REPRODUCTIVE IMPACTS OF ARSENIC EXPOSURE IN MUMMICHOGS MEDIATED BY MRP1

Nikki L. Maples, Janis S. K. Peterson, and Lisa J. Bain
Department of Biological Sciences, University of Texas at El Paso, El Paso, TX 79968

Arsenic is a common pollutant of both surface and ground water, and can be found in relatively high concentrations in drinking water, and is considered to be a human carcinogen, although the exact mechanism of action is not well understood. The new drinking-water standard for arsenic has come under much scrutiny from congress, the scientific community, and the public recently. Thus, knowledge of the mode of arsenic toxicity, as well as the potential for alterations in human reproductive function, needs to be further investigated. This is best done in a species such as the mummichog (*Fundulus heteroclitus*) that is easily manipulated, breeds in a synchronous pattern, and one in which the developing embryos can be readily monitored. Recently, investigators have suggested that arsenic may work through an estrogenic mode of action, as rats exposed to an environmentally relevant drinking water level of arsenic had a significant reduction in plasma levels of estrogen, along with decreased ovarian, uterine, and vaginal weights (Chattopadhyay, S., et al., J. Toxicol. Sci. 24:425-431, 1999). We hypothesize that the part of the mechanism of arsenic toxicity may be due to the multidrug resistance-associated protein-1 (MRP1/ABCC1) and its ability to transport both conjugates of arsenic as well as 17β-estradiol glucuronide, which will result in an a decrease in estradiol levels, an increase in oxidative stress, and ultimately causes lowered reproductive fitness.

Adult mummichogs were collected near MDIBL and half were exposed to 0.4ppm sodium arsenate for four days. The fish were placed in clean 70% seawater, allowed to spawn, and the total number of eggs produced, their viability and hatchability, and the survival of the hatchlings up to four days was examined. The total number of eggs produced did not differ between the groups, but the viability of the eggs was reduced by almost half in the tanks where both parents were exposed to arsenic. The failure of seemingly viable embryos to hatch was increased 2-fold in tanks where either one of the parents or both the parents were exposed. The survival of the hatchlings to four days was not different between any of the groups. However, it does appear that arsenic exposure is causing some reproductive and developmental impacts in these organisms. Next, serum estradiol and testosterone levels, and hepatic MRP1 levels were examined in the adults. None of the levels differed significantly between exposure groups. Glutathione S-transferase activity and total glutathione concentration was examined in both the adults and the hatchlings as a measure of conjugative ability and potential oxidative stress. Neither the enzyme activity nor glutathione levels was different in either the adults or the hatchlings. We are currently examining differential gene expression in the adults and the hatchlings in an attempt to discern the mechanism of action of arsenic. We hope that these techniques will reveal groups of genes up- or down-regulated that play an important role in arsenic's toxicity, with particular interest in its ability to alter reproductive function. (Supported in part by the CMTS grant P30 ES03828-16).