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Mini-review: toxicity of mercury as a consequence of enzyme alteration

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Abstract Mercury, in both its elemental and bonded states, is noted for its negative effects on biological organisms. Recent anthropogenic and environmental disasters have spurred numerous comparative studies. These studies attempted to detail the biochemical implications of mercury ingestion, in low, persistent concentrations as well as elevated acute dosages. The studies propose models for mercuric action on healthy cells; which is centered on the element's disruption of key enzymatic processes at deposition sites. Mercury's high affinity for the sulfhydryl moieties of enzyme catalytic sites is a common motif for enzyme inactivation. These permanent covalent modifications inactivate the enzyme, thereby inducing devastating effects on an organism's metabolic functions. Mercury has been shown to be highly nonspecific in its binding to sulfhydryl moieties, and highly varied in terms of how it is encountered by living organisms. This review focuses on mercury's effects on a wide swath of enzymes, with emphasis on how these alterations deleteriously affect several metabolic pathways.

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Introduction

Mercury as an element remains closely associated with its toxicity to living organisms, particularly mammals. Research on mercury typically delves into its negative effects on the development and function of the subject's various biological systems. Efforts have been put forth to create well-rounded comparative studies for symptoms of mercury toxicity in humans (Bernhoft 2011). Mercury's toxicity is generally not restricted to a specific structure within the host body. Rather than affecting a singular mechanism or structure, mercury's toxicity is highly varied, depending on both the chemical structure of the ingested mercury and its route of exposure (Bernhoft 2011). This increased variability in chemical structure, routes of exposure, and mercury's concentration upon exposure leads to a grand multitude of affected targets, including, but not limited to vascular, neuronal, and adipose cells (Alnuaimi et al. 2012; Azevedo et al. 2012).

Many biochemical reactions that sustain life are made possible via the action of enzymatic proteins. For example, enzymatic dysfunction by mercury exposure has ties with metabolic syndrome (MetS) in humans (Tinkov et al. 2015). Likewise, research into

the degenerative effects of mercury exposure has highlighted the importance of understanding the primary enzymatic proteins affected in the process. Dysfunction of these complex and highly regulated biochemical systems may explain many of the negative symptoms of mercury poisoning (Bernhoft 2011; Hong et al. 2013; Tinkov et al. 2015). The goal of this review is twofold: (1) to present known symptoms of mercury exposure in humans as they correlate with enzyme dysfunction and (2) to provide details on the action of mercury on enzymatic pathways at the molecular level. Tracing the route of mercury toxicity from enzyme dysfunction to the eventual symptoms would greatly benefit future biomedical research. Each of the enzymatic pathways listed and discussed in this review could provide insights for potential treatments that target the dysfunction at its source.

Mercury: forms and sources

Mercury in the environment exists in a multitude of physical and chemical states, ranging from liquid (elemental mercury), solid (mercuric salts, mercury moieties within organic compounds) to gaseous (mercury vapor) states (Azevedo et al. 2012; Bernhoft 2011). The physical state of mercury correlates directly with its source within the environment. While mercury is only a small component within the earth's crust (0.5 ppm), it is typically found within biological organisms as the distinct result of bioaccumulation. Bioaccumulation is a process that describes the ascension and accumulation of mercurial compounds from one species to another (Vassallo et al. 2011). Gaseous mercury (Hg°) typically arises from split (outgassed) rocks and volcanic activity, the products of which eventually settle from the atmosphere into aqueous environments. This leads to the production of organic mercury compounds (methyl-, ethyl-mercury) which are then bioaccumulated by the surrounding wildlife (Bernhoft 2011). Methylmercury (MeHg) has been reported as the leading mercurial species found in fish tissue (Yachiguchi et al. 2014). Mercury contamination typically arises from industrial processes, including the mining and utilization of coal, the production of batteries, and the production of unregulated skin treatment e.g. in homeopathic remedies (Bernhoft 2011; Orct et al. 2015).

