Glutathione modulation influences methyl mercury induced neurotoxicity in primary cell cultures of neurons and astrocytes

NeuroToxicology
Volume 27, Issue 4, July 2006, Pages 492-500

Parvinder Kaura, Michael Aschnerb and Tore Syversena

FROM ABSTRACT:

Methyl mercury (MeHg) is highly neurotoxic and may lead to numerous neurodegenerative disorders.

In this study, we investigated the role of glutathione (GSH) and reactive oxygen species (ROS) in methyl mercury induced neurotoxicity, using primary cell cultures of cerebellar neurons and astrocytes.

To evaluate the effect of glutathione on methyl mercury induced cytotoxicity, ROS and glutathione were measured.

N-Acetyl Cysteine (NAC) supplementation increased intracellular glutathione and provided protection against methyl mercury induced oxidative stress.

In summary, depletion of glutathione increases methyl mercury accumulation and enhances methyl mercury induced oxidative stress and conversely, supplementation with glutathione precursor NAC protects against MeHg exposure in vitro.

Abbreviations:

MeHg	methyl mercury
GSH	glutathione
ROS	reactive oxygen species
NAC	N-acetyl cysteine

THESE AUTHORS ALSO NOTE:

"Methyl mercury (MeHg) is a potent neurotoxicant that affects both the developing and mature central nervous system (CNS)."

Methyl mercury is a ubiquitous environmental toxicant.

"The CNS damage caused by methyl mercury is irreparable and different in adult brain versus fetal brain." **[Important]**

"Severe neurological disturbances, such as paresthesia, ataxia, sensory and speech impairment, and constriction of the visual field are caused by methyl mercury poisoning."

"Contaminated fish from polluted areas, vaccines and dental amalgams also pose as a potential source of mercury exposure in humans." **[Important]**

Signs and symptoms of methyl mercury toxicity in adults are confined to the nervous system where it affects primarily the cerebellum and the visual cortex.

The adult human brain consumes more than 20% of the oxygen utilized by the body, indicating that ROS are generated at high rates during oxidative metabolism of the brain. [This means that because the brain uses the most oxygen, it generates the greatest amounts of oxygen free radicals.]

"Antioxidants provide cellular defense against ROS, with glutathione constituting the most important and abundant component." **[Important]**

The availability of cysteine is the rate-limiting factor for synthesis of neuronal GSH. **[IMPORTANT: glutathione is a tripeptide: glutamate-cysteine-glycine]**

Methyl mercury toxicity leads to depletion of GSH and generation of ROS.

Glutathione has s critical role in modulating methyl mercury neurotoxicity.

N-Acetyl Cysteine (NAC) is a source of cysteine for building glutathione.

NAC is an effective antidote against methyl mercury poisoning.

DISCUSSION

This study shows that depletion of glutathione increases the intracellular concentration of methyl mercury in neurons and therefore influences the generation of ROS.

Methyl mercury causes a depletion of neuronal glutathione.

N-Acetyl Cysteine (NAC) is an acetylated analog of cysteine, which easily crosses the cell membrane and is rapidly deacetylated inside the cell to become available for glutathione synthesis. **[Important]**

This study shows that NAC was effective in preventing methyl mercury induced glutathione loss.

"The present study demonstrates that neurons were more vulnerable to methyl mercury induced glutathione depletion, indicating that glutathione status likely represents a key factor in the neuropathologic and cell specific effects of methyl mercury." **[Important]**

ROS are the mediators of methyl mercury induced neurotoxicity.

Glutathione modulates the effects of methyl mercury induced ROS generation.

"In summary, the present study demonstrates that maintenance of adequate glutathione levels protects against methyl mercury induced oxidative stress in primary cell cultures of neurons and astrocytes."

"Modulation of glutathione levels effectively changes the intracellular concentration of methyl mercury which in turn will alter the risk of methyl mercury induced oxidative stress."

KEY POINTS FROM DAN MURPHY

1) Methyl mercury (MeHg) is highly neurotoxic and leads to numerous neurodegenerative disorders.

2) N-Acetyl Cysteine (NAC) supplementation increased intracellular glutathione and provided protection against methyl mercury induced oxidative stress.

3) Depletion of glutathione increases methyl mercury accumulation and enhances methyl mercury induced oxidative stress.

4) Supplementation with glutathione precursor N-Acetyl Cysteine (NAC) protects against methyl mercury exposure in vitro.

5) "Methyl mercury is a potent neurotoxicant that affects both the developing and mature central nervous system."

6) Methyl mercury is a ubiquitous environmental toxicant.

7) "The CNS damage caused by methyl mercury is irreparable and different in adult brain versus fetal brain." **[Important]**

8) Methyl mercury poisoning leads to severe neurological disturbances, including paresthesia, ataxia, sensory, visual and speech impairments.

9) "Contaminated fish from polluted areas, vaccines and dental amalgams also pose as a potential source of Hg exposure in humans." **[Important]**

10) In adults, methyl mercury toxicity primarily affects the cerebellum and the visual cortex of the cerebrum.

11) The adult human brain consumes more than 20% of the oxygen utilized by the body, and it therefore generates the greatest amounts of oxygen free radicals.

12) Antioxidants provide defense against reactive oxygen species (ROS), with glutathione (GSH) being the most important antioxidant. **[Important]**

13) **[Glutathione is a tripeptide: glutamate-cysteine-glycine].** The availability of cysteine is the rate-limiting factor for synthesis of neuronal glutathione.

14) Methyl mercury toxicity depletes glutathione and increases the generation of reactive oxygen species (ROS) free radicals.

15) Glutathione is critical in protecting the brain from methyl mercury neurotoxicity.

16) N-Acetyl Cysteine (NAC) is a source of cysteine for building glutathione.

17) NAC is an effective antidote against methyl mercury poisoning.

18) Depletion of glutathione increases the intracellular concentration of methyl mercury in neurons and increases the generation of ROS.

19) NAC is effective in preventing methyl mercury induced glutathione loss.

COMMENTS FROM DAN MURPHY

Methyl mercury is a ubiquitous environmental toxicant that damages the brain of both children and adults. Besides the environment, humans are exposed to methyl mercury from eating fish, from vaccines, and from dental amalgams. Methyl mercury damages the nervous system by drastically accelerating the genesis of oxygen free radicals. Much of the neuronal damage caused by methyl mercury is irreversible. This study shows that our primary protection from this ubiquitous neurotoxicant is maintaining levels of the detoxifying antioxidant glutathione. This study, and many other studies referenced in this article, show that supplementation with N-acetyl-cysteine (NAC) will drastically elevate the brain's levels of glutathione, and thereby protect the brain form methyl mercury genesis and damage from free radicals. As I have noted in other articles, the three best strategies for maintaining brain glutathione levels are:

Glutathione: Glutamate-Cysteine-Glyceine; The Rate Limiting Factor Is Cysteine.

A) Convert BAD Homocysteine to GOOD Cysteine by using B6, B12, Folic Acid, and riboflavin to recharge glutathione (**Complete Omega-3 Co-Factors** From Nutri-West: 800-443-3333: Take 2 Capsules Per Day)

B) Take NAC, N-Acetyl Cysteine (**Complete Glutathione** From Nutri-West: 800-443-3333: Take 2 – 6 Capsules Per Day)

C) Take undenatured Whey Protein (**Complete Whey-G** From Nutri-West: 800-443-3333: Take 1 – 2 Tablespoons Per Day)