SCCWRP # 996

Derivation and Evaluation of Putative Adverse Outcome Pathways for the Effects of Cyclooxygenase Inhibitors on Reproductive Processes in Female Fish

Dalma Martinovic-Weigelt[1], Alvina C. Mehinto[2,3], Gerald T. Ankley[4], Jason P. Berninger[4], Timothy W. Collette[5], John M. Davis[5], Nancy D. Denslow[2], Elizabeth J. Durhan[4], Evan Eid[4], Drew R. Ekman[5], Kathleen M. Jensen[4], Michael D. Kahl[4], Carlie A. LaLone[4], Quincy Teng[5], Daniel L. Villeneuve[4]

[1]Biology Department, University of St. Thomas, Saint Paul, MI

[2]Departments of Physiological Sciences and Biochemistry and Molecular Biology, University of Florida, Gainesville, FL

[3]Southern California Coastal Water Research Project, Costa Mesa, CA

[4]U.S. Environmental Protection Agency, National Health and Environmental Effects Research Laboratory, Mid-Continent Ecology Division, Duluth, MI

[5]U.S. Environmental Protection Agency, National Exposure Research Laboratory, Ecosystems Research Division, Athens, GA

ABSTRACT

Cyclooxygenase (COX) inhibitors are ubiquitous in aquatic systems and have been detected in fish tissues. The exposure of fish to these pharmaceuticals is concerning because COX inhibitors disrupt the synthesis of prostaglandins (PGs), which modulate a variety of essential biological functions, including reproduction. In this study, we investigated the effects of well-characterized mammalian COX inhibitors on female fathead minnow reproductive health. Fish (n¼8) were exposed for 96h to water containing indomethacin (IN; 100 mg/l), ibuprofen (IB; 200 mg/l) or celecoxib (CX; 20 mg/l), and evaluated for effects on liver metabolome and ovarian gene expression. Metabolomic profiles of IN, IB and CX were not significantly different from control or one another. Exposure to IB and CX resulted in differential expression of comparable numbers of genes (IB¼433, CX¼545). In contrast, 2558 genes were differentially expressed in IN-treated fish. Functional analyses (canonical pathway and gene set enrichment) indicated extensive effects of IN on PG synthesis pathway, oocyte meiosis, and several other processes consistent with physiological roles of PGs. Transcriptomic data were congruent with PG data; IN-reduced plasma PG F2a concentration, whereas IB and CX did not. Five putative AOPs were developed linking the assumed molecular initiating event of COX inhibition, with PG reduction and the adverse outcome of reproductive failure via reduction of: (1) ovulation, (2) reproductive behaviors mediated by exogenous or endogenous PGs, and (3) oocyte maturation in fish. These pathways were developed using, in part, empirical data from the present study and other publicly available data.

Due to distribution restrictions, the full-text version of this article is available by request only.

Please contact pubrequest@sccwrp.org to request a copy.