

Mercury toxicity and antioxidants: part I: role of glutathione and alpha-lipoic acid in the treatment of mercury toxicity - Mercury Toxicity - Brief Article

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Glutathione in Heavy Metal Binding

Glutathione is the most common low-molecular weight sulfhydryl-containing compound in mammalian cells, present in millimolar amounts in most cells. (26) As a result of the binding of mercury to glutathione and the subsequent elimination of intracellular glutathione, levels of reduced glutathione are lowered in several specific types of cells on exposure to all forms of mercury. Glial cells, (27) human erythrocytes, (28) and mammalian renal tissue (24) have all been found to have significantly lowered levels of reduced glutathione, a major source of oxidant protection. Mercury, as well as cadmium, generates highly toxic hydroxyl radicals from the breakdown of hydrogen peroxide, which further deplete glutathione stores. (27) There is evidence that glutathione depletion can lead to neurological damage; low levels of glutathione have been found in Parkinson's disease and cerebral ischemia-reperfusion injury. (29)

Glutathione, as both a carrier of mercury and an antioxidant, has three specific roles in protecting the body from mercury toxicity. First, glutathione, specifically binding with methylmercury, forms a complex that prevents mercury from binding to cellular proteins and causing damage to both enzymes and tissue. (30) Glutathione-mercury complexes also reduce intracellular damage by preventing mercury from entering tissue cells and becoming an intracellular toxin.

Second, glutathione-mercury complexes have been found in the liver, kidney, and brain, and appear to be the primary form in which mercury is transported and eliminated from the body. (24) The transport mechanism is unclear, but complexes of glutathione and mercury are the predominant form of mercury in both the bile and the urine. (31) Glutathione and cysteine, acting as carriers of mercury, actually appear to control the rate of mercury efflux into bile; the rate of mercury secretion in bile appears to be independent of actual bile flow. When bile flow rate is increased or decreased, the content of mercury in the bile changes inversely so net mercury efflux from the liver remains unchanged. (32) However, increasing bile levels of both glutathione and cysteine increases the biliary secretion of methylmercury in rats. (13) Other studies have confirmed this data in animal models. (33-35) Conversely, glutathione depletion inhibits biliary secretion of methylmercury in animal models and blocking glutathione production appears to shut down biliary release of mercury. (35)

Cells of the blood-brain barrier (brain capillary endothelial cells) release mercury in a glutathione complex. Inhibiting glutathione production in these cells inhibits their ability to release mercury. (23) Mercury accumulates in the central nervous system primarily in astrocytes, the cells that provide the first line of defense for the central nervous system against toxic compounds. (36) Astrocytes are the first cells in brain tissue to encounter metals crossing the blood brain barrier. They also contain high levels of metallothionein and glutathione, both carriers for heavy metals. It is hypothesized that astrocytes are the

main depot of mercury in the brain. (37) In studies with astrocytes, the addition of glutathione, glutathione stimulators, or glutathione precursors significantly enhances the release of mercury from these cells in a complex with glutathione. Fujiyama et al (38) also suggest that conjugation with glutathione is the major pathway for mercury efflux from astrocytes. Glutathione also increases mercury elimination from renal tissue. Studies in mammalian renal cells reveal glutathione is 50 percent as effective as the chelating agent DMSA (2,3-dimercaptosuccinic acid) in preventing inorganic mercury accumulation in renal cells. (39)

Third, glutathione increases the antioxidant capacity of the cell, providing a defense against hydrogen peroxide, singlet oxygen, hydroxyl radicals, and lipid peroxides produced by mercury. (30) The addition of glutathione to cell cultures exposed to methylmercury also prevented the reduction of cellular levels of glutathione peroxidase, a crucial antioxidant enzyme necessary for protection against the damaging effects of lipid peroxidation. (30)

As an antioxidant, glutathione appears to protect against renal damage resulting from inorganic mercury toxicity. The co-incubation of rat renal cells with glutathione and inorganic mercury was significantly more protective of renal cell injury when compared to inorganic mercury exposure alone. (40) Antioxidant levels--specifically glutathione, vitamin E, and ascorbic acid--are depleted in renal tissue exposed to mercuric chloride (inorganic mercury), and the addition of glutathione increased levels of both vitamin E and ascorbic acid in renal cells exposed to mercuric chloride. (24)

Mammalian cell lines resistant to mercury toxicity have been cloned. (41) They do not readily accumulate mercury and are resistant to the toxic effects of methylmercury or inorganic mercury. An outstanding characteristic of this cell line is that glutathione levels are five times greater in these cells than the parent cells from which they originated. The authors of this study conclude that the mechanisms of resistance were primarily due to glutathione's ability to facilitate mercury efflux from cells and the protective binding of mercury by glutathione to prevent cellular damage.

