Organophosphate Flame Retardant Alterations to Energy Homeostasis in PPARg and ERa KO Mouse Models of Diet-Induced Obesity

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Endocrine disrupting chemicals (EDC) are becoming increasingly prevalent in the environment and many are shown to accumulate within human tissues and interact with endogenous hormone receptors. One such EDC is organophosphate flame-retardants (OPFR). OPFR interact with multiple hormone receptors involved in homeostasis, including estrogen receptors (ER) and peroxisome proliferator-activated receptor (PPAR) γ. We have previously observed that exposure to a mixture of OPFR in adult wild-type (WT) mice induces varying sex-dependent alterations of energy homeostasis, orexigenic and anorexigenic peptide hormones, feeding behavior, and activity. This dysregulation of energy homeostasis can cause an increase in susceptibility to metabolic disorders. In the current study, we repeated the previous adult exposure experiments, this time with knockout mouse strains for ERα (ERKO), and brain-specific knockout of PPARγ (PPARKO). We continued our use of a common mixture of OPFR {tris(1,3-dichloro-2-propyl)phosphate, triphenyl phosphate, and tricresyl phosphate, 1 mg/kg/day each} for 4 weeks continuing the comparison between low-fat diet (LFD, 10% kcal fat) and a high fat (HFD, 45% kcal fat) to generate a diet-induced obesity model. We recorded body weight, crude food intake, body composition, meal patterns, glucose and insulin tolerance, and plasma peptide hormone levels. As in the WT experiments, body-weight gain was increased by HFD for both strains, however, the increased weight-gain for males on a HFD induced by OPFR exposure in WT was absent in both strains, suggesting the lack of these nuclear receptors eliminates OPFR influence on body-weight gain. No weight gain OPFR effects were seen in females. Furthermore, while OPFR altered fat/lean mass in WT male mice, male mice of either KO saw no effects, whereas female ERKO mice exhibited the pattern of male WT OPFR effects. Interestingly, while OPFR decreased feeding efficiency in WT females, in ERKO there was no difference in females, and instead this pattern was now observed in males. Additionally, the OPFR food intake reduction seen in WT was absent in both ERKO and PPARKO. Notably, peptide hormones insulin, leptin, and ghrelin were drastically altered, predominantly in female mice of both KO strains, suggesting both a PPARγ and ERα role in OPFR effects. Lastly, insulin tolerance abolished diet effects in the OPFR exposed ERKO males, while we observed a rescue of HFD effect by OPFR exposure in PPARKO. We are currently processing hypothalamic samples for protein and gene expression. In summary, our data indicates that the influence of adult OPFR exposure on diet-induced obesity is mediated, in part, by ERα and PPARγ.