**Endocrine Disruptors: Modeling the Intracellular Response**

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Over the past decade, international media reports have captured significant public attention and concern for the potential adverse effects of endocrine disrupting chemicals (EDCs) on reproduction and development in both humans and wildlife. During certain life stages, such as the differentiation of the central nervous system and reproductive tract, EDCs can interfere with the tightly regulated endocrine system, and even small transient perturbations in hormone concentrations can have considerable long-term pathologic effects. Chemicals capable of acting as endocrine disruptors are ubiquitous with sources that include household detergents, pesticides, plastics, pharmaceutical estrogens, industrial chemicals, and byproducts of incineration, paper production, and fuel combustion. Ecological exposures to EDCs are primarily from industrial and wastewater treatment effluents, while human exposures are mainly through the food chain.

The deleterious effects induced by exposure to EDCs can be mediated through alterations in the enzymes involved in steroid synthesis. We are developing a mechanistic mathematical model of the intratesticular and intraovarian metabolic network that mediates steroid synthesis to identify and link new robust molecular biomarkers of exposure that are indicative of the ultimate adverse effects. The model describes the biosynthetic pathways for the conversion of cholesterol to the sex steroid hormones (estradiol, testosterone, and ketotestosterone) secreted by the testes and ovaries in fish. The model includes the intermediate metabolites and enzymatic reactions for the multiple pathways involved in the biosynthesis of the sex steroids. The initial concentrations and enzyme kinetic reaction rates were taken from the literature or set to biologically reasonable values. Computer simulations were performed to examine the predicted time-varying steroid concentrations and compared with the limited amount of available, relevant, experimental data. This predictive model allows for an improved understanding of the source-to-outcome linkages necessary for effective use of molecular biomarkers of exposure for risk assessments with EDCs. Since the biosynthetic pathways for the sex steroids are evolutionarily conserved to a significant extent, this computational model is likely to also be relevant for mammalian species.



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