Aromatase inhibition in a transcriptional network context

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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 minnow ovaries (FHM, *Pimephales promelas*) to a model aromatase inhibitor, fadrozole, using a transcriptional network inference approach. Fish were exposed for 8 days to 0, or 30mg/L fadrozole and samples and then left in clean water for 8 more days. Samples were analyzed for significant changes in the gene expression with a 15,000 probe FHM microarray. The top 1674 significantly changed genes based upon 1.5-fold change and $P < 0.05$ across all the time points, including some additional genes relevant to the Hypothalamus-Pituitary-Gonadal (HPG) axis as well as sex steroid levels, were chosen for network modeling. In order to gain biological understanding of the significantly expressed genes, we also analyzed the functional annotations. Some of the gene overrepresented ontology annotations were lipid, fatty acid and steroid metabolism, signal transduction, oxidoreductase, kinases, localization, cell signalling, and calcium ion transport. StAR-related lipid transfer was the most highly connected gene in the network model. Key HPG genes such as chorionic gonadotropin beta, low density lipoprotein, steroidogenic acute regulatory protein, cytochrome P450 family members, and estrogen receptor were found significantly expressed with the fadrozole exposure and were present in the steroidogenic network obtained from the source network.

Our results showed that the inferred network was extremely successful in detecting HPG axes interactions. Some of these interactions that were previously known included gonadotropin-releasing hormone receptor and its interaction with G-proteins, adenylate cyclase, and gonadotropin. The interaction network also suggested the role of calcium in association with cAMP in the stimulation of steroidogenesis in the gonads. *This abstract does not necessarily reflect USEPA policy.*