METABOLISM

Hepatic insulin resistance—missing link identified

Increased levels of hepatic acetyl CoA resulting from macrophage-induced lipolysis of white adipose tissue (WAT) are responsible for the failure of insulin to suppress gluconeogenesis in type 2 diabetes mellitus (T2DM), according to new research. The findings challenge the existing view that inflammation-mediated hepatic insulin resistance results from adipokine-mediated inhibition of hepatic insulin signalling and enhanced activation of the gluconeogenic pathway.

“We were interested in understanding the molecular mechanism by which insulin suppresses hepatic glucose production and how this process goes awry in patients with T2DM,” explains lead investigator Gerald Shulman. Using a novel metabolomics approach that enabled rates of whole-body lipolysis, glucose turnover and intrahepatic fluxes (including hepatic acetyl CoA levels) to be simultaneously measured in rapidly frozen-clamped livers of mice,

insulin suppression of hepatic acetyl CoA levels—and consequent inhibition of pyruvate carboxylase activity—was shown to be the major mechanism by which insulin suppresses hepatic glucose production *in vivo*. Furthermore, defects in the regulation of this mechanism that result in increased levels of hepatic acetyl CoA led to fasting and postprandial hyperglycaemia.

“These results have important clinical implications for the pathogenesis of T2DM and identify macrophage-induced WAT lipolysis and hepatic acetyl CoA as novel potential therapeutic targets for T2DM,” concludes Shulman.

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Original article Perry, R. J. *et al.* Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. *Cell* doi:10.1016/j.cell.2015.01.012