

Mathematical Model of Metabolic Pathways of Steroidogenesis to Predict Molecular Response for Endocrine Disrupting Chemicals

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There is increasing evidence that exposure to endocrine disrupting chemicals (EDCs) in the environment can induce adverse effects on reproduction and development in both humans and wildlife, mediated through hormonal disturbances. These adverse effects induced in the tightly regulated endocrine pathways can be mediated through inhibition of the enzymes involved in steroidogenesis. We are developing a mechanistic mathematical model of the intratesticular and intraovarian metabolic network that mediates steroid synthesis, and the kinetics for enzyme inhibition by EDCs to predict the time and dose-response. The deterministic model describes the biosynthetic pathways for the conversion of cholesterol to the steroid sex hormones (e.g. testosterone and estradiol) and the gamete maturation inducing hormones (progestins) secreted by the gonads in fish. The model includes the intermediate metabolites and enzymatic reactions for the pathways involved in steroidogenesis. The initial concentrations and enzyme reaction rates were taken from the literature or set to biologically reasonable values. Computer simulations were performed to compare the model predicted time and dose-response with experimental data. Preliminary results show that the predicted time and dose-response behavior of the secreted hormone concentrations is comparable to experimental data. This mechanistic model allows for a better understanding of the dynamic dose-response behavior at the molecular level, and the identification of biomarkers that can be indicative of the ultimate adverse effects. Since the steroidogenic pathways are evolutionarily conserved in vertebrates to a significant extent, this model is likely to also be relevant for mammals. *This work was reviewed by the U.S. EPA and approved for publication but does not necessarily reflect Agency policy.*