The Role of alpha-Lipoic Acid

In 1966, German physicians began using alpha-lipoic acid (ALA) therapeutically in patients with diabetic polyneuropathy and liver cirrhosis because of their observation that these patients had lower levels of circulating lipoic acid. (42) The application was subsequently extended to heavy metal intoxication and toxic mushroom poisoning.

According to Jones and Cherian, (43) an ideal heavy metal chelator should be able to enter the cell easily, chelate the heavy metal from its complex with metallothionein or other proteins, and increase the excretion of the metal without its redistribution to other organs or tissues. Although no human clinical trial has investigated the use of ALA as a chelating agent in mercury toxicity, there is evidence ALA satisfies at least two of the above criteria; i.e., absorption into the intracellular environment and complexing metals previously bound to other sulfhydryl proteins.

ALA produced endogenously is bound to proteins, but can also be found unbound in the circulation, after exogenous lipoic acid supplementation. (41) In this form it is chemically

able to trap circulating heavy metals, thus preventing cellular damage caused by metal toxicity. (41) Lipoic acid is lipophilic and is able to penetrate cell membranes and reach high intracellular concentrations within 30 seconds of its administration. (44)

The fact that free ALA crosses the blood-brain barrier is significant because the brain readily accumulates lead and mercury, where these metals are stored intracellularly in glial tissue. (36,45) Oral doses of 10 mg/kg ALA in rats have reached peak levels in the cerebral cortex, spinal cord, and peripheral nerves within 30 minutes of administration, and studies of chronic daily dosing conclude ALA reaches all areas of the CNS and peripheral nervous system. (46) ALA has been shown to decrease lipid peroxidation in brain and sciatic nerve tissue (47) and when given orally to rats, decreased lipid peroxidation in brain tissue by 50 percent. (46) In diabetic neuropathy, free lipoic acid may prevent glucose-related oxidative damage by entering nerve tissue where it acts as both an antioxidant and heavy metal-binding agent. (28)

ALA has been administered to humans in doses up to 1,200 mg intravenously without toxicity, and in oral daily doses of as much as 600 mg three times daily. The only side effects reported are infrequent nausea and vomiting. No side effects have been reported in oral administration of up to 1,800 mg daily. (41,48) Doses of 500-1,000 mg have been well tolerated in placebo-controlled studies. (49) Extrapolation of pharmacokinetic and toxicity data demonstrate safe human dosages would not be exceeded with oral doses of several grams per day. (41)

ALA has been shown to increase both intra- and extracellular levels of glutathione in T-cell cultures, human erythrocytes, glial cells, and peripheral blood lymphocytes. (50) In rats, oral dosing of 150 mg/kg/day for eight weeks significantly increased glutathione levels in the blood and liver. (51) ALA has been shown to increase intracellular glutathione by 30-70 percent in murine neuroblastoma and melanoma cell lines, and in the lung, liver, and kidney cells of mice that had received intraperitoneal injections of 4, 8, or 16 mg/kg ALA for 11 days. (52,53) Levels of intracellular glutathione have been shown to increase by 16 percent in T-cell cultures at concentrations of 10-100 [micro]M (concentrations achievable with oral and intravenous supplementation of ALA). (50) A single oral dose of 600 mg ALA was able to produce a serum concentration of 13.8 [+ or -] 7.2 [micro]M and levels of 100-200 [micro]M have been reported after 600 mg intravenous administration. (54)

Increases in glutathione levels seen with ALA administration are not only from the reduction of oxidized glutathione (one of the functions of ALA) but also from the synthesis of glutathione. (46) ALA is reduced to dihydrolipoic acid (DHLA), itself a potent antioxidant. DHLA is able to regenerate oxidized ascorbate, glutathione, coenzyme Q, and vitamin E, (28) and is responsible for the ability of ALA to increase intracellular glutathione levels (Figure 1). (55)