General symptoms

In humans, the general symptoms of mercury depend on the chemical form of mercury and the method of exposure. Mercury's physiochemical properties make it a potent indirect inducer of oxidative stress in biological systems (Orct et al. 2015; Tinkov et al. 2015). Mercury's ability to readily form complexes with sulfur, thiol, and nitrogen containing ligands has been implicated in the indirect production of reactive oxygen species (ROS) by means of enzyme depletion/inactivation (Tinkov et al. 2015). Hyperaccumulation of ROS's can result in a host of symptoms ranging from organ and cardiovascular damage, to high blood pressure and metabolic syndrome (Tinkov et al. 2015; Yachiguchi et al. 2014).

On the other hand, inorganic mercury, typically in the form of vaporous mercury, tends to cause chemical alterations to the tertiary and quaternary structures of proteins. These chemical alterations are due to the element's affinity for sulfhydryl/selenohydryl groups (Bernhoft 2011). Mercury's competitive binding to Zn^{2+} and Mg^{2+} dependent enzymes, inhibition of specific marker enzymes, and alterations of the concentration of essential elements in the body have also been reported (Bapu et al. 2002). Mercurial salts (particularly $HgCl_2$) exist as a known form of consumed mercury (Azevedo et al. 2012; Bernhoft 2011). Mercury chlorides are noted for targeting the gastrointestinal tracts and kidney's, leading to symptoms ranging from ambiguous abdominal pain, to bloody diarrhea caused by mercury induced necrosis of gut tissue (Bernhoft 2011). Mercury does not remain static once it enters a biological organism. In the case of mammals, it is actively transported and chemically interconverted between multiple reactive forms, each of which displays different targets and symptoms once deposited (Tinkov et al. 2015). Mercury alters enzyme functionality (either inactivating or stimulating the enzyme), which leads to dramatic changes in metabolic processes. Table 1 provides a summary of the enzymes discussed within this review and the effects of mercury on these enzymes.

Effects on central nervous system (CNS) enzymes and other CNS functions

Methylmercury's propensity for causing neurodegenerative diseases can be correlated to its ability to raise the

Table 1 The effects of mercury on several key enzymes

Enzyme	Function	Effect of mercury	Citation
Paraoxonase	LDL oxidation	Inactivation by ROS production	Azevedo et al. (2012)
Glutathione peroxidase	Antioxidant	Inactivation by ROS production	Azevedo et al. (2012)
Phospholipase D	COX-1, COX-2 functionality	Inactivation by ROS production Covalent modification induced inactivation	Vassallo et al. (2011)
Epoxygenase/hydroxylase	Arachidonic acid metabolism	Oxidative stress induced alterations to gene expression levels	Amara et al. (2014)
Alkaline phosphatase	Bacterial phosphorus recycling	Direct covalent modification induced inactivation	Alnuaimi et al. (2012)
Fumarase	Dehydration reactions of tca cycle	Denaturing protein's active site	Xu and Imlay (2012)
Lipoxygenase	Lipid metabolism/ peroxidation	Overstimulation by ROS production	Chen et al. 2012
ATPase	ATP hydrolysis	Direct covalent modification induced inactivation	Vassallo et al. (2011)
Oxide synthase	No production	Overstimulation in low dosages, Inactivation at high dosages	Omanwar et al. (2013); Vassallo et al. (2011); Wiggers et al. (2008)
Mitogen activated protein kinases	Signal transduction/ immune response	Inactivation by ROS production	Haase et al. (2010)
Rhodanese, 3-mercaptopyruvate sulfur transferase	Cysteine metabolism	Direct covalent modification	Sura et al. (2011)
Sulfur transferase	Cysteine metabolism	Induced inactivation by ROS production	Sura et al. (2011)

levels of reactive free radicals (O^{2-}) within the central nervous system (CNS). Incubation of astrocytes in the presence of methylmercury has been shown to result in hydrogen peroxide, superoxide anion, and peroxynitrite hyperproduction (Tinkov et al. 2015). These free radicals expose central nervous system enzymes to a certain degree of oxidative stress, inhibiting their function (Azevedo et al. 2012). Noted CNS enzymes affected by mercury are: alkaline phosphatase, acid phosphatase, alpha mannosidase, and succinic dehydrogenase. The activity of all of these decreased in the presence of mercury (Bapu et al. 2002).

