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The Role of Mercury and Cadmium Heavy Metals in Vascular Disease, Hypertension, Coronary Heart Disease, and Myocardial Infarction

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INTRODUCTION

There is increasing concern regarding the overall health effects of exposure to various heavy metals in the environment. This is particularly true of mercury and less so with cadmium, lead, aluminum, and arsenic. The cardiovascular consequences of mercury and cadmium toxicity have not been carefully evaluated until recently. This paper will critically review the vascular consequences of mercury and cadmium toxicity in humans as it relates to hypertension, generalized atherosclerosis, coronary heart disease (CHD), myocardial infarction (MI), cerebrovascular accidents (CVA), carotid artery disease, renal dysfunction, and total mortality.

MERCURY

Types of Mercury

Mercury exists in 3 basic forms: elemental, inorganic, and organic (Table 1).[1-5] Dental amalgams are the most common source for elemental mercury vapor, which is a stable monoatomic gas. Inorganic mercury, which is a divalent compound, is the toxic species found in human tissue after conversion from the other forms. Organic mercury in the form of methyl and ethyl mercury is primarily from fish, sea mammals, and thimerosal vaccines. Although dental amalgams historically have been the major source of human exposure, fish and sea mammals are becoming an increasingly important environmental source of potential mercury toxicity.[6-9]

TABLE 1 Mercury Types[1-4,44]

1. Elemental	Mercury vapor (Hg°) Stable monoatomic Gas	Dental amalgams
2. Inorganic	Divalent mercury (Hg^{2+})	Toxic species in human tissue after conversion
3. Organic	Methyl mercury (CH_3Hg+) Ethyl mercury (CH_3CH_3Hg+)	Fish, sea mammals Thimerosal vaccines

Mercury Biotransformation and Biomethylation

Mercury from various sources, including elemental mercury from earth sources or inhaled mercury vapor, methyl and ethyl mercury, is converted by biomethylation to inorganic divalent mercury, the toxic form in human organs and tissues (Figure 1).[10] Divalent mercury is soluble and stable in water and undergoes biomethylation to methyl mercury, which is found in high concentrations in certain fish and sea mammals.

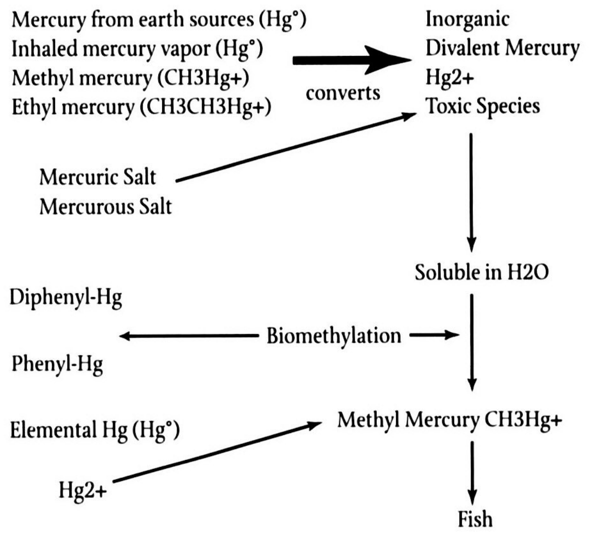

FIGURE 1 Mercury Biotransformation and Biomethylation

The Environmental Protection Agency has determined the safe daily intake of mercury to be less than 0.1 µg/kg/day (about 7 µg/day for a 154 lb person).[11] It is estimated that 1 dental amalgam filling releases about 3-17 µgs of mercury vapor per day. The typical amalgam is composed of 50% mercury, 25% silver, 25% tin, copper, and nickel.[12-14] Fish and sea mammals provide about 2-3 µg per day depending on the type and amount consumed.[15-18] The long-lived, large predatory fish such as swordfish, tilefish, shark, and king mackerel contain about 1 µg of methyl mercury per gram. Pike, whale, bass, tuna, and trout contain about 0.1-0.5 µg of mercury per gram. Nine vaccines containing thimerosal (now off the US market) would give an estimated exposure of 62 µg of organic mercury.[19-22] All other sources of mercury provide about 0.3 µg per day.[23-26]

