

DIABETES

Very-low-calorie diet reverses T2DM in rats

Studies in animal models have previously demonstrated that a very-low-calorie diet (VLCD) is just as effective at reducing plasma glucose concentrations as bariatric surgery. These findings suggest that the forced caloric restriction that occurs with bariatric surgery is the reason for the effect of bariatric surgery on the symptoms of type 2 diabetes mellitus (T2DM), but the molecular mechanisms have remained unclear. Now, Gerald Shulman, Rachel Perry and colleagues show that a VLCD reverses T2DM via a combination of three beneficial effects on hepatic glucose metabolism.

“We reasoned that if we could identify the molecular mechanisms that explain the effect of caloric restriction to rapidly reverse T2DM, this could help identify potential therapeutic targets,” explains Perry, lead author on the study. The authors studied a rat model in which T2DM is

induced by a combination of high-fat diet and low-dose streptozotocin, which ablates some, but not all, of the pancreatic β -cells. Perry and colleagues applied a method they developed called positional isotope NMR tracer analysis (PINTA) to examine, for the first time, the rates of all key metabolic pathways that contribute to endogenous glucose production in this rat model of T2DM. Following these initial experiments, the authors assessed the effect of caloric restriction on these pathways, which allowed them to generate the most complete picture of hepatic metabolism in a rat model of T2DM to date.

The authors found that a VLCD reduces the rate of net hepatic glycogenolysis; lowers acetyl-CoA-dependent activation of pyruvate carboxylase, which reduces the conversion of lactate and amino acids into glucose through gluconeogenesis; and reduces

ectopic lipid accumulation in the liver, which suppresses diacylglycerol (DAG)-protein kinase C ϵ (PKC ϵ)-mediated hepatic insulin resistance.

“Although these mechanisms have previously been identified, and all have been shown to contribute to insulin resistance and hyperglycemia in T2DM, this study is the first to demonstrate reductions in each of these three pathways as contributors to the glucose-lowering effect of caloric restriction,” concludes Perry. “Our data suggest that therapies targeting any, or better yet all, of these pathways could potentially be beneficial to patients with T2DM.”

Alan Morris

“...Perry and colleagues show that a VLCD reverses T2DM via a combination of three beneficial effects on hepatic glucose metabolism.”



ORIGINAL ARTICLE Perry, R. J. et al. Mechanisms by which a very-low-calorie diet reverses hyperglycemia in a rat model of type 2 diabetes. *Cell Metab.* <http://dx.doi.org/10.1016/j.cmet.2017.10.004> (2017)

FURTHER READING Petersen, M. C. et al. Regulation of hepatic glucose metabolism in health and disease. *Nat. Rev. Endocrinol.* **13**, 572–587 (2017)