Adaptive Responses to Prochloraz Exposure that Alter Dose-Response and Time-Course Behaviors

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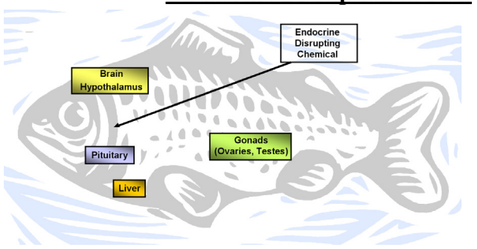
research & development

Science Question

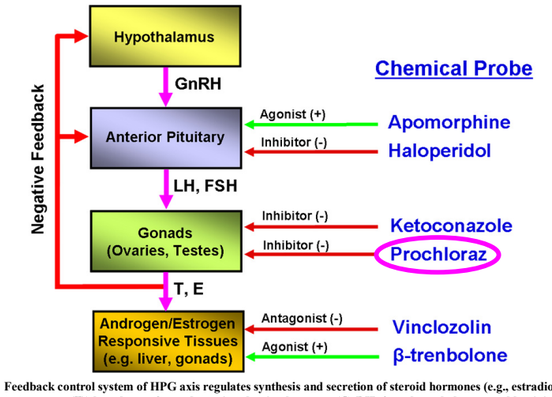
- Dose response and time-course are major determinants of health risk.
- The NRC report "Toxicity Testing in the 21st Century: A Vision and a Strategy" emphasized that adaptive changes within organisms exposed to environmental stress can alter dose-response behaviors to minimize the effects of stressors.
- Better understanding of adaptive mechanisms is needed to refine descriptions of dose-response behavior for risk assessments.

Endocrine Disruption in Fish



Adverse health effects in an intact organism consequent to changes in endocrine function

Effect on Hypothalamic-Pituitary-Gonadal (HPG) Axis

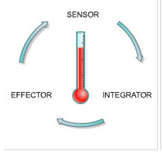


Feedback control system of HPG axis regulates synthesis and secretion of steroid hormones (e.g., estradiol (E), testosterone (T)) by release of gonadotropin releasing hormone (GnRH) from hypothalamus, and luteinizing hormone (LH) and follicle stimulationg hormone (FSH) from pituitary

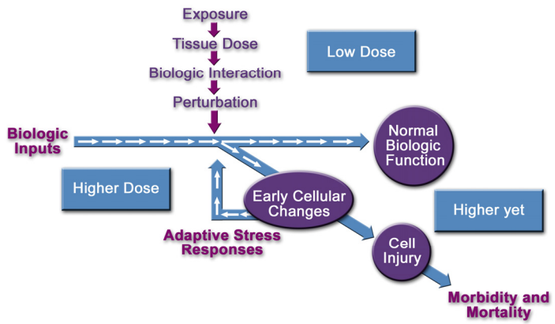
Adaptation to Environmental Stress: An Aspect of Homeostasis

We cannot survive unless we are able to control the internal environment of our bodies, despite continual changes in our surroundings. This activity demonstrates how homeostatic control is achieved—information passes from sensors to integrators to effectors, forming a negative feedback loop that constantly adjusts physiological parameters to fall within a narrow, optimal range.

(http://wps.prenhall.com/esm_freeman_biosci_1/7/1955/500605.cw/index.html)



Adaptation and Compensation in Risk Assessment

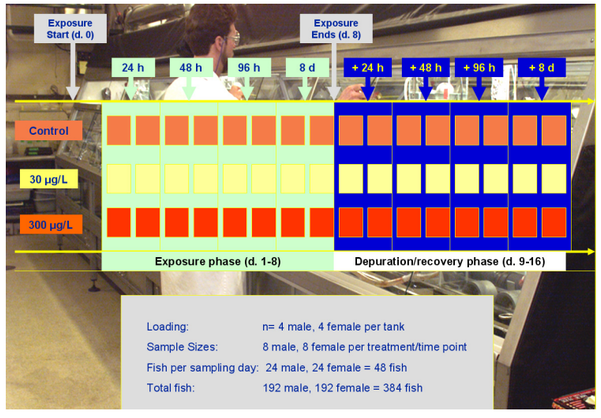


Research Goals

The main goal of this research is to develop a computational model of the HPG axis in fathead minnows that will help us to understand and characterize how the feedback regulatory loops in the axis generate adaptive responses to toxicant stress. An existing dose-response and time course dataset for prochloraz will be analyzed and additional data may be collected as needed to address issues that arise during model development. The approach being taken will be extendable to other chemicals that interact with the HPG axis and may thereby ultimately provide a generic capability for generating useful predictions of dose-response and time-course for disruptions of the HPG axis in small fish.

