COMPUTATIONAL MODEL OF ADRENAL STEROIDOGENESIS TO PREDICT BIOCHEMICAL RESPONSE TO ENDOCRINE DISRUPTERS

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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 various endocrine disrupters (ED), some of which are environmental contaminants. We developed a dynamic computational model of the metabolic network of adrenal steroidogenesis to predict the synthesis and secretion of adrenocortical steroids, and the biochemical responses to ED. The deterministic model describes the biosynthetic pathways for the conversion of cholesterol to adrenocortical steroids, and the kinetics for enzyme inhibition by the ED, metyrapone. Experiments were performed using H295R human adrenocarcinoma cells to measure concentrations of 14 steroids using LC/MS/MS and ELISA methods, and model parameters were estimated using an iterative optimization algorithm. Model-predicted steroid concentrations closely correspond to the dynamic dose-response data from the experiments. A sensitivity analysis of the model parameters identified metabolic processes that most influence the concentrations of the primary steroids produced by the adrenal gland: aldosterone and cortisol. Our study demonstrates the feasibility of using the computational model of adrenal steroidogenesis to predict the *in vitro* adrenocortical steroid concentrations using H295R cells. This capability could be useful to help define mechanisms of action for poorly characterized chemicals and mixtures in support of the H295R steroidogenesis screening system, and predictive risk assessments. *This work was reviewed by the U.S. EPA and approved for publication but does not necessarily reflect Agency policy.*

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