Important Facts about Mercury

Mercury is the most dangerous of all the heavy metals.[27] It will modify the distribution and retention of other heavy metals.[28-30] Mercury has no known physiological role in human metabolism, and the human body has no mechanisms to excrete mercury actively.[31] Mercury, thus, accumulates during life so that the average 70 kg person has a total body burden of about 13 mg of mercury.[32] Mercury has a high affinity for sulfhydryl groups (-SH), various enzymes and amino acids, N-acetylcysteine (NAC), alpha lipoic acid (ALA), and glutathione (GSH), which provide about 10-50% of the plasma protein antioxidant capacity.[33-35] Lower availability of these antioxidants reduces oxidant defense and increases oxidative stress. Selenium antagonizes some of the adverse effects of mercury by forming a seleno-mercury complex in tissue that is less toxic.[36-43]

Physiological Basis of Mercury Toxicity

Mercury induces mitochondrial dysfunction and oxidative stress.[44-46] The primary mitochondrial dysfunction occurs at the ubiquinone-cytochrome B region and with NADH dehydrogenase causing displacement of Fe++ and Cu+ ions in the a3Cub center of cytochrome C (Figure 2). This results in depolarization and auto-oxidation of the inner mitochondrial membrane with lipid peroxidation and severe mitochondrial dysfunction. Physiologic consequences include increased hydrogen peroxide, depletion of mitochondrial glutathione by over 50%, increased lipid peroxidation markers, such as TBARS, by over 70%, oxidation of pyridine nucleotides, such as NAD(p)H, and altered calcium homeostasis.[47-49] This severe mitochondrial dysfunction increases oxidative stress and reduces antioxidant defenses, creating significant health implications.

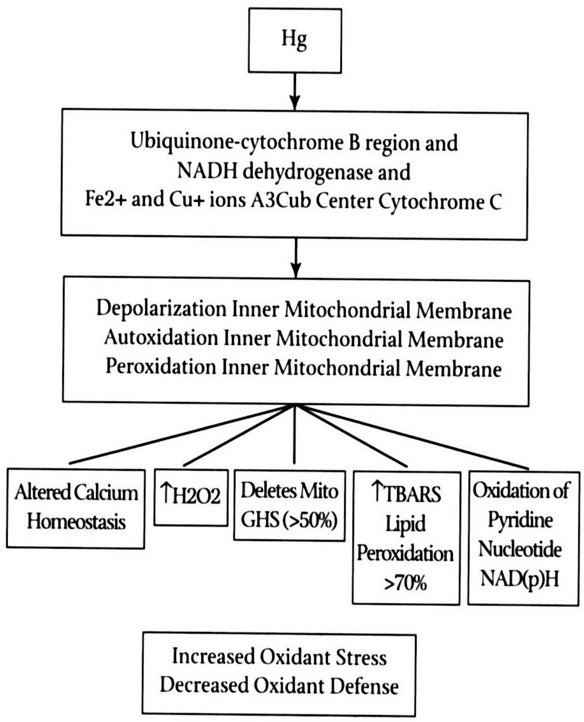

FIGURE 2 Pathophysiologic Basis of Mercury Toxicity, Mitochondrial Dysfunction and Oxidative Stress

The primary 3 sources of mercury-induced lipid peroxidation include the Fenton reaction, affinity for sulfhydryl groups, and selenium deficiency.[50] Mercury serves as a direct catalyst in Fenton-type reactions and as an indirect catalyst via iron stimulation, which increases the production of radical oxygen species and superoxide anion.[51] Mercury's high affinity for sulfhydryl groups (-SH), such as glutathione, NAC, and ALA, which comprise much of the antioxidant capacity of plasma, reduces both membrane and plasma antioxidant defense. Finally, the formation of insoluble complexes of mercury with selenium reduces selenium availability, which is a necessary cofactor for glutathione peroxidase (GPx) activity to break down hydrogen peroxides and various other toxic peroxidation products. Thus, plasma and intracellular antioxidant capacity is reduced.[52]

Vascular Biological Effects of Mercury

Numerous toxic effects of mercury have been demonstrated in vitro and in both animal and human studies (Table 2 provides details with references, and Table 3 provides a summary).

