Professor of Physiological Chemistry, and professor of medicine and cellular & molecular physiology at Yale School of Medicine—decided to investigate whether an agent that had originally been used for weight loss more than 70 years ago could be reformulated to safely treat NAFLD/NASH and type 2 diabetes in rodent models of these diseases.

Based on their earlier studies, the researchers determined that toxicity associated with the agent—mitochondrial protonophore 2,4-dinitrophenol (DNP)—was related to its peak plasma concentrations. They discovered that DNP's efficacy in reducing liver fat and liver inflammation could be achieved with plasma concentrations that were more than a 100-fold less than the toxic levels.

"Besides reversing fatty liver disease in a rodent model of NALFD, a low-dose intragastric infusion of DNP that was 100-fold lower than toxic levels also significantly reduced blood glucose, triglyceride, and insulin concentrations in a rodent model of NAFLD and type 2 diabetes", said Shulman, who is also an investigator with the Howard Hughes Medical Institute.

In the next phase of the study, Shulman and his team developed a new oral, controlled-release form of DNP, known as CRMP, which maintained the drug at concentrations that were more than a 100-fold lower than the toxic threshold. Administered once daily, CRMP delivered similar positive results, reversing fatty liver, insulin resistance, and hyperglycemia in rat models of NAFLD and type 2 diabetes, as well as liver inflammation and liver fibrosis in a rodent model of NASH, with no adverse effects.

"Given these promising results in animal models of NAFLD/NASH and type 2 diabetes we are pursuing additional preclinical safety studies to take this mitochondrial protonophore approach to the clinic" said Shulman.

More information:
www.sciencemag.org/lookup/doi/ … 1126/science.aaa0672

Provided by Yale University