GLUTAMATE-CYSTEINE LIGASE MODIFIER SUBUNIT AS A POSSIBLE MODULATING FACTOR IN METHYLMERCURY-INDUCED DEVELOPMENTAL TOXICITY

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By
Sally Shoshana White

Thesis Advisors

Marla J. Berry
Jane Schoonmaker

Abstract

The US EPA recently released a fish-consumption advisory, recommending that pregnant mothers reduce their intake of certain fish. Concentrations of methylmercury (MeHg) in commonly consumed fish have raised concern for the health of women of childbearing age and their developing children. Previous experiments have implicated glutathione (GSH), an endogenous, tri-peptide antioxidant, as an ameliorative factor in MeHg toxicity. GSH biosynthesis is rate-limited by glutamate-cysteine ligase (GCL), a heterodimeric enzyme consisting of a catalytic and a modifier subunit (GCLC and GCLM, respectively). To examine the roles of GCLM and GSH synthesis in MeHg-induced developmental toxicity, experiments were conducted employing *Gclm* knockout and hemizygous mice. Eight breeding pairs were established and on gestational day 14, females were inoculated with MeHg or sesame oil vehicle. The animals were sacrificed on gestational day 17, with dissection of the embryos, placenta, and yolk sacs, and maternal brain, liver, and kidney. The genotype of each embryo was determined and tissues were assayed for *Gclm* transcription and GCLM protein expression. While the scale of this experiment was found to be insufficient for definitive assessment of the roles of GCLM and GSH biosynthesis in MeHg toxicity, the work described here may provide pilot data for the design of future experiments. Additional results from such experiments should provide a better understanding of the fundamental processes involved in MeHg-induced developmental toxicity, and suggest public health strategies for protecting developing children from such injury.