Studies find that mercury:

- Increases free radical production[53-60]
- Inactivates antioxidant defenses[61-63]
- Binds to thiol-containing molecules[64-68]
- Binds to selenium, forming seleno-mercury complexes that reduce selenium availability for GPx activity[69-73]
- Inactivates glutathione, catalase, and superoxide dismutase[74-77]
- Increases lipid peroxidation[78-81]
- Increases oxidation of LDL (oxLDL)
- Increases plasma oxLDL complexes[82]

TABLE 2 Vascular Biologic Effects of Mercury

1. Increases free radical production[53-60]
2. Inactivates antioxidant defenses[53-55]
3. Binds to thiol-containing molecules[53-55,67,68]
4. Binds to Se, forming Se-Hg complex-mercury selenide, which decreases Se available for cofactor with GPx[53-55]
5. Inactivates glutathione, catalase, and SOD[74-77]
6. Increases lipid peroxidation in all organs[78-81]
7. Increases oxLDL27 and oxLDL immune complexes[27]
8. Increases platelet aggregation[83]
9. Increases coagulation/thrombosis: increases Factor VIII PF4 and thrombin and reduces protein C[85,86]
10. Inhibits endothelial cell formation and migration[87]
11. Increases apoptosis[88]
12. Reduces monocyte function and phagocytosis[88]
    - Immune function is impaired
13. Increases inflammation[88]

TABLE 3 Summary of Vascular Biologic Effects of Mercury

1. Oxidative stress
2. Inflammation
3. Thrombosis
4. Vascular smooth muscle (VSM) proliferation and migration
5. Endothelial dysfunction
6. Dyslipidemia (oxHDL and paraoxonase)
7. Immune dysfunction
8. Mitochondrial dysfunction

Thrombosis is potentiated by increased platelet aggregation[83] and by increases in Factor VIII, platelet factor,[84] and thrombin, with reductions in protein C.[85,86] Endothelial cell formation and migration are reduced, which decreases vascular endothelial repair, decreases nitric oxide, and causes endothelial dysfunction.[87] Apoptosis is increased,[88] monocyte function and phagocytosis are impaired,[89] immune function is reduced,[90] and vascular inflammation is increased.[91] There is an increased production and release of superoxide anion from human neutrophils and monocytes,[92,93] depolarization of the inner mitochondrial membrane with severe mitochondrial dysfunction,[94-96] and disruption of plasma membrane lipid integrity by translocation of phosphatidyl serine (PS).[97] Finally, mercury stimulates proliferation of vascular smooth muscle cells[98] and inactivates paraoxonase, an extracellular antioxidative enzyme related to HDL, CHD, and MI risk.[99,100]

In summary, the overall vascular effects of mercury include oxidative stress, inflammation, thrombosis, VSM proliferation and migration, endothelial dysfunction, dyslipidemia, immune dysfunction, and mitochondrial dysfunction. All of these functional abnormalities have the potential to increase the risk for hypertension and vascular disease.

Clinical Vascular Consequences of Mercury Toxicity

The clinical consequences of mercury toxicity include hypertension,[101-104] CHD,[105-107] MI,[108-110] increase in carotid intimal medial thickness (IMT) and carotid obstruction,[111] CVA,[112] generalized atherosclerosis,[113] renal dysfunction and proteinuria,[114] and an overall increase in total mortality.[115]

Coronary Heart Disease and Myocardial Infarction

In rabbits exposed to inhaled mercury vapor, the cardiovascular and cardiac pathology included bradycardia, thrombosis in small and medium caliber arteries, focal necrosis with thickening of the endocardium of the perivalvular regions, papillary muscles and valves, and endothelial proliferation with inflammatory foci and focal edema, endothelial proliferation, inflammation, and fibrosis of the ascending aorta.[116]

