Predicting Biochemical Responses to Endocrine Active Compounds: Mathematical Model of Steroidogenesis in Small Fish Ovaries

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Sex steroids, which have an important role in a wide range of physiological processes, are synthesized primarily in the gonads and adrenal glands through a series of enzyme-mediated reactions. The activity of steroidogenic enzymes can be altered by a variety of endocrine active compounds (EAC), some of which are therapeutics and others that are environmental contaminants. A mathematical model of the intraovarian metabolic network was developed to predict the synthesis and secretion of testosterone (T) and estradiol (E2), and the kinetics for steroidogenic enzyme inhibition by EAC. Model predictions were compared to data from an *in vitro* steroidogenesis assay with ovary preparations from a small fish model, the fathead minnow. Model parameters were estimated using an iterative optimization algorithm. Model-predicted concentrations of T and E2 closely corresponded to the experimental time-course data from control experiments. In experiments with the EAC, fadrozole (FAD), model-predicted behavior was consistent with E2 data, but not fully supported by T data. To address this discrepancy between the data and model predictions, we revised our model by including the additional high dose inhibitory effects of FAD on the steroidogenic pathway as described in the literature. A relative sensitivity analysis of the model parameters identified specific transport and metabolic processes that most influence the steady-state concentrations of T and E2 that included secretion of T from the ovary and conversion of T to E2. Our study demonstrates the feasibility of using the model to predict steady-state T and E2 concentrations, *in vitro*. This capability could be useful for environmental health assessments and pharmaceutical development with EAC. *This work was reviewed by the U.S. EPA and approved for publication but does not necessarily reflect Agency policy.*