Mechanistic Computational Model of Steroidogenesis in H295R Cells: Predicting Biochemical Response to Endocrine Active Chemicals

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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 a variety of endocrine active chemicals (EAC), some of which are therapeutics and others that are environmental contaminants. We are developing a dynamic mathematical model of the metabolic network of adrenal steroidogenesis to predict the synthesis and secretion of adrenocortical steroids (e.g. mineralocorticoids, glucocorticoids, androgens and estrogens), and the biochemical responses to EAC. The deterministic model describes the biosynthetic pathways for the conversion of cholesterol to adrenocortical steroids, and the kinetics for enzyme inhibition by the EAC, aminoglutethimide and metyrapone. Model predictions were compared to data from an *in vitro* steroidogenesis assay using H295R human adrenocarcinoma cells that express the enzymes needed to produce all adrenocortical steroids. Concentrations of 12 steroids were simultaneously measured with a newly developed LC/MS/MS method. Model parameters were estimated using an iterative optimization algorithm. Results show that model-predicted concentrations of adrenal steroids are comparable to time-course data from baseline studies. Our study demonstrates the feasibility of using the mechanistic steroidogenesis model to predict adrenocortical steroid concentrations *in vitro* using H295R cells. This capability could be useful to help define mechanisms of actions for poorly characterized chemicals in support of predictive environmental risk assessments, and to screen drug candidates based on steroidogenic effects in the early phase of drug development. *This work was reviewed by the U.S. EPA and approved for publication but does not necessarily reflect Agency policy.*