In a case control study in 9 counties of 684 men with their first MI, there was a significant association of toenail mercury content, adipose tissue DHA, and first MI.[117] There was a 15% higher toenail mercury content as assessed by neutron activation analysis (NAA) in the men with their first MI compared to the control group (95% CI; 5-25%). The risk-adjusted OR for MI was 2.16 in the highest vs the lowest quintile (P=.006, 95% CI; 1.09-4.29). The adipose DHA was directly proportional to the mercury toenail content (P<.001) and the DHA content was inversely correlated to MI with an OR of 0.59 in the highest versus the lowest quintile (P=.02, 95% CI; 0.30-1.19). This important study concluded that there exists a positive, monotonic increase in the risk of MI with mercury toenail content above the 0.25 µg/g level, which was even steeper when adjusted for the DHA adipose tissue content. Mercury diminishes the cardiovascular protection of fish consumption. Another study substantiated these results—the highest quartile of DHA with the lowest quartile of mercury was associated with a 67% reduction in CHD (P<.016).[118]

In another large, nested case control study of 33,733 male healthcare professionals between the ages of 40-75 years (Health Professionals Follow-Up Study), no association between mercury toenail content assessed by NAA and CHD was found.[119] However, if dentists were excluded, there was a nonsignificant correlation of toenail mercury and CHD. Also, subjects with the highest tertile of mercury and the lowest serum selenium level had a significant increase in CHD.

Other human studies have shown mixed results.[120-124] One study of mercury miners showed no relationship between CHD and mercury levels.[125] However, another study of European mercury miners showed a significant relationship between mercury exposure and total mortality (increase 8%), hypertension (increase 46%), CHD (increase 36%), renal disease (increase 55%), and CVA (increase 36%).[126] A Finnish study found a significant relationship between hair mercury, 24-hour urine mercury, and cardiovascular events.[127] In patients with hair mercury in the highest tertile (over 2 µg/g) and increased 24-hour urinary mercury, CHD and MI risk was increased 2-fold (P=.005), cardiovascular death increased by 2.9 times (P=.014) and circulating oxLDL and immune complexes to oxLDL increased significantly. The Gothenburg Study showed no relationship between serum mercury content and the number of amalgam fillings and CHD or MI.[128]

Carotid Atherosclerosis

High hair mercury content correlates with increased carotid IMT and carotid atherosclerosis.[129] A study of 1,014 men between the ages of 42-60 years found an increase in mean carotid IMT over 4 years (P=.0007). Each increase of 1 µg in hair content equaled an 8 µmol increase in carotid IMT, a 7.3% increase over the mean. There was a 0.042 mm/4-year difference in the highest quintile versus the lowest quintile, which correlated to a 32% greater increase (P<.05). In addition, mercury hair content was proportional to blood pressure, fibrinogen levels, waist-hip ratio, and low HDL cholesterol; all were significant at P=.0002.

Hypertension

The association of mercury toxicity and hypertension in humans is convincing.[130-133] Mercury miners were found to have significant increases in systolic blood pressure (P<.01) that correlated with lipid peroxidation and overall oxidative stress (P<.01).[134] European mercury miners had a 46% greater incidence of hypertension vs aged-matched controls. Other studies have shown significant correlations with hair mercury content, hypertension, and carotid IMT.[135]

In acute and probably chronic mercury intoxication, mercury binds to the sulfhydryl group S-adenosyl methionine (SAMe) and inactivates this enzyme, which is a necessary cofactor for catecholamine-O-methyl transferase (COMT), the enzyme needed to convert norepinephrine, epinephrine, and dopamine by methoxylation.[136] This results in a clinical syndrome that resembles a pheochromocytoma crisis with malignant hypertension in acute mercury intoxication and significant increases in urinary catecholamines in chronic mercury toxicity. This can be a very helpful clinical clue to mercury-induced hypertension. Mercury also induces renal dysfunction and proteinuria, which contribute to sodium retention and hypertension.[137-140] Studies have shown an increase in renal insufficiency in mercury miners of 55%.[141] Mercury concentrates in the renal tubules and glomerulus and results in proteinuria, fibrosis, and chronic renal insufficiency and dysfunction.[142,143]

CADMIUM

The role of cadmium in cardiovascular disease and hypertension is less convincing than that of mercury due to methodological flaws and study design in most of the published human studies.[144-151] Cadmium exposure is uncommon in most of the population unless there is oral consumption of polluted water or chronic inhalation exposure from cigarettes.[152] Twenty cigarettes will release about 30 µg of cadmium, of which 2-4 µg is actually inhaled.[153] The oral absorption of cadmium in tap water is 13-19% or about 2-4 µg per day.[154] Absorption of cadmium is increased in the presence of low dietary calcium, iron, and protein.[155] Cadmium concentrates in all organs, but mostly in kidney, liver, and pancreas, and has a half-life of over 30 years in renal tissue.[156]

