

Effects of antiandrogen flutamide on steroidogenesis and gene expression in female fathead minnow ovary

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Mechanisms underlying reproductive impacts of antiandrogens in fish are not well-characterized and effective biomarkers of antiandrogen exposure are lacking. This work sought to identify genes and pathways affected by antiandrogen exposure in the fathead minnow (*Pimephales promelas*), and compare these to previous results for zebrafish (*Danio rerio*). A time-course study with exposure to flutamide, an antiandrogenic pharmaceutical, was conducted with female fathead minnows. Sexually mature fish were exposed to flutamide (50 or 500 µg/L) for up to 8 d followed by a recovery period in control water. Fish were sampled after 1, 2, 4, and 8 d of both exposure and recovery. Plasma and ex vivo steroid concentrations were determined, and changes in gene expression in ovary tissue were evaluated within and across time-points using quantitative real-time polymerase chain reaction and a custom 15K fathead minnow microarray. Ex vivo estradiol and testosterone, and plasma estradiol levels were significantly reduced in fish exposed to 500 µg/L flutamide for 2 d. When microarray gene expression data were pooled across 2 and 4 d time points and across flutamide concentration level, 455 significantly altered (≥ 1.3 fold change relative to controls, $P < 0.05$) genes were detected. Of these, only four genes were in common with those reported to be altered in female zebrafish. However, based on Ingenuity Pathway Analysis of the 455 differentially-expressed genes, there were some similarities in enriched canonical pathways between flutamide-exposed female fathead minnows and zebrafish. Identification of genes and pathways impacted across fish species may support biomarker development for reproductive effects associated with antiandrogens.