MODELING THE BRAIN-PITUITARY-GONADAL AXIS IN SALMON

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The biological effects of many endocrine disruptors are diverse and may involve disturbances in normal pituitary and gonad function. As an aid to better understand the complexity the brain-pituitary-gonad axis (BPG) in fish and the effects of specific disturbances in sex steroid or gonadotropin secretion, we developed a biologically based pharmacodynamic model capable of accurately predicting the normal functioning of the BPG axis in salmon. This first-generation model consisted of a set of 13 equations whose formulation were guided by published values for plasma concentrations of pituitary- (FSH, LH) and ovary- (estradiol, 17,20-dihydroxy-4-pregnene-3-one) derived hormones measured in Coho Salmon over an annual spawning period. In addition, the model incorporated pertinent features of previously published mammalian models and indirect response pharmacodynamic models. Model-based equations include a description of gonadotropin releasing hormone (GRH) synthesis and release from the hypothalamus, which is controlled by environmental variables such as photoperiod and water temperature. GRH stimulated the biosynthesis of messenger RNA for FSH and LH, which were also influenced by estradiol concentration in plasma. The level of estradiol in the plasma was regulated by the oocytes, which moved along a maturation progression. Estradiol was synthesized at a basal rate and as oocytes matured, stimulation of its biosynthesis occurred. Oocytes progressed by a periodical function of time with basal levels eventually leading to final oocyte maturation and spawning. Applications of the fish BPG model include aiding risk assessments of endocrine disruptors by providing a systems biological approach for interpreting the significance of alterations in hormone synthesis on reproduction. The BPG model can be integrated with toxicogenomic data, allowing a whole fish perspective on altered gene expression and endocrine function.