Per- and Polyfluoroalkyl Substances in Enterohepatic Bile Acid Homeostasis

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Per- and polyfluoroalkyl substances (PFAS), or "forever chemicals," are environmental pollutants with high resistance to degradation. An estimated 98% of the U.S. population has detectable levels of PFAS in their bodies (Coulson, 2024). Nuclear receptors, such as Farnesoid X Receptor (FXR), Peroxisome Proliferator-Activated Receptor α (PPARα), Constitutively Active Receptor (CAR), and Pregnane X Receptor (PXR), are ligand-activated transcription factors that play a crucial role in regulating lipid and bile acid synthesis, transport, and detoxification. The purpose of this study was to investigate the effects of PFAS on the activation of CAR, PPARα, FXR-FGF15/19 axis, and PXR in mice and their regulation of gene expression in lipid and bile acid homeostasis. Eight-week-old CD-1 female mice received 0, 0.4, 1.2, and 4 μg/mL of Perfluorononanoic acid (PFNA) via drinking water for 8 weeks. Gene expression at mRNA levels was quantified using RT-qPCR. Ileal Fgf15 shows dose response inhibition; however, both classic and alternative bile acid synthesis pathways show no significant change. Cyp2b10 and Cyp3a11 were dose-dependently induced, indicating activation of CAR and PXR-mediated detox pathways. Cyp4a10, a PPARα target gene involved in fatty acid oxidation, showed up to 16-fold induction. Cd36 and Fabp1, PPARα target genes associated with lipid transport and metabolism, showed upward regulation, indicating PFAS-induced PPARα activation and increased intracellular lipid load. These changes imply PFAS exposure disrupts bile acid detoxification and hepatic lipid metabolism. This study provides insight into how forever chemicals disrupt lipid and bile acid homeostasis and can contribute to the pathogenesis of liver diseases. Supported by NJ ACTS NIH R25TR004777 CREST Program.