Computational Steroidogenesis Model to Predict Biochemical Response to Endocrine Active Chemicals: Model Development and Cross Validation

Miyuki Breen,[a,b] Michael S. Breen,[c] Natsuko Terasaki,[d]
Makoto Yamazaki,[d] Rory B. Conolly[a]

[a]National Center for Computational Toxicology, US EPA, RTP, NC 27711, USA
[b]Biomathematics Program, Department of Statistics, North Carolina State University, Raleigh, NC 27695, USA
[c]National Exposure Research Laboratory, US EPA, RTP, NC 27711, USA
[d]Molecular Toxicology Group, Safety Research Laboratory, Mitsubishi Tanabe Pharma Corporation, Kisarazu, Chiba 292-0818, Japan

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. We previously developed a deterministic model which describes the biosynthetic pathways for the conversion of cholesterol to adrenocortical steroids, and the kinetics for enzyme inhibition by the EAC, metyrapone. In this study, we extended our model for a multiple enzyme inhibitor, aminoglutethimide. Experiments were performed using H295R human adrenocarcinoma cells, and concentrations of 12 steroids were simultaneously measured with a newly developed LC/MS/MS method. We performed cross validation of our model for the baseline data across multiple experimental studies. Results show that the model simulation closely corresponds to the time-course baseline data. Our study demonstrates the feasibility of using the *in silico* mechanistic steroidogenesis model 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 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.*