Aside from inhibiting CNS enzymes, methyl mercury inhibits the construction of neurons via inhibition of microtubule organization. Mercury-associated neuropathology, in the presence of methylmercury chloride, has also been reported. This is characterized by a complete architectural disruption of neuronal elements within the cerebellum, due to mercury's strong binding to protein and sulfhydryl groups (Bapu et al. 2002). Cell signal receptors are also affected, with methylmercury interfering with muscarinic, nicotinic, and dopaminergic receptors. Neuronal activity is further impeded by methylmercury's blockage of Ca^{2+} channels within the neurons. In mice, the blockage of adequate neuronal tubulin formation, action potential, and enzyme activity led to deficient neuron development, severely impeding the mice's motor and mnemonic functions (Azevedo et al. 2012). In humans, methylmercury can result in ataxia, paresthesias and dysarthria via the damage it induces to the nervous system (Bjorklund 2015). On the other hand, the mechanism of action involving mercury and Alzheimer's disease has been shown to involve the reduced enzymatic activity of neprilysin (Chin-Chan et al. 2015). Neprilysin, a metalloprotease, has been noted as the major peptidase in amyloid beta-degradation. Incubation of purified neprilysin with mercury at a 20 μM concentration elicited a decrease in its enzymatic activity, which suggests protein oxidation due to mercury's oxidative character (Chin-Chan et al. 2015).

Effects on vascular enzymes' activities

Mercury's affinity for sulfhydride functional groups leads to the deactivation of several key enzymatic proteins within the vascular system (Vassallo et al. 2011; Wiggers et al. 2008). These mercury-sulfhydryl condensations can inhibit ATP hydrolysis within vascular cells via direct inhibition of Na^+/K^+-ATPase and Ca^{2+}-ATPase enzymes (Vassallo et al. 2011). Inorganic mercury ($HgCl_2$) has noted effects on the enzymatic mechanisms influencing the constriction of vascular endothelial cells (Omanwar et al. 2013; Vassallo et al. 2011; Wiggers et al. 2008). Comparative studies on rat aortic contraction reveal the effects of mercury-induced nitric oxide (NO) inhibition on the enzymatic activity of the endothelial nitric oxide synthase (NOS) pathway (Omanwar et al. 2013). $HgCl_2$-treated erythrocytes have likewise been reported to induce a decrease in endothelial NOS activity as well (Harisa et al. 2013). These decreases in NO biosynthesis are associated with oxidative stress, which can be induced by the presence of $HgCl_2$ (Omanwar et al. 2013; Harisa et al. 2013).

Vasorelaxation and vasoconstriction are both dependent on the bioavailability of NO due to the oxides role in the stimulation of cyclic GMP (cGMP), the main mediator of intracellular calcium ion concentrations with vascular aortic endothelial tissue (Vassallo et al. 2011). Vasorelaxation/constriction dysfunction arises as biphasic consequences of $HgCl_2$ exposure at low and high dosages respectively (Omanwar et al. 2013). NOS, the enzyme responsible for the biological catalysis of NO from metabolic intermediates (L-arginine), is the primary enzyme affected by $HgCl_2$, and the primary cause behind endothelial vascular dysfunction (Omanwar et al. 2013; Vassallo et al. 2011; Wiggers et al. 2008). In all three studies, persistent dosages of low concentration mercuric chloride lead to a stimulation of NOS, resulting in a sharp increase of bioavailable NO. This triggered a signaling cascade where the increased NO lead to increased synthesis of cGMP, culminating in an increased evacuation of Ca^{2+} ions from the endothelial cytosol. This signaling cascade produced uncontrollable vasorelaxation in analyzed specimens. In contrast, persistent high dose specimens experienced competitive inhibition of NOS caused by reactive oxidative species (free oxygen radicals) produced by the high concentrations of mercuric chloride. The sudden reduction in available cGMP caused an influx of calcium ions into the cytosol, resulting in the constriction of the surrounding smooth muscle tissue, leading to uncontrolled endothelial constriction. Exposure to lower concentrations of mercury (0.7 μg/kg for 30 days) resulted in an increase of phenylephrine production. Likewise, concentrations of acetylcholine were found to decrease after the 30 days of exposure, leading to a reduction in vasodilation mediated by the neurotransmitter. The increased production of phenylephrine (a vasoconstrictor) and reduction in acetylcholine (a vasodilator) resulted in increased vasoconstriction.

