

Email from Nick Ralston to Angela Nugent, 06/08/11

Ralston, Nick
to:
Angela Nugent
06/08/2011 03:35 PM

Dear Angela,

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There has been a lot of work done on this issue (I am attaching a review we published last year in Toxicology). For example, the article by Carvalho et al., (2008) provides a good biochemical assessment of the irreversible inhibition of selenoenzymes that is caused by high mercury exposures.

Selenium is an essential trace element that the body needs to maintain activity of antioxidant enzymes that prevent and reverse oxidative damage in the brain. Since mercury selectively binds selenium, it irreversibly inhibits the various forms of these vital enzymes. Since mercury toxicity has only been observed under conditions where mercury exposures exceeded dietary selenium intakes, the results of all the epidemiological studies support the contention of Carvalho et al that the molecular mechanism of mercury toxicity occurs as a result of selenium-sequestration by mercury. Animal and cell culture studies find these same relationships. Mercury toxicity occurs when mercury exposures . Since selenium is the most powerful intracellular nucleophile (negatively charged reactive group) binding partner with the highest known affinity for mercury, it is particularly vulnerable to soft electrophilic (having positively charged reactive groups such as mercury) toxicants. Since methylmercury that are able to cross the placental and/or blood brain barriers, it selectively interrupts selenium metabolism in the brain, a feat that makes it particularly toxic in these vital but vulnerable tissues.

The studies of Carvalho coincide with and confirm the long-standing expectation of selenium-physiologists and biochemists that the molecular mechanism of mercury toxicity occurs through irreversible inhibition of selenoenzymes. Since it has been known since the late 1960's that supplemental selenium prevents development of signs and symptoms of mercury toxicity, the work by Carvalho and others simply confirms the mechanism responsible for selenium's "protective effect" is simply preventing loss of the vital but vulnerable selenium-dependent enzymes that the brain and endocrine system require for normal health and growth, especially during fetal development.

I don't want to hit you with too much on this subject at once, but here is an overview of the physiological and environmental importance of selenium in the mercury issue from the description I provided to speaker invitees to the 5th International Selenium-Mercury Symposium:

Selenium (Se) is an essential trace element that is required for the function of enzymes (selenoenzymes) that protect brain tissues from oxidative damage. Mercury (Hg) binds to Se with extremely high affinities (Kd 10⁻⁴⁵), that are a million times greater than Hg's affinity for sulfur (Kd 10⁻³⁹). Therefore, Hg and methylmercury (MeHg) become increasingly potent neurotoxicants as their tissue concentrations approach and especially as they exceed those of Se (~1µM). Methylmercury covalently

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binds with the Se present at active sites of selenoenzymes. Therefore, MeHg is, by definition, a highly specific, irreversible selenoenzyme inhibitor.

Since the intracellular abundance of sulfur is five log orders greater than that of Se, binding to thiols is kinetically favored. However, because the Se of selenocysteine (Sec) present in the active sites of selenoenzymes is the most potent intracellular nucleophile, Hg is predominantly bound to Se at equilibrium rather than with thiols. Provided sufficient Se is available to replace Se lost to binding with MeHg and maintain selenoenzyme activities without interruption, no increase in oxidative damage would be expected to occur. However, if Se-sequestration by MeHg exceeds the rate of Se replacement, selenoenzyme depletion and increased oxidative damage would be expected to occur. The physiological and environmental effects of Hg-Se interactions both involve chemical reactions that result in formation of HgSe. But understanding the significance of HgSe formation requires careful consideration of the implications of depleting the amount of available Se within an organism, or the diminishing the amount of Hg available in an ecosystem.

Physiological effects of mercury on selenium involve Hg-dependent Se-sequestration. These effects occur through primary mechanisms involving irreversible inhibition of selenoenzymes and secondary mechanisms that occur when these selenoenzyme functions are lost. This may explain why the toxicity of MeHg becomes more severe when Se status is poor, but has less discernable effects when Se status is enriched or when Se levels exceed MeHg intakes.

Environmental effects of selenium on mercury involve Se-dependent Hg-retirement. These effects appear to occur through food chain mechanisms related to the formation of HgSe in the tissues of prey species, which is poorly absorbed by predators. This may explain why Hg bioaccumulation is enhanced in freshwater fish from regions with low-Se status and diminished in fish from regions with enriched environmental Se availability. Although I am not part of the group addressing the freshwater fish issue, I will send you a PowerPoint describing the findings of the EPA funded research I am doing (I am currently preparing this presentation but won't have it done until tomorrow). Our studies have confirmed that mercury bioaccumulation in fish is inversely related to environmental availability of selenium. We are just the latest among a series of research groups that have found this effect.

I will be happy to discuss any or all of these topics further if you wish.

Sincerely,

Nick
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Attached articles:

Carvalho, C. et al. 2008 Inhibition of the Human Thioredoxin System; A Molecular Mechanism of Mercury Toxicity. *The Journal of Biological Chemistry*. 283 11913–11923.

Ralston, N. and Raymond, L. 2010. Dietary selenium's protective effects against methylmercury toxicity. *Toxicology*. 278 112–123