AWRA 2007 SUMMER SPECIALTY CONFERENCE
Vail, Colorado
June 25-27, 2007

THE USE OF ZEBRAFISH TO ASSESS THE EFFECTS OF PHARMACEUTICALS IN THE AQUATIC ENVIRONMENT: LINKING WHOLE ANIMAL PHYSIOLOGY TO THE EXPRESSION OF SELECT GENES CONTROLLING STEROIDOGENESIS AND OVULATION

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ABSTRACT: Human use pharmaceuticals enter the aquatic environment through the discharge of effluents from wastewater treatment plants where they may impact aquatic organisms and also be a source of contamination of drinking water. There is little information on the potential biological effects in fish and wildlife exposed to pharmaceuticals. In this study, we utilized sexually-mature females or breeding groups of zebrafish to evaluate the effects of selected pharmaceuticals and endogenous steroid hormones on various measures of reproduction. The pharmaceuticals tested included non-steroidal anti-inflammatory drugs (NSAID), the oral contraceptive drug ethynyl estradiol, and the serotonin reuptake inhibitor fluoxetine, which is the active ingredient in ProzacTM . The endogenous hormones tested included 17β-estradiol and 17α, 20β dihydroxy progesterone (17α, 20βP). These studies evaluated the effects of these drugs on egg production as a measure of reproductive fitness. Other endpoints evaluated included ovarian steroid and prostaglandin levels and the mRNA levels of selected genes within the steroid hormone and the arachidonic acid (AA) metabolic pathway were quantified by real-time PCR. NSAIDs, ethynyl estradiol and fluoxetine when tested individually caused a significant reduction in egg production but the underlying mechanisms mediating this effect differed. As expected, the mechanisms by which NSAIDs reduce egg production involves reduced levels of PG and this reduction may involve both enzymatic and mRNA inhibition. The NSAIDs indomethacin and diclofenac tended to reduce the mRNA expression of PGE2 synthase and cytosolic phospholipase A2 (cPLA2). The reduced egg production caused by the drugs fluoxetine and ethynyl estradiol does not seem to involve the AA pathway; rather these drugs significantly reduced the expression of selected genes within the steroid biosynthetic pathway. Other studies showed the importance of steroid hormones in the regulation of AA metabolism. Female zebrafish exposed to estradiol had significantly reduced mRNA levels of cPLA2, COX1, and PGE2 synthase, while 17α, 20βP only reduced COX1 and PGE2 synthase levels. Collectively, these studies have demonstrated the utility of zebrafish as a lab model for dissecting the reproductive toxicity of pharmaceuticals in the aquatic environment.

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