Hepatic acyl-CoA:diacylglycerol acyltransferase (DGAT) overexpression, diacylglycerol, and insulin sensitivity

Lipid accumulation in organs is strongly associated with insulin resistance. However, the causal relationship is uncertain. For hepatic steatosis, this relationship has given rise to many studies and theories. One hypothesis, suggested as unifying (1), posits that accumulation of diacylglycerol induces hepatic insulin resistance by interfering with insulin signaling. We previously tested the relationship between hepatic steatosis and insulin resistance by generating transgenic mice that overexpress triacylglycerol (TG) synthesis enzymes [acyl-CoA:diacylglycerol acyltransferases (DGATs)] in the liver (2).

Analysis of two lines that overexpressed DGAT2 (low- and high-expressors) refuted the DG hypothesis: hepatic DG accumulation (and other lipids such as TG, fatty acyl CoAs, and ceramides) did not lead to insulin resistance. We extensively analyzed the low-expressor line. Multiple cohorts of mice studied in several laboratories showed normal values for blood glucose and insulin, glucose- and insulin-tolerance tests, hyperinsulinemic-euglycemic clamps, and multiple assays of insulin signaling.

In PNAS (3), Jornayvaz et al. reclamped the same DGAT2 low-expressor line and reported that steatosis was associated with hepatic insulin resistance. What could account for the different results? One possibility might be differences in lipid levels. We found fivefold more TG and approximately 1.5-fold more DG in DGAT2 low-expressors (2.1-fold increase) than controls. Jornayvaz et al. (3) found a modest two- to threefold increase in TG and an approximately 12-fold increase in DG. From the biochemistry of DGATs, it is difficult to explain why DGAT2 overexpression would yield a disproportionate accumulation of its substrate relative to its product (i.e., TG). Interestingly, and potentially as a consequence of these differences in hepatic lipids, Jornayvaz et al. (3) found abnormalities with hyperinsulinemic-euglycemic clamps (performed with 3 mU/kg/min insulin). We found normal insulin sensitivity with this assay (2 mU/kg/min insulin). However, clamp studies are fraught with difficulties evaluating glucose homeostasis in the mouse. The Vanderbilt experience and recommendations for evaluating glucose homeostasis in the mouse. Am J Physiol Endocrinol Metab 297: E849–E855.


1 To whom correspondence should be addressed: E-mail: bfarese@gladstone.ucsf.edu.

Author contributions: M.M., M.C.L., M.J.W., B.K.H., C.N., R.V.F., Sr., A.L.H., and R.V.F., Jr., wrote the paper. The authors declare no conflict of interest.