



POTENTIAL IMPACT OF SELENIUM ON MERCURY TOXICITY

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Project Description

Numerous studies have applied hair analysis as a means of determining mercury exposure; however, it appears that certain variables may dramatically influence mercury deposition into hair. Identifying these variables is of great interest since hair mercury analysis results are used worldwide as an indication of mercury exposure and body burden. A recent study of Midwestern residents' fish consumption in which individual methylmercury exposures were compared to the individuals' analyzed hair mercury concentrations indicated that their actual mercury exposure was ~6 times higher than their hair mercury levels suggested. Recognizing that residents of the Midwest have enhanced selenium status and that selenium counters methylmercury's toxic effects, the observed reduction in mercury distribution into hair may be the result of higher selenium status in the population studied. Further evaluation of mercury–selenium interactions led to better understanding of the actual mechanism of mercury toxicity. We now believe that the mechanism of mercury-dependent neurotoxicity may occur through selenium sequestration leading to elimination of selenium-dependent physiological processes in the brain.

Goal

This study examines the biochemistry of selenium–mercury interactions in order to evaluate selenium's effects on the distribution of mercury into hair and the mechanism of mercury toxicity. The key components of this program are represented in the following tasks: 1) *in vivo* studies examining the effect of low, normal, and supplemental dietary selenium on methylmercury accumulation in hair, brain, liver, kidney, testes, and blood and 2) *in vitro* studies examining the direct binding activities of selenomolecules and methylmercury through affinity chromatography to perform quantitative isolation experiments to identify novel mercury binding molecules.

Rationale

Selenium supplementation counteracts the negative impacts of exposure to methylmercury, particularly in regard to developmental neurotoxicity [1, 2]. However, when supplemental selenium is provided, mercury accumulation in brain tissues is not reduced, but can actually be magnified [3]. The incorporated mercury accumulates within brain lysosomes [4], apparently in the form of insoluble mercury selenides. Until recently, the mechanism of mercury toxicity and the mechanism of the selenium-dependent detoxification effect remained unknown. Likewise, mercury's binding partners, their thermodynamic binding affinities, and the molecular and compartmental kinetics of mercury in transition from initial consumption and eventual elimination have never been fully established. Establishing these facets of mercury's interactions with

selenium-dependent physiological processes will provide the means of assessing strategic intervention to counteract mercury-dependent pathologies.

Approach

In Vivo Study: Thirty-two weanling Long Evans rats will be split into four weight-matched groups and fed diets consisting of the basal torula yeast-based diet supplemented to 0.05 or 1 ppm selenium with or without methylmercury present at 0.5 ppm for 8 weeks. At the end of the study, hair samples will be collected before the rats are terminated by cardiac exsanguination and brain, liver, kidney, testes, and blood samples obtained. The effects of dietary methylmercury and selenium on selenoprotein distributions and selenoenzyme activities in these tissues will be compared. The effect of selenium status on distribution of mercury into hair will be assessed.

In Vitro Study: The direct binding interactions between methylmercury and its potential binding partners will use mercury affinity chromatography to perform quantitative binding experiments. Tissue homogenates will be used to perform prospective examinations to seek and attempt to identify methylmercury's physiological binding partners.

