MASTER'S THESIS

Effects of In Utero Exposure to PFOS on Placental Functions In Mice

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ABSTRACT

Since the mid-20th century, environmental pollution has been raising public awareness. There are many different types of pollutants found in the environment (air, soil, and water) and in living organisms (wildlife and humans). Endocrine-disrupting chemicals (EDCs) are pollutants that affect the endocrine system of organisms. EDCs include chemicals such as phthalates, bisphenol A (BPA), dichlorodiphenyltrichloroethane (DDT), and perfluorinated compounds (PFCs). When accumulated in the body, EDCs can cause many harmful health outcomes including developmental and reproductive toxicity. There is a need to investigate the clinical significance of EDC-induced disorders and the mechanisms that underlie them. This study focused on perfluorooctane sulfonic acid (PFOS), one of the most widely used EDCs. PFOS is commonly used to protect paper, leather, and other waterproof products due to its unique aqueous surface tension and thermal resistance properties. PFOS has been shown to make fetal growth restrictions by interfering with placental function. However, the underlying mechanisms are unknown. In chapter 2, pregnant CD-1 mice were fed PFOS at 1 mg/kg/day and 3 mg/kg/day from GD4.5 to GD17.5. MeAIB and MeG analogs were injected into mothers at GD17.5. Mouse liver, placenta, and fetal liver were collected two hours after injection. The liver and body weights were recorded. Using LC/MSMS, the concentrations of PFOS, amino acids, and glucose analogs in the tissues were measured. The placental histology was analyzed with hematoxylin and eosin (H&E) staining and immunohistochemistry (IHC) staining. Real-time PCR and western blots were used to measure the expression levels of transporter proteins in the placenta. The rest of the mice left for baby delivery for further study. The data revealed that high doses of PFOS in utero caused a significant decrease in placental transport efficiency of glucose and amino acid analogs. There was

a significant reduction in SNAT4 mRNA expression. As a result, PFOS disrupted the transport of nutrients from the mother to the fetus, resulting in fetal growth restriction.

Through placental transfer, PFOS accumulated in offspring and likely altered their hepatic metabolism. The underlying mechanism of prenatal hepatotoxicity caused by PFOS at different developmental stages has not yet been elucidated. A study was conducted in chapter 3 examining the effects of prenatal exposure to PFOS on hepatic lipid and energy metabolism in male offspring at GD17.5, PND21, and PND80. Offspring (PND 21-80) were exposed to 4 different diets. They were given a standard diet and water, a high-fat diet and standard water (HFD), a standard diet and high sucrose water (HSW), or a high-fat diet and high sucrose water (HFHS). At PND80, blood glucose levels were tested after one night of fasting. All mice were then dissected. After livers were collected from mice with GD17.5, PND21, and PND80, the liver and body weights were recorded. The mRNA expression levels of genes associated with lipid and energy metabolism were measured by real-time PCR. The results of this study indicate that prenatal PFOS exposure induces steatosis in male mice in a time- and dose-dependent manner. In two experimental groups, prenatal exposure to PFOS altered the lipid and energy metabolism of the liver during the fetal phase, leading to increased liver weight, but decreased body weight. The severity of the effects gradually decreased during the postnatal period. In PND21, the prenatal PFOS exposure effects still existed in the high-dose group. The interference effects on lipid and energy metabolism were intensified under the high-fat diet challenge, as evidenced by the cytoplasmic vesicles accumulating in the livers. As a whole, this study stressed the dangers of prenatal PFOS exposure via maternal transfer, and how high fat intake can intensify the effects of PFOS. Future studies will examine the epigenetic effects of PFOS on liver DNA, the mixed effects of EDCs on fetal growth, and sex-specific effects of prenatal PFOS exposure on liver function in offspring.