Effects on cardiovascular enzymes' activities

Inorganic mercury's damage to the body's vascular structures continues with its effects on the cardiovascular system. In particular, high doses of inorganic mercury inhibit the function of the cardiovascular enzyme paraoxonase (Azevedo et al. 2012). Paraoxonase, in its fully functioning state, is involved in the oxidation of low-density lipoproteins (LDL), the primary carriers of cholesterol within the cardiovascular system (Azevedo et al. 2012; Kawakami et al. 2011). The high free radical production caused by $HgCl_2$ induced the inhibition of antioxidant enzymes e.g. glutathione peroxidase which leads to decreased functionality of paraoxonase (Azevedo et al. 2012). Accumulation of unoxidized LDL within the arteries typically leads to increased arterial blood pressure and thus results to hypertension and myocardial infarction.

Organic mercury, such as methyl-mercury (MeHg) can further stress the cardiovascular system via its induction of phospholipase D (PLP-D). MeHg affects PLP-D in one of two ways: by oxidative stress via a production of free radicals, and via thioredoxin alterations via reactions with PLP-D functional groups. PLP-D facilitates the formation of COX 1-catalyzed eicosanoids and COX-2 catalyzed prostanoids, two series of molecules with noted contractile effects on cardiovascular tissue (Azevedo et al. 2012; Vassallo et al. 2011). In human patients diagnosed with elevated mercury levels following several years of cigarette use, systolic and diastolic blood pressure were found to be in direct correlation to mercury levels accumulated in hair strands. A lipid profile revealed an increased level of plasma triglycerides, and LDL cholesterol relative to similarly aged non-smokers

(Hong et al. 2013). Mercury further damages cardiovascular tissue by altering the expression of key cardiac cytochrome enzymes, primarily those in the epoxygenase and hydroxylase families. Epoxygenase and hydroxylase are directly involved in the formation of arachidonic acid. Mercury ions actively decrease the ratio of epoxygenase to hydroxylase reactions within the cardiac muscle, leading to cardiotoxicity if left untreated (Amara et al. 2014).

Effects on adipose tissue enzymes' mRNA expressions

In mammalian species, white adipose tissue (WAT) serves dual functions. Aside from its role as an energy store, WAT cells are necessary for the maintenance of homeostasis via the production of the bioactive adipokines. These adipokines (primarily adiponectin, leptin and resistin) aid in the modulation of insulin secretion and insulin signal resistance. The adipokines, along with hormones like glucagon and epinephrine, are critical to functional lipid metabolism. In mice fed with a high fat diet supplemented with daily $HgCl_2$ injections, WAT cells were shown to decrease in size and functionality as the metal accumulated within the cells. Over time, a marked decrease in blood glucose levels arose as plasma insulin levels decreased. As accumulated $HgCl_2$ reduced the size of WAT cells, it also decreased the mRNA expression of AMPKα1-2; two important enzyme isoforms that regulate energy balance within mice, and as a result, determine the mass of accumulated adipocyte tissue. The reduction in WAT cell size was theorized to be caused by an increase in the base size of the smallest WAT cells, which differentiated at a much faster rate than their larger counterparts. This increase in small WAT cell size was correlated with reduced PPARy (adipocyte differentiation suppressor) mRNA expression levels. $HgCl_2$ affected the genetic expression of other genes necessary in lipid metabolism, primarily causing a decrease in FAT/CD36 mRNA transcription (Kawakami et al. 2011).