ALA, through its reduction to DHLA and oxidation back to ALA, has the ability to continuously provide cysteine, the rate-limiting amino acid for glutathione production. ALA is rapidly reduced to DHLA and released in the extracellular environment where it reduces extracellular cystine to cysteine and increases the uptake of cysteine into the cell, (50) increasing glutathione production. ALA does this through enzyme-catalyzed

reactions using NADH or NADPH, the metabolic power resulting from glucose metabolism (Figure 2). (51)

ALA and Binding of Copper, Iron, Platinum, and Lead

ALA and DHLA have been shown to form complexes with manganese (Mn^{2+}), zinc (Zn^{2+}), cadmium (Cd^{2+}), lead (Pb^{2+}), cobalt (Co^{2+}), nickel (Ni^{2+}), and iron (Fe^{2+}) ions. (55) In many cases, ALA-mediated heavy-metal binding prevents free-radical caused tissue damage or enzyme inactivation. (56)

In the case of iron and copper, complexing with ALA can protect cells from damage caused by iron- or copper induced lipid peroxidation. (41) ALA has been shown to bind copper in human lipoproteins (57) and, as a result, to inhibit copper-induced peroxidation of low density lipoproteins. ALA has been used to treat Wilson's disease, effectively increasing renal copper excretion and normalizing liver function. (58)

ALA is also able to form complexes with ferritin-bound iron both in vitro and in vivo. (59) ALA has the ability to displace protein or vitamin C bound to iron and bind to Fe^{2+} . DHLA can facilitate the release of iron from the ferritin molecule and bind iron. (41)

The brain, particularly the substantia nigra and the globus pallidus, contains high levels of iron. (46) The high iron content and an increased level of unsaturated fatty acids lead to increased levels of tissue peroxidation. (46) ALA has been found to suppress the free radicals initiated by reactions with iron in the substantia nigra and other parts of the CNS. (46)

ALA has also been shown to protect against cisplatin-induced renal damage in rats by binding to platinum that is responsible for renal toxicity. (60) At dosages of 25-100 mg/kg (equivalent to 7 grams per 70 kg human adult), ALA restored normal levels of antioxidant enzyme activity, increased reduced glutathione levels, and significantly decreased renal tissue platinum content. The dose of cisplatin used in the study (16 mg/kg) is similar to clinical use in cancer treatment. Although the potential toxicity of this high dose of ALA is unknown, it is much higher than the 300-1800 mg typically used clinically. (46,48,49)

An intraperitoneal injection of 25 mg/kg ALA given to rats for seven days was able to significantly alter the oxidative stress induced by lead toxicity. (61) ALA administration increased glutathione levels 207 percent in the lead-exposed rats and decreased malondialdehyde levels in the brain, kidneys, and red blood cells, three of the four main targets of lead toxicity. (61) Further studies in cell lines of the fourth target, the reproductive system, found ALA had a protective effect in hamster ovarian cells, decreasing oxidative stress that causes cellular damage and death as a result of lipid peroxidation. (61) Because lead exposure was high (2,000 ppm injected daily into rats for five weeks) and the length of time ALA was administered was short (seven days), there may not have been enough time to see decreases in levels of lead in the brain or kidneys, if that effect were to take place. There were significant improvements in cell viability in ovarian cells exposed to lead that did not result from direct ALA-iron binding, suggesting

ALA has a protective effect in lead toxicity aside from its ability to bind and excrete lead. (61)

ALA and Cadmium, Arsenic, and Mercury

Cadmium, arsenic, and mercury toxicity all involve similar pathways of cellular damage; i.e., mitochondrial damage, inhibition of mitochondrial enzymes, suppression of protein synthesis, and production of free radicals. (62) All three have a strong affinity for sulfhydryl-containing ligands (glutathione, alpha-lipoic acid, etc.), and each result in depressed levels of reduced glutathione. (63) The efficacy of ALA as an antioxidant and heavy metal-complexing agent in cadmium, arsenic, and mercury toxicity has been studied in animals--with results that may be applicable to heavy metal toxicity in humans.

