

Mechanisms of Perfluorooctanoic acid stimulation of pubertal mammary gland in C57Bl/6 mice

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Perfluorooctanoic acid (PFOA) is a synthetic, widely used perfluorinated carboxylic acid and persistent environmental pollutant. PFOA is an agonist of peroxisome proliferator activated receptor α (PPAR α) and PFOA exposure causes hepatocellular hypertrophy, tumorigenesis and developmental toxicity in rodents, depending on the presence of PPAR α . Our recent study revealed a stimulatory effect of peripubertal PFOA exposure (5 mg/kg) on mammary gland development in C57Bl/6 mice. The present study was designed to examine the underlying mechanism(s). The presence of ovaries was required for PFOA exposure (5 mg/kg) to stimulate mammary gland development and PFOA exposure significantly increased serum progesterone levels in ovary intact C57Bl/6 mice. No significant effect of PFOA on serum estradiol level or sex hormone binding proteins was detected. However, PFOA treatment resulted in increased mammary gland levels of estrogen receptor α (ER α), amphiregulin (Areg), a downstream target of ER action, and IGF-I, the latter both potent mammary gland growth factors. PFOA exposure significantly decreased the levels of liver metabolic enzymes related to steroid hormone metabolism/excretion, and significantly increased the levels of enzymes involved in steroid hormone synthesis in ovary. Importantly, PFOA mammary gland stimulation was also obtained in PPAR α knockout C57Bl/6 pubertal mice. These results indicate that PFOA likely stimulates mammary gland development by modifying the systemic hormonal milieu through its effects on the ovary and liver and is independent of the expression of PPAR α .

This work was supported by the Breast Cancer and the Environment Research Centers Grant U01 ES/CA 012800 from the National Institute of Environment Health Science (NIEHS) and the National Cancer Institute (NCI), National Institutes of Health (NIH), Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIEHS or NCI, NIH.

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