Using Magnetic Resonance to Probe Lipid Synthesis in Response to Ketogenic Diet

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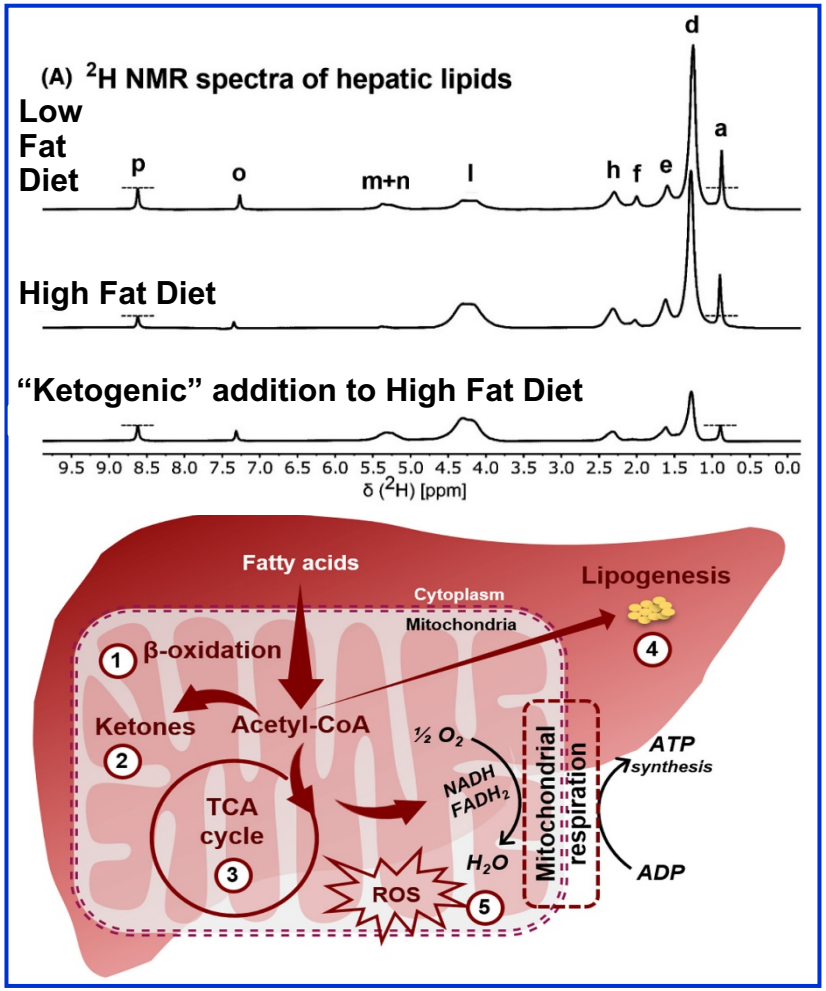
Funding: G.S. Boebinger (NSF DMR-1644779); N. Sunny and M.E. Merritt (NIH R01DK112865)

Non-alcoholic Fatty Liver Disease (NAFLD) is a metabolic dysregulation of fatty acid synthesis and oxidation that leads to lipid accumulation in the liver. NAFLD is a burgeoning world health issue, with a current estimate of 25% incidence in the USA. Initial stage NAFLD is innocuous, but in a sub-population of ~10%, it can progress to non-alcoholic steatohepatitis, which can lead to liver failure and the need for transplant, perhaps becoming the main cause for liver transplantation in the next 5 years.

Prior work focused primarily on the metabolic effects of increasing levels of circulating fatty acids on the accumulation of hepatic lipid stores. Here, we further examine the effect of a ketogenic diet on *de novo* lipogenesis (DNL) in the liver tissue of mice fed one of three diets: low fat (LF), high fat (HF), or HF plus increased branched-chain amino acids (HF-Kt) diet, as shown in the deuterium magnetic resonance (DMR) spectra at the top of the figure.

The chemical selectivity DMR allows detection of site specific ^2H enrichment in liver fats after exposure to 1% D_2O added to the drinking water for 4 days. DNL is accurately determined by the enrichment achieved at the methyl position of the fatty acids (labeled a). This methyl peak can only be labeled if the entire fatty acid was synthesized from the most basic starting element, acetyl-CoA. This data shows addition of a ketogenic diet in the context of high fats significantly slows the DNL process.

Using MR estimates of DNL, as well as mass spectrometry based estimates of TCA cycle turnover (bottom panel), we can directly assay the changes in central hepatic metabolism. While the HF-Kt diet slows DNL, it also has complicated multi-factorial effects on hepatic energy homeostasis including an increase of reactive oxygen species (ROS) production. Future work will develop DMR for *in vivo* use.



Instrumentation: AMRIS Facility, Gainesville, FL; *14.1 T Bruker Bio-Spin equipped with 1.7mm TCI CryoProbe and Avance Neo Console*

Citation: Muyyarikkandy, M.S.; McLeod, M.; Maguire, M.; Mahar, R.; Kattapuram, N.; Zhang, C.E.; Surugihalli, C.; Muralidaran, V.; Vavilikolanu, K.; Mathews, C.E.; Merritt, M.E.; Sunny, N.E., *Branched chain amino acids and carbohydrate restriction exacerbate ketogenesis and hepatic mitochondrial oxidative dysfunction during NAFLD,* FASEB Journal, *The FASEB Journal*. 2020;00:1–18, doi.org/10.1096/fj.202001495R