ALA, at concentrations of 5 mM, was able to protect rat hepatocytes from cadmium toxicity (200 [micro]M) by preventing decreases in total glutathione and increases in lipid peroxidation. (63) Another cadmium study investigated 1.5-6.0 mM concentrations of ALA or 17-89 [micro]M DHLA in rat hepatocytes exposed to cadmium. (64) Both protocols decreased cadmium uptake by hepatocytes and normalized hepatocyte glutathione levels, leading to increased cell viability and survival despite the cadmium toxicity. ALA has also been shown (at a 30 mg/kg injected dose) to completely prevent damage that occurs from cadmium-induced lipid peroxidation in rat brain, heart, and testes. (65) In addition, ALA completely restored glutathione levels in the rat brain that had declined 63 percent with cadmium exposure.

A frequently quoted article referring to ALA as a heavy metal-complexing agent is the study by Grunert. (66) Published in 1960, the investigation used a dog and rat model in which simultaneous injection of sodium arsenate and ALA in both animals protected them from fatal arsenic toxicity. It has been shown that in acute arsenic intoxication, lipoic acid can form a complex with arsenic that renders the arsenic nontoxic. (41) Studies dosing mice with arsenic have shown ALA prevents intestinal uptake of arsenic and reduces the toxic effect of arsenic on enzyme inhibition. (49)

ALA has been shown to affect the release of glutathione into bile secretions. In animal studies, increasing amounts of glutathione in bile has been shown to dramatically increase the release of inorganic mercury. ALA given intravenously to rats at doses of 37.5-300 [micro] M/kg was shown to increase inorganic mercury release in bile by 1,200-4,000 percent immediately after mercury exposure. (67) Levels of released inorganic mercury remained at a 300-700 percent elevation, even three hours after dosing with ALA. If mercury was injected 24 hours prior to the administration of ALA, the increase in release of inorganic mercury was substantially less, but was still elevated 140-330 percent. A lower dose of ALA (37.5 [micro]M/kg) was more effective than higher doses at increasing the biliary elimination of methylmercury.

There was disconcerting evidence from this study, however, that ALA may also alter the tissue distribution of mercury and other heavy metals.

Although levels of inorganic mercury and methylmercury in the kidney dropped significantly, levels of inorganic mercury also increased significantly in the brain, lung, heart, and liver tissue. Methylmercury levels had also increased in the brain, intestine and

muscle of the rats given ALA. The same phenomenon occurred in rats exposed to cadmium and given the same doses of ALA. Levels of cadmium in the liver dropped (where cadmium is most frequently stored) but increased in the kidney and muscle. The same was true in rats given copper and ALA; all tissues examined had increased levels of copper, except for the liver (where copper usually accumulates) where levels had dropped. (67) In all cases the pattern was the same; the tissues that concentrated the metal (blood, spleen, and kidneys in the case of methylmercury) had reduced concentrations, while other tissues appeared to have a greater concentration.

Grunert subjected mice to lethal doses of mercuric chloride accompanied with ALA. (66) He found the ALA-to-mercury ratio was crucial in determining the outcome. A ratio of 6-8 moles ALA per mole mercuric chloride was necessary to allow the mice to survive mercury poisoning. A lower level of ALA actually increased the mercury toxicity (a molar ratio of 2 moles ALA to 1 mole mercuric chloride or lower) above control levels. The level of mercuric chloride used in this experiment, 20 mg/kg, is high and would only be seen in acute mercury poisoning.

In another study of mercury intoxication, an injection of 10 mg/kg/day ALA in rats given an injection of 1 mg/kg/day mercuric chloride prevented damage to nerve tissue caused by lipid peroxidation. (68) ALA significantly reduced lipid peroxidation in the mercury-exposed rats while elevating levels of the antioxidants glutathione, ascorbate, and tocopherol. The mechanism of protection was hypothesized to be the scavenging of peroxy radicals formed in the brain and nervous system, although the authors believed direct complexing of inorganic mercury by ALA was also a possibility.

ALA versus Dithiol-based Chelating Agents (DMPS, DMSA)

The ability of ALA to bind inorganic mercury from rabbit renal tissue was compared to glutathione and the chelators 2,3-dimercaptopropane-1-sulfonate (DMPS), meso-2,3-dimercapto-succinic acid (DMSA), penicillamine, and ethylenediaminetetra acetic acid (EDTA) (Figure 3). (69)

[FIGURE 3 OMITTED]

DMPS was the most efficient chelator, removing 86 percent of the mercury in three hours, with DMSA being the next-most efficient, removing 65 percent of the mercury. In the same time period, penicillamine removed 60 percent, glutathione removed 50 percent, ALA removed 35 percent, and EDTA removed 20 percent. Only the levels reached by DMSA and DMPS, however, were statistically significantly different from baseline ($p < 0.05$). Therefore, the effect of ALA and glutathione may show only a trend or an apparent effect and are not comparable to DMPS and DMSA. Although the actual effect of a chelator or heavy metal-complexing agent cannot be determined in a three-hour time period, and acute doses of 10 mg/kg of inorganic mercury would be considered highly toxic in an adult human, there is evidence from this study that ALA is a less efficient binder of inorganic mercury than the recognized chelating agents, DMSA and DMPS. All of the substances were used at a concentration of 10 mM, a level difficult to reach with ALA oral supplementation.

