Predicting Adaptive Response to Fadrozole Exposure: Computational Model of the Fathead Minnows Hypothalamic-Pituitary-Gonadal Axis

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Exposure to endocrine disrupting chemicals can affect reproduction and development in both humans and wildlife. We are developing a mechanistic mathematical model of the hypothalamic-pituitary-gonadal (HPG) axis in female fathead minnows to predict dose-response and time-course (DRTC) behaviors for endocrine effects of fadrozole. The model includes two feedback regulatory loops within the HPG axis that mediate adaptive responses to endocrine stress. One regulatory loop controls the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion from brain, and the other regulates LH and FSH receptor recycling in ovary. Fathead minnows were exposed to fadrozole at 0.5, 3, or 30 μg/L for 8 days followed by a 20-day recovery phase, with samples collected for plasma 17β-estradiol (E_2) and vitellogenin concentrations during exposure and post-exposure. Adaptive changes in plasma E_2 levels occurred during exposure and overshoot occurred post-exposure. Comparing the model-predicted DRTC with experimental data provided insight into how the feedback control mechanisms embedded in the HPG axis mediate these changes. As this work progresses we will obtain a refined understanding of how adaptive responses within the HPG axis of fathead minnows affect DRTC behaviors for fadrozole.