Effects of mercury on some biological functions

Tinkov et al. (2015)'s review provides an excellent compendium of the underlying effects of mercury accumulation culminating in symptoms commonly associated with *metabolic syndrome*. These symptoms include obesity, hypertension, organ damage, insulin damage and endoplasmic reticulum stress. Tinkov et al. (2015) study noted a 70 % difference in mercury hair levels between healthy patients and those suffering from metabolic syndrome as evidence of a correlation between mercury and metabolic syndrome. Their studies demonstrated mercury's ability to induce extensive lipid peroxidation as well as the production of mitochondrial ROS via the suppression of antioxidant biomolecules and the enzymes. More specifically, mercury induced hypertension is theorized to arise from mercury's activation of the renin-angiotensin aldosterone system (RAAS). In addition, Tinkov et al. (2015) noted that methylmercury may be capable of inducing insulin resistance via alterations to β-cell functionality. Methylmercury also causes a disruption of glucose homeostasis, which may indirectly play a role in exacerbating metabolic syndrome induced obesity.

Kinase mediated phosphorylation/dephosphorylation reactions typically culminate in activated signal transduction across the organism's immune system (Haase et al. 2010). Inorganic mercury ions trigger *inhibition of mitogen activated protein kinases* (MAPKs). This is particularly damaging as MAPKs are the prime regulators of T cell function (Haase et al. 2010). Initial binding of mercury to purified MAPKs showed no loss of enzyme functionality by means of covalent modification to the active sulfhydryl moiety of MAPK. Inactivation occurred as prolonged exposure to mercury ion triggered the formation reactive oxygen species (ROS) mediated cascades within the cell. ROS induces a release of cellular zinc ions, which, in conjunction to ROS oxidizes the MAPK and renders it permanently inactive (Haase et al. 2010). On the other hand, comparative studies performed on the frog species *Xenopus laevis* show that inorganic mercury chloride affects *metabolism of cysteine* within the heart muscle, brain, liver, kidneys, skeletal muscle, and testes. $HgCl_2$ ions affect rhodanese, 3-mercaptopyruvate sulfurtransferase (MPST) and γ-crystathionase (Sura et al. 2011). $HgCl_2$ ions can readily bind to these enzymes' functional sulfhydride groups, leading to a reduction in their substrate reactivity. In the liver, $HgCl_2$ negatively affected glutathione biosynthesis, along with rhodanese activity. In addition, generation of free radical species by $HgCl_2$ via a decrease in reduced glutathione activity, blocks the function of the sulfur transferase via

interactions with its reactive sulfhydride groups (Sura et al. 2011).

Analysis of mouse leg muscle extracts incubated with varying levels of $Hg(NO_3)_2$ (0–10 μM) revealed a decrease in the expected levels of NADH despite the seemingly unaltered concentrations of two skeletal muscle glycolysis metabolites, glucose-6-phosphate and fructose-6-phosphate. Sequential decreases in $Hg(NO_3)_2$ concentrations within muscle extracts did not result in an increase of hexokinase (HK, involved in the synthesis of glucose-6-phosphate) and phosphofructokinase (PFK, involved in the synthesis of fructose-6-phosphate) as would be assumed. The levels of enzymatic activity remained constant following the high-to-low model of treatments. Such a phenomenon is indicative of permanent inhibition, as the levels of enzymatic activity fail to return to normal as the inhibitor is removed from the sample. In addition, experimental results of incubating HK and PFK in concentration-specific mercury showed that product (glucose-6-phosphate and fructose-6-phosphate) concentrations remained constant. These results suggest that at low pollutant concentrations, the effects of mercury, and perhaps other heavy metals, is silent at the metabolite concentration level, with the turnover rate of the enzyme shaping the heavy metal's long-term effects (Ramirez-Bajo et al. 2014).