In another comparison study, ALA (25 mg/kg/day) resulted in an insignificant decrease in blood and tissue lead in rats with lead toxicity when compared to the dithiol-based chelating agent, DMSA (dosed at 90 mg/kg/day) (Table 2). (61)

Both DMSA and DMPS have been shown to be clinically effective heavy metal chelators in human studies of mercury toxicity, (70-75) particularly since they both chelate inorganic and organic mercury. (71) DMSA acts only as an extracellular chelator, whereas DMPS enters hepatocytes (73) and renal cells, (76) although it is still considered primarily an extracellular chelator. (73) DMSA is less toxic because of its inability to enter cells or bile, (73) with an [LD.sub.50] of 13.73 mM/ kg, approximately twice the [LD.sub.50] of DMPS, which is 6.53 mM/kg. (73) While DMSA has been found to be more effective than DMPS at removing mercury from the brain, (77) DMPS appears to be more effective at removing mercury from the kidney. (78)

Conclusion

Many unanswered questions remain regarding ALA and heavy metal detoxification, especially pertaining to mercury. The amount of ALA supplemented versus the amount of toxic metal stored in the tissues is important, and has been clearly detailed in animal trials. A molar ratio of 6-8:1 (ALA:mercury) is necessary for protection and viability in mercury studies; a ratio of 2:3 has been seen in arsenic studies. (66) The ability of ALA to assist or prevent movement of heavy metals from the liver appears to be element-specific. In a previously mentioned study, the biliary release of methylmercury, cadmium, zinc, and copper was inhibited by ALA. (69)

The evidence that ALA may mobilize heavy metals to other tissues from tissues where the metals are most concentrated, specifically the brain, is troublesome. An explanation for this finding may lie in the complexing of heavy metals with glutathione and lipoic acid. Inorganic mercury forms stable complexes with ALA or DHLA and could be excreted with DHLA independent of available glutathione. (67) As Gregus et al (67) hypothesize, injected lipoic acid could complex with glutathione as it passes through the liver, preventing glutathione from carrying other heavy metals such as cadmium, or transition metals such as zinc and copper, into bile. Speculation aside, there is clear evidence ALA and its reduced form DHLA have the ability to act as both intra- and extracellular heavy metal-complexing agents, with little known toxicity and patterns of heavy metal mobilization and transport not yet understood in humans. In the absence of data from human trials, however, it can only be suggested that ALA be used as an adjunct to chelation with the standard dithiols, DMPS and DMSA.

Mercury toxicity is a significant clinical entity, as it is ubiquitous in the environment and poses serious risk to human health. The pathology of mercury toxicity in humans is diverse and encompasses direct damage to tissues and enzyme function as well as indirect damage as a result of oxidant stress.

Glutathione has been shown to be a significant factor in heavy metal mobilization and excretion, specifically with application to mercury, cadmium, and arsenic. Glutathione depletion and glutathione supplementation have specific effects on mercury toxicity, both by altering antioxidant status in the body and by directly affecting excretion of mercury and other heavy metals in the bile.

Lipoic acid has been shown, by its increasing of cellular glutathione levels, to support the mobilization and excretion of mercury, and to decrease cellular damage and neurotoxicity. The reduced form of ALA, DHLA, appears to have direct heavy metal-binding effects. When compared to pharmaceutical dithiol-chelating agents, ALA appears to be able to bind and mobilize heavy metals from tissue, although with much weaker an effect.

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Lyn Patrick. ND--1984 graduate, Bastyr University; associate editor, *Alternative Medicine Review*; private practice, Tucson, Arizona, 1984-2002.

Correspondence address: 21415 Hwy 140, Hesperus, CO 81326 Email:
lpatrick@frontier.net

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