Sex-Dependent Effects of Eicosapentaenoic Acid and UCP1 Deficiency on Hepatic Steatosis in Diet-Induced Obese Mice

Kembra Albracht-Schulte,1 Salvador Galindo,1 Sarah Anjum,1 Mandana Pahlavani,2 Latha Ramalingam,1 Nishan Kalupahana,3 William Festuccia,4 Shane Scoggin,1 Chanaka Kahathuduwa,5 and Naima Moustaid-Moussa 1

1Texas Tech University; 2UT Southwestern Medical Center; 3University of Peradeniya; 4University of Sao Paulo; and 5Texas Tech University Health Sciences Center

Objectives: Nonalcoholic fatty liver disease (NAFLD), characterized by hepatic triglyceride (TG) accumulation, is associated with expansion of white adipose tissue (WAT). By contrast, brown adipose tissue (BAT) may prevent obesity and NAFLD through activity of mitochondrial uncoupling protein 1 (UCP1), which is involved in energy dissipation. Previous studies in our lab have shown that eicosapentaenoic acid (EPA) ameliorates obesity and hepatic steatosis in high-fat (HF) fed male, B6 mice at thermoneutral conditions, independent of UCP1. However, it is unknown whether similar effects of EPA and UCP1 deficiency will be observed at ambient temperature, and whether they differ by sex. Thus, the goal of this project was to investigate sex-dependent mechanisms of EPA in the livers of diet-induced obese, wild type (WT) and UCP1 knockout (KO) mice housed at ambient temperature.

Methods: WT and UCP1 KO B6 male and female mice were fed a HF diet (45% kcal fat; WT-HF, KO-HF) or HF diet supplemented with 36g/kg EPA (WT-EPA, KO-EPA) for 14 weeks. Body weight (BW), liver histology, and specific metabolic gene expression profiles were assessed.

Results: Although BW significantly varied by sex, diet, and genotype, UCP1 inactivation did not significantly increase BW compared to WT in either sex. Hepatic TG accumulation varied significantly by genotype with no significant differences seen with EPA supplementation in either sex. However, markers of lipogenesis were sex-dependently impacted by genotype and diet: there were no significant differences in markers of lipogenesis (Fasn and Acaca) with UCP1 KO or EPA supplementation in males; while these markers were reduced in female KO mice compared to female WT with no response to EPA. By contrast, lipogenic markers were reduced with EPA in female WT mice.

Conclusions: Our findings reveal an association between NAFLD and UCP1 deficiency, indicating the importance of this mitochondrial protein in limiting hepatic lipid accumulation, particularly in females. These findings also suggest a genotypic difference in response to dietary EPA supplementation on the livers of male and female mice, with beneficial effects reported in the female WT group.

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