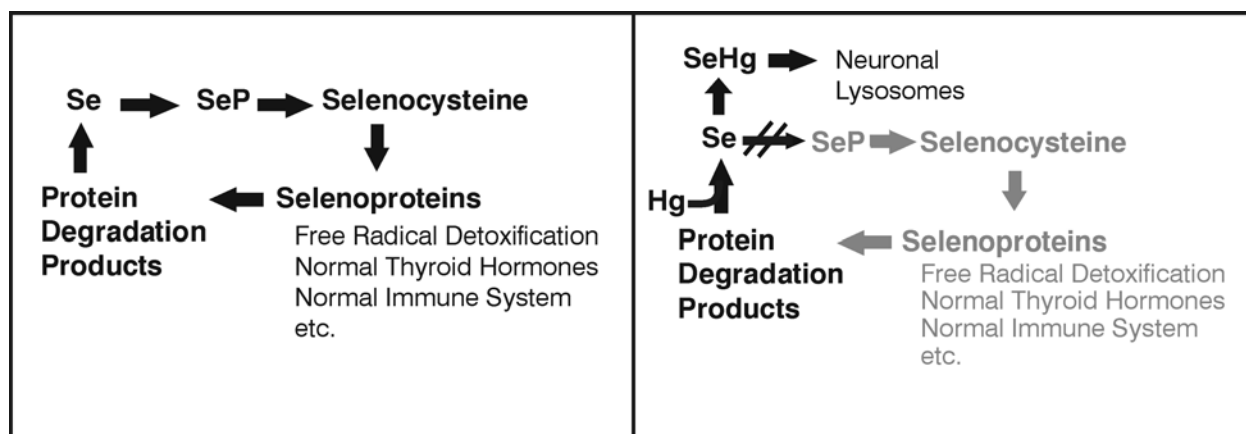
Progress

During the course of background research for this project, it became clear that the relationship between selenium and mercury may not simply be that selenium has a protective effect against mercury toxicity through its ability to bind up the mercury. Instead, the symptoms and signs of mercury toxicity may occur as a result of mercury-dependent selenium sequestration, reducing the availability of selenium necessary for synthesis of the essential selenoenzymes.

The lack of these enzymes could be particularly dangerous in neuronal tissues since there are no back-up systems for free radical detoxification in brain cells. Elimination of the selenium-dependent free radical detoxification enzymes may cause cell damage and cell death in fetal brains when maternal methylmercury consumption is excessive relative to selenium. Once the redox state of the cytosol switches from its normal reducing environment into an oxidizing environment, the biochemical pathway to synthesis of essential selenomolecules may be abolished, leading to a sustained loss of redox control. Thus even brief exposures to excess mercury may result in self-perpetuating deficiencies in selenoenzyme synthesis we have termed the "selenium tailspin." Neuronal cells that are damaged or destroyed by such mercury-dependent defects in selenoenzyme metabolism will not behave normally (Figure 1). Such damaged cells will not generate ensuing generations of neurons during the essential early stages of fetal brain development.

Status

A memorandum of understanding between the Grand Forks Human Nutrition Research Center (GFHNRC) and the EERC has been filed with the area office for the Northern Plains Office of the U.S. Department of Agriculture (USDA). The animal protocol has been filed and animal diets designed, and the animals are scheduled to arrive in January for study completion in February 2003. The license for authorization to apply radioactive materials in laboratory facilities has been applied for, and 0.5 mCi of $^{203}\text{HgCl}_2$ has been synthesized.



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Figure 1. Normal Selenoenzyme Synthesis vs. Interruption of the Cycle by Mercury

Potential Users/Technology Transfer

It is anticipated the results from our experiments will be used by the U.S. Environmental Protection Agency, the U.S. Department of Energy, USDA, the U.S. Food and Drug Administration, and the World Health Organization in their efforts to responsively intervene in mercury toxicity issues in populations at risk. Knowing the mechanism of methylmercury's toxic effects will permit regulatory agencies to more effectively assess risk in various global environments where selenium status protects against or predisposes for pathologies arising from mercury exposure. If our hypothesis is verified, we propose remedial selenium supplementation may be instituted to protect against methylmercury toxicity in those at-risk populations whose diets are inherently low in selenium.

References

1. Watanabe, C. Selenium Deficiency and Brain Functions: The Significance for Methylmercury Toxicity. *Nippon Eiseigaku Zasshi* **2001**, 55 (4), 581–589.
2. Watanabe, C.; Yin, K.; Kasanuma, Y.; Satoh, H. In Utero Exposure to Methylmercury and Selenium Deficiency Converge on the Neurobehavioral Outcome in Mice. *Neurotoxicol. Teratol.* **1999**, 21 (1), 83–88.
3. Whanger, P.D. Selenium in the Treatment of Heavy Metal Poisoning and Chemical Carcinogenesis. *J. Trace. Elem. Electrol. Health Dis.* **1992**, 6 (4), 209–21.
4. Moller-Madsen, B.; Danscher, G. Localization of Mercury in CNS of the Rat. IV. The Effect of Selenium on Orally Administered Organic and Inorganic Mercury. *Toxicol. Appl. Pharmacol.* **1991**, 108 (3), 457–73.