



IUGR AND DEVELOPMENT ALTER HEPATIC PEMT LEVELS IN THE RAT

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Intrauterine growth restriction (IUGR) is a phenomenon in which the fetus fails to achieve its genetic growth potential *in-utero*. IUGR dysregulates circulating docosahexaenoic acid (DHA), an ω -3 fatty acid essential for organogenesis and favorable neonatal outcomes. This leads to metabolic issues, such as lipid accumulation in the liver. Our group showed, in a rat model, that IUGR induces sex-divergent outcomes, with increased liver lipid accumulation in juvenile males and successful clearing of excess liver lipid in juvenile females. We also showed that DHA supplementation reduces hepatic lipids in male juvenile IUGR rats. The export of lipids from the liver in the form of very low-density lipoproteins (VLDL) is influenced by the phosphatidylethanolamine methyltransferase (PEMT) phospholipid methylation pathway. Higher hepatic lipid concentration is associated with lower PEMT activity. The temporal changes in PEMT expression throughout development and the effects of IUGR and DHA supplementation on PEMT are unknown. We hypothesize that PEMT expression changes during development and that IUGR reduces PEMT expression in male rats. We also hypothesize that DHA supplementation normalizes hepatic PEMT levels. To test our hypothesis, we measured liver PEMT mRNA throughout development (birth to postnatal day 21) in control rats. We also measured mRNA and protein levels of PEMT in control and IUGR rats at day 21. Rats were randomly assigned as control or IUGR. IUGR was induced by bilateral uterine artery ligation. mRNA levels were measured using real-time RT PCR, relative to HPRT and GAPDH. Protein levels were measured using western blot. Our results show that liver PEMT mRNA levels peak at postnatal day 21, with a secondary peak at day 7, for both sexes. Contrary to our hypothesis, IUGR does not result in a decrease in liver PEMT mRNA or protein. Instead, IUGR increases PEMT protein in the liver of both female and male rats. DHA supplementation normalizes female hepatic PEMT protein levels, but not male hepatic PEMT protein levels. We conclude that IUGR induces altered hepatic PEMT expression in female and male rats, which is normalized with DHA only in females. We speculate that hepatic lipid clearance in male IUGR rats is independent of PEMT levels and may be related to PEMT activity and other elements of the PEMT pathway, such as choline availability. Ongoing studies are evaluating the effect of IUGR on PEMT, choline, and hepatic lipid accumulation from day 0 to day 21.