
Inhibition of enzymes involved in the synthesis of sex steroids can substantially impact developmental and reproductive processes controlled by the hypothalamic-pituitary-gonadal (HPG) axis. A key steroidogenic enzyme that has received little attention from a toxicological perspective is 3β-hydroxysteroid dehydrogenase (3β-HSD). A number of environmental contaminants and plant flavonoid compounds have been shown to inhibit 3β-HSD activity, indicating that this may be an environmentally-relevant mechanism of HPG axis disruption. In these studies we exposed reproductively-mature fathead minnows (Pimephales promelas) to the model 3β-HSD inhibitor trilostane at test concentrations ranging from 50 to 1500 µg/L for up to 21 d. Shorter-term time-course exposures included a clean water recovery phase. Exposure to trilostane caused a significant reduction in fecundity. Plasma concentrations of 17β-estradiol (E2) in females were rapidly depressed within hours of exposure and were accompanied by decreases in plasma concentrations of the estrogen-responsive protein vitellogenin (VTG). Decreased vitellogenesis in vivo was consistent with inhibition of in vitro production of E2 by fathead minnow ovaries. Plasma E2 and VTG concentrations quickly returned to control levels during the recovery phase. Up-regulation of ovarian expression of gene products for follicle stumulating hormone receptor (fshr), and the cytochrome P450-based enzyme aromatase suggested active compensation in trilostane-exposed animals. The effects on HPG function in exposed males were less pronounced, however, trilostane significantly increased gonadosomatic
index and, similar to females, caused up-regulation of gonadal fshr. The results of these studies support the hypothesis that 3β-HSD inhibition can cause reproductive dysfunction in fish. The data obtained from the time-course studies provide additional insights as to direct impacts, compensatory responses, and recovery from effects associated with 3β-HSD perturbation. The return of E2 and VTG to control levels in fish removed from the trilostane exposure demonstrates the highly dynamic, adaptive nature of the HPG axis in response to stressors. This information is important to the design and interpretation of approaches for assessing the occurrence and effects of HPG-active chemicals both in the lab and field. *This abstract does not necessarily reflect U.S. EPA policy.*