Brevetoxins (BTX) are neurotoxins produced by Karenia spp., associated with recurrent blooms of “red tide” along the Gulf of Mexico coast. Numerous studies have shown that BTXs are rapidly metabolized in shellfish and mammals. However, there is limited research on BTX metabolism in fish, despite growing evidence that fish serve as vectors for BTX transfer in marine food webs. In this study, we investigated the in vitro biotransformation of BTX-2 (a major constituent of Karenia spp. toxin profiles) using hepatic microsomes prepared from several species of northern Gulf of Mexico fish as well as commercially available human microsomes. Metabolism assays focused on Phase I reactions mediated by cytochrome P450 monooxygenase enzymes (CYP), which had been confirmed active in the prepared microsomes using CYP-specific standard substrates prior to the BTX-2 biotransformation experiments. Samples were analyzed by UHPLC-HRMS(/MS) to monitor BTX-2 depletion and to aid in the identification of BTX metabolites. Our results showed that the fish liver microsomes rapidly depleted BTX-2, resulting in 70–98% reduction within 1 hr of incubation. We observed simultaneous production of several functionalized metabolites (22 in total), including previously identified congeners like BTX-3 and BTX-B5, which were verified by comparison with a commercial reference standard, as well as BTX-9. Comparison of metabolite formation across species suggests that variable metabolic pathways may lead to divergent BTX profiles, including significantly higher formation of BTX-3 by the herbivorous Emerald parrotfish (N. usta) microsomes, and evidence of human-specific BTX biotransformation pathways. These results confirm that fish are capable of similar BTX biotransformation as reported for shellfish and mammals, and provide evidence to support variation in BTX-2 metabolism across fish species. Collectively, these data have important implications for the determination of the ecotoxicological fate of BTXs in marine food webs.

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