Serum and urinary cadmium reflect recent exposure, but not total body burden.[157] Cadmium binds to metallothionein,[158] substitutes for zinc and copper in metalloenzymes,[159] and has a high affinity for sulfhydryl groups, similar to mercury.[160]

Animal studies show that cadmium toxicity causes aortic and coronary atherosclerosis, reduces cardiac output, alters the cardiac conduction system, reduces ATP, increases cholesterol and free fatty acids, increases blood pressure, and induces renal tubular dysfunction, proteinuria, and chronic renal insufficiency.[161-165] These effects are mitigated by calcium administration.

Human studies attempting to show a relationship between cadmium and cardiovascular disease or hypertension are subject to many methodological errors, so that accurate conclusions are difficult to draw.[166-168] In human autopsy studies, there is a poor correlation between renal cadmium content and hypertension.[169] In those studies where hypertension and cadmium coexist, the mechanisms include increases in urinary catecholamines, renal toxicity with proteinuria, sodium retention, increased intracellular calcium, and alteration in Na+/K+ ATPase.[170] Cadmium concentrates in the renal cortex and tubules and there reduces the expression of renal cortical CYP4A11.[171] CYP4A11 is involved in the hydroxylation of PUFA and affects sodium balance through 20 HETE. The combination of increased renal tubular sodium reabsorption, direct renal toxicity, and proteinuria increases the risk of hypertension.[172]

Cadmium also increases metallothinein in renal tubular cells and other tissues, which alters intracellular zinc.[173] This reduces zinc-dependent ligand binding to DNA and reduces PPAR expression, and may increase free fatty acids, lipids, glucose, and blood pressure. It is possible that some degree of insulin resistance occurs, which contributes to many of the associated metabolic disturbances noted above.

It is quite likely that chronic high exposure to cadmium in smokers, those drinking polluted water, and those with the CYP4A11 genetic alteration could have cadmium-induced hypertension and cardiovascular disease, but additional human studies are required to confirm this association.

SUMMARY

1. Mercury, cadmium, and other heavy metals have a high affinity for sulfhydryl (-SH) groups, inactivating numerous enzymatic reactions, amino acids, and sulfur-containing antioxidants (NAC, ALA, GSH), with subsequent decreased oxidant defense and increased oxidative stress. Both bind to metallothionein and substitute for zinc, copper, and other trace metals reducing the effectiveness of metalloenzymes.

2. Mercury induces mitochondrial dysfunction with reduction in ATP, depletion of glutathione, and increased lipid peroxidation; increased oxidative stress is common.

3. Selenium antagonizes mercury toxicity.

4. The overall vascular effects of mercury include oxidative stress, inflammation, thrombosis, vascular smooth muscle dysfunction, endothelial dysfunction, dyslipidemia, immune dysfunction, and mitochondrial dysfunction.

5. The clinical consequences of mercury toxicity include hypertension, CHD, MI, increased carotid IMT and obstruction, CVA, generalized atherosclerosis, and renal dysfunction with proteinuria. Pathological, biochemical, and functional medicine correlations are significant and logical.

6. Mercury diminishes the protective effect of fish and omega-3 fatty acids.

7. Mercury, cadmium, and other heavy metals inactivate COMT, which increases serum and urinary epinephrine, norepinephrine, and dopamine. This effect will increase blood pressure and may be a clinical clue to heavy metal toxicity.

8. Cadmium concentrates in the kidney, particularly inducing proteinuria and renal dysfunction; it is associated with hypertension, but less so with CHD. Renal cadmium reduces CYP4A11 and PPARs, which may be related to hypertension, sodium retention, glucose intolerance, dyslipidemia, and zinc deficiency. Dietary calcium may mitigate some of the toxicity of cadmium.

9. Heavy metal toxicity, especially mercury and cadmium, should be evaluated in any patient with hypertension, CHD, or other vascular disease. Specific testing for acute and chronic toxicity and total body burden using hair, toenail, urine, serum, etc. with baseline and provoked evaluation should be done.

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