GREAT LAKES FISHERY COMMISSION

Using a comparative transcriptomics approach to increase potency and specific of lampricide treatments

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ABSTRACT:

Control of invasive sea lamprey (*Petromyzon marinus*) in the Laurentian Great Lakes of North America uses lampricides, which consist of 3-trifluoromethyl-4-nitrophenol (TFM) and niclosamide. Lampricides are thought to inhibit aerobic energy synthesis, with TFM having a relatively greater selective action against lampreys. While the toxicity and physiological effects of TFM are known in sea lamprey, the impacts associated with exposure to TFM and niclosamide in non-target species and to TFM:niclosamide mixtures, in general, have not been well characterized in fishes. We quantified the physiological and transcriptomic responses of larval sea lamprey and bluegill (*Lepomis macrochirus*), a tolerant non-target species. Exposures consisted of each lampricide alone (TFM at the species-specific 24 h LC10; niclosamide at 1.5% of the mixture's TFM concentration) or a mixture of the two (larval sea lamprey at TFM 24 h LC10 + 1.5% niclosamide; bluegill at sea lamprey's TFM 24 h LC99.9 + 1.5% niclosamide) for 24 h. Tissues (brain, skeletal muscle, and liver for physiological assessments; and gill and liver for transcriptomics) were sampled at 6, 12, and 24 h of exposure. We also measured the tissue concentrations of the different lampricide treatments to estimate uptake and detoxification. In larval sea lamprey, TFM had little effect on brain and skeletal muscle, but niclosamide resulted in a depletion of high energy substrates in both tissues. The mixture-exposed lamprey showed depletion of high energy substrates, accumulation of lactate, and high mortality rates. Bluegill were largely unaffected by the lampricide exposures. However, bluegill had lower concentrations of TFM and niclosamide in their tissues when compared to sea lamprey. We confirmed that non-target bluegill showed high tolerance to lampricide exposure, an effect potentially mediated through a high detoxification capacity relative

to sea lamprey. We then used RNA sequencing to identify specific mRNA transcripts that responded to the lampricide treatments in the two species. We found considerable interspecific variation in the transcriptomic responses to TFM exposure, where transcripts association with detoxification were more diverse and responsive in bluegill relative to sea lamprey, including the upregulation of a specific version of the UGT enzyme (i.e., *ugt3*) that is not present in the sea lamprey genome. The niclosamide treatment resulted in an upregulation of several transcripts associated with detoxification (*cyp*, *ugt*, *sult*, *gst*), which may help contribute to the relatively high detoxification capacity in bluegill. Conversely, the TFM:niclosamide mixture resulted in an enrichment of processes related to arrested cell cycle and growth, and cell death alongside a diverse detoxification gene response in bluegill. In the sea lamprey, the niclosamide treatment resulted in no differentially expressed genes, TFM- and mixture-treated fish had several differentially expressed genes that were associated with the cell cycle, DNA damage, metabolism, immune function, and detoxification. Surprisingly, there was no common differential expression of genes among treatments in sea lamprey, suggesting that the mechanism associated with the interaction between the lampricides leading to increased mortality is occurring at a different level of biological organization (e.g., protein or tissue level). Overall, our findings strongly suggest that the relatively high tolerance of bluegill to lampricides is due to these fish having an inherently high capacity and flexible detoxification response to such compounds at the level of the transcriptome and that the detoxification of both lampricides likely involves the use of phase I and II biotransformation genes.