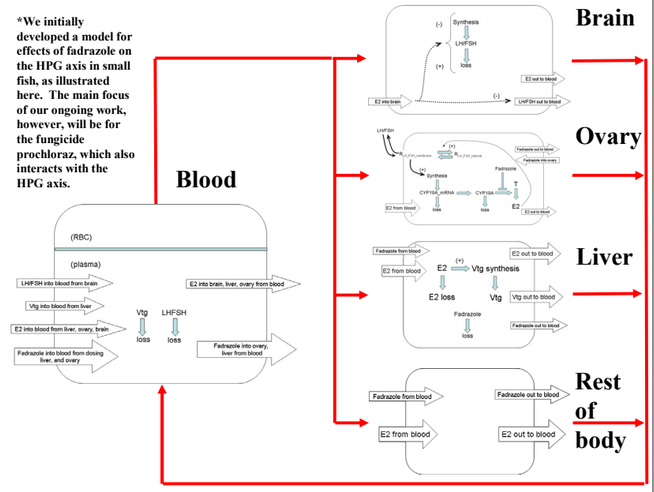
Methods/Approach

Fathead Minnows Exposed to Prochloraz



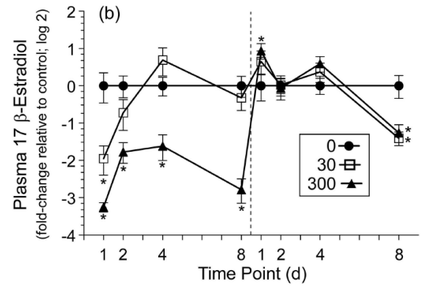
Computational Model of HPG Axis*

*We initially developed a model for effects of fadrazole on the HPG axis in small fish, as illustrated here. The main focus of our ongoing work, however, will be for the fungicide prochloraz, which also interacts with the HPG axis.



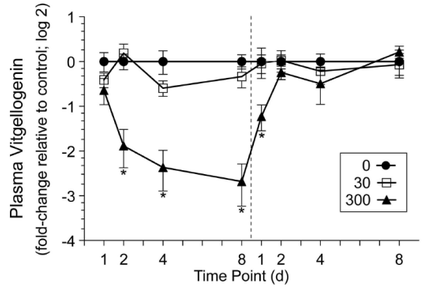
Results/Conclusions

Prochloraz data (µg/L)



Low dose – compensation during exposure

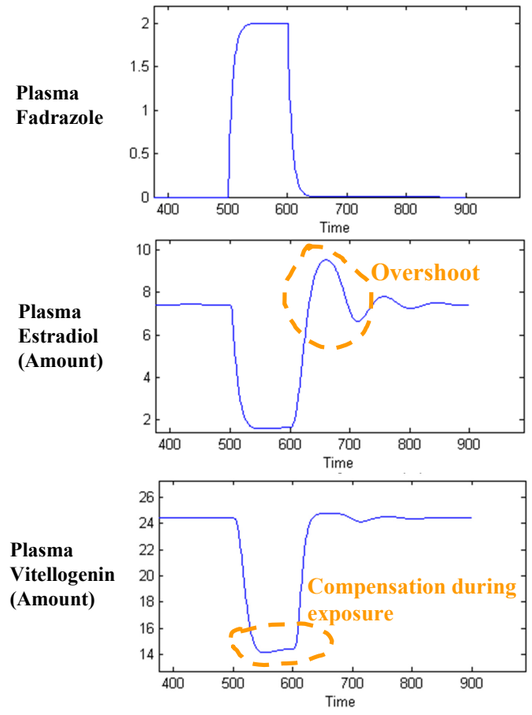
High dose – post-exposure recovery with overshoot



High dose – recovery

Vitellogenin: yolk protein with production induced by estradiol

1st-Generation Model-Predictions



Impact and Outcomes

- The 1st generation model of the HPG axis fish generates overshoot behaviors that are qualitatively similar to the overshoots seen in the Prochloraz data (see Results/Conclusions).
- The 1st generation model generates behaviors suggestive of adaptation during exposure, but not as clearly as the overshoots.

Future Directions

- Refine the 1st generation model to develop a model of prochloraz interactions with the HPG axis in small fish. This will involve identification of appropriate physiological and biochemical parameter values and description of Prochloraz-specific interactions with the HPG axis.
- Perform sensitivity analysis to identify critical biological parameters.
- Rigorously evaluate model's ability to predict adaptive response of HPG axis to prochloraz.

References

National Research Council. 2007. Toxicity Testing in the 21st Century: A Vision and a strategy. National Academy Press, Washington, DC.