Mathematical Model of Steroidogenesis to Predict Dynamic Response to Endocrine Disruptors

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research & development

Project ID (IIID-5)

Science Question

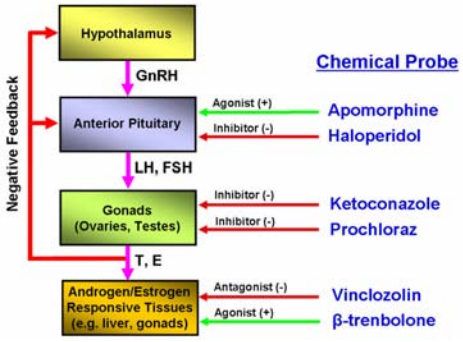
- Adverse hormonal changes in the tightly regulated endocrine pathways can be induced from exposure to exogenous endocrine disruptors
- Chemicals capable of acting as endocrine disruptors are ubiquitous with environmental sources that include household detergents, pesticides, plastics, pharmaceutical estrogens, industrial chemicals, and byproducts of incineration and fuel combustion
- Ecological exposures to endocrine disruptors are primarily from industrial and waste water treatment effluents, while human exposures are mainly through the food chain
- The adverse effects induced by exposure to endocrine disruptors can be mediated through alterations in the enzymes involved in steroid synthesis

Endocrine Disruption in Fish

Fathead Minnow

- Convincing evidence that fish are affected at individual and population levels
- Fish may serve as effective environmental sentinels for possible effects in other vertebrates

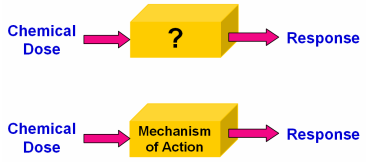
Effect on Hypothalamic-Pituitary-Gonadal (HPG) Axis



Feedback control system of HPG axis regulates synthesis and secretion of sex steroid hormones (e.g. estradiol (E), testosterone (T)) by release of gonadotropin releasing hormone (GnRH) from hypothalamus, and luteinizing hormone (LH) and follicle stimulationg hormone (FSH) from pituitary

Research Goals

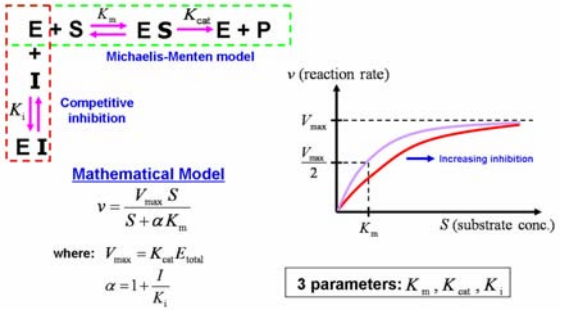
Mechanistic Computational Systems Biology Modeling



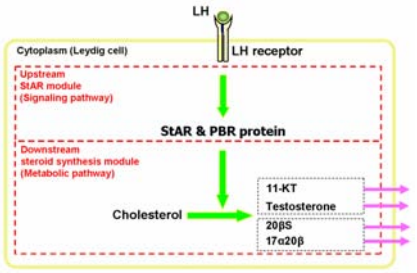
- Improve our understanding of the dynamic behavior of the intracellular biochemical pathways
- Generate and test hypotheses
- Help plan experiments and analyze complex "omics" data
- Predict dose-response at the molecular level
- Identify and link new molecular biomarkers of exposure

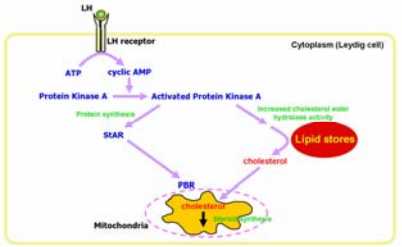
Methods/Approach

Enzyme Kinetics

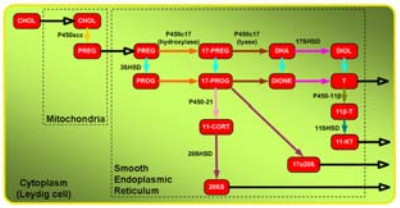


Modular Design of Intratesticular Steroidogenesis





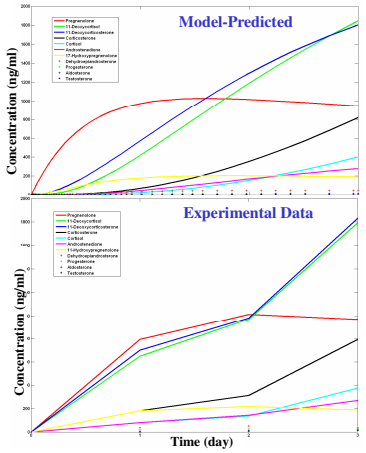
Upstream StAR Module



Downstream Steroid Synthesis Module

Results/Conclusions

Steroidogenesis in Human H295R Cells



Impact and Outcomes

- Improve our understanding of the dynamic dose-response behavior at the molecular level
- Identify and link new molecular biomarkers that are indicative of the possible ultimate adverse effects from endocrine disruptors to better understand source-to-outcome linkages in support of risk assessments

Future Directions

- Estimate model parameters for in vitro and in vivo fish data, and human H295R cells data
- Compare steroidogenesis in fish and mammals and publish comparative manuscript
- Couple steroidogenesis model with physiologically-based pharmacokinetic (PBPK) model of HPG axis

References

1. Payne AH, Hales DB. Overview of Steroidogenic Enzymes in the Pathway from Cholesterol to Active Steroid Hormones. Endocrine Review 25: 947-70, 2004.
2. Kavlock RJ, Ankley GT. A perspective on the risk assessment process for endocrine-disruptive effects on wildlife and human health. Risk Anal. 16(6):731-9, 1996.
3. Terasaki N, *et al.* Assessment of the effects of chemicals on steroidogenesis using human H295R cells by simultaneous measurement of a dozen steroid hormones. Society of Toxicology Annual Meeting, 2006. (Poster)

Long Term Goal III