ADAPTATION, COMPENSATION, AND RECOVERY: UNRAVELING THE MECHANISMS THROUGH GENOMICS

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A variety of chemicals in the environment have the potential to inhibit aromatase, an enzyme critical to estrogen synthesis. We examined the responses of female fathead minnows (*Pimephales promelas*) to a model aromatase inhibitor, fadrozole, using transcriptional network inference. Fish were exposed for 8 days to 0, 3, or 30μg/L fadrozol and then held in clean water for 8 extra days. We analyzed *ex vivo* steroid production, plasma steroid levels, and plasma vitellogenin concentrations in the ovary, as well as gene expression using 15,000 probe microarrays. As expected, plasma concentrations of estradiol (E2) and vitellogenin were significantly reduced within 24h of exposure to fadrozole. Plasma E2 concentrations recovered rapidly once fadrozole delivery stopped. We then used gene expression analysis to try to understand the dose and time-dependent changes in the different exposure phases (adaptation and compensation), and the recovery phase. Of all the differentially expressed genes (fold change>2, $p<0.01$), 194 were exclusively in the exposure phase and 128 were exclusive in the recovery phase, with 23 genes including aromatase, common between the two phases. A dynamic model for steroid production previously developed was able to predict steroid hormone levels during the exposure phase, but failed to predict the hormone overproduction found at the beginning of the recovery phase. We then used a mutual information approach to develop static networks to try to understand the mechanisms involved in the processes of adaptation, compensation, and recovery, and the missing links in the hormone overproduction. The results will be compared to a similar exposure using prochloraz to see if the mechanisms used for the different exposure and recovery phases are conserved using different compounds.