Similar to mercury's effects on vascular, neuronal, and WAT enzymes, mercury inhibits reactivity via its association with the cysteine residues of both HK and PFK (Azevedo et al. 2012; Kawakami et al. 2011; Ramirez-Bajo et al. 2014; Vassallo et al. 2011). Inhibition of these enzymes occurs by disrupting their stability, as in the case of hexokinase, or their ability to bind to ATP, as in the case of phosphofructokinase (Ramirez-Bajo et al. 2014). HK and PFK's inhibition in the presence of mercury was compared to glyceraldehyde phosphate isomerase (GPI) and aldolase (ALD), which lacked cysteine residues; experiment results showed that no inhibition was present in the latter enzymes, attributed to their lack of cysteine residues (Ramirez-Bajo et al. 2014). Mercury, both organic and inorganic, displayed similar inhibitory effects in glycogen phosphorylase (GP). The inactivation of GP comes about via irreversible mercury-thiol bond formation between the catalytic binding site of glycogen phosphorylase and the introduced mercuric ion (Xu et al. 2013). Inhibition was noted as being dose dependent and in direct relation to concentrations of mercury ions (0–0.8 μm). Cumulatively, the inhibition of glycolytic enzymes exhibits a marked increase in metabolic malfunction and muscle tissue disorders leading to a loss of functionality within the organism (Xu et al. 2013).

Mercuric interactions with selenium

Selenium (Se) has been at the forefront of biomedical research dealing with the treatment of mercury poisoning (Bjørklund 2015). Selenium's interactions with mercury (particularly methylmercury) have been extensively studied (Ralston and Raymond 2010; Bjørklund 2015). Selenide forms very stable metal complexes with a range of metals (Bjørklund 2015). Selenium reacts readily with methylmercury, and can thus function similarly to other known metal-chelating compounds (Bjorklund 2015). Complexation with selenium renders methylmercury relatively inert, removing it from the biochemical milieu before it can interact with the moieties of proteins (Bjorklund 2015; Ralston and Raymond 2010). Selenium-mercury compounds are inert within the organism, with a solubility product of 10^{-64}. HgSe is totally insoluble in living organisms and can thus be more easily targeted for removal (Bjørklund 2015; Li et al. 2014).

Methylmercury was shown to have an adverse effect on the immune system of Balb/c mice. Mice subjected to high dosages of mercury in their drinking water experienced a marked decrease in the proliferation of T and B lymphocytes, two cells critical for adequate immune response. This decrease was found to be solely dose dependent. Increased levels of mercury lead to the inhibition of natural killer cell activity, eventually rendering the mice's immune response ineffective (Li et al. 2014). Following treatments of pure mercury in water, researchers fed the mice water contaminated with selenium at varying concentrations. At low selenium concentrations, researchers noted a promotion of immune-cell activity. At high concentrations, these same activities were inhibited. Selenium was then incorporated into the mercury contaminated water, at varying ratios relative the concentration of mercury. When in conjunction, selenium demonstrated a protective effect, reducing the general effectiveness of mercury's inhibition on T/B lymphocyte proliferation. Dosages of selenium

greater than 0.03 mM induced immunotoxic effects within the mice, leading researchers to conclude that that protective range of selenium is limited to a molar ration of 1:1 relative to mercury (Li et al. 2014). Selenite converts similar mercury ion sequestration and has been shown to restore function to mercury inactivated enzymes (Carvalho et al. 2011). A concentration of 5 μM of selenite, in conjunction with NADPH, was shown to remove mercury ions via the formation of a mercury-selenide complex. In addition, the aforementioned concentration functioned in restoring catalytic activity to a mercury inhibited selenoenzyme thioredoxin reductase (Carvalho et al. 2011).

Conclusions

The biological damages caused by mercury toxicity are indeed numerous. Mercury causes major dysfunction in cellular function via its inhibition of enzymes and proteins. This dysfunction can be noted across a wide swath of living organisms, across an equally large scale of proteins. Due to its high affinity for cysteine moieties, the metal is quick to alter the tertiary and quaternary structures of most proteins it comes in contact with. The metal is a potent producer of reactive oxidizing free radicals, which can impede the functions of key vascular, adipocyte, and glycolytic enzymes via competitive inhibition. The closely interconnected nature of metabolic biochemical pathways insures that these inhibitions have a veritable domino effect on the biochemical well-being of an organism. The roles enzymes play in the maintenance of biochemical reactions within living organisms cannot be understated, and as such it is of great medicinal importance to study not only the visible symptoms of mercury toxicity, but also the enzymatic dysfunctions that eventually culminate in said visible symptoms. Improved understanding of the enzymes affected by mercury could potentially lead to new therapies for patients exhibiting chronic mercury toxicity.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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