
MERCURY IN MEDICINE AND HEALTH SERVICE

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Abstract

People are most often exposed to mercury in water, amalgam dental fillings, vaccines with ethylmercury as a preservative and in methylmercury containing fish. Foetuses and children are most susceptible to toxic mercury, which passes to their organisms through the placenta or with mother's milk.

Distribution of mercury in organs depends on the type of compound absorbed and duration of exposure. Mercury is mainly absorbed through the respiratory system.

There are two types of mercury poisoning: acute and chronic. The critical organs for acute poisoning with mercury vapour are the lungs. Acute poisoning develops when large amounts of mercury are inhaled, which may lead to acute bronchitis, bronchiolitis and pneumonia. Chronic exposure to mercury vapour primarily affects the central nervous system.

Mercury is considered as a contributing factor in aetiology of numerous disorders, including neurologic, renal, immunological, cardiologic, reproductive or even genetic abnormalities. Studies have demonstrated the correlation between mercury toxicity and pathogenesis of Alzheimer's or Parkinson's disease, autism and multiple sclerosis.

Mercury may be involved in four processes which lead to genotoxicity: generation of free radicals and oxidative stress, effects on microtubules and on DNA repair mechanisms as well as direct interaction with DNA molecules.

Keywords: mercury, methylmercury, ethylmercury, thiomersal, toxicity.

RĘĆ W MEDYCYNIE I LECZNICTWIE

Abstrakt

Człowiek najbardziej narażony jest na kontakt z rtęcią zawartą w wodzie, amalgamatach w plombach dentystycznych emitujących pary rtęci, szczepionkach z etylortęcią stosowaną jako środek konserwujący, metylortęcią w rybach.

Plód i dzieci są bardziej podatne na toksyczną rtęć. Matki spożywające w swojej diecie toksyczną rtęć mogą narazić na jej działanie swoje potomstwo, ponieważ rtęć może przechodzić przez barierę łożyskową lub z mlekiem matki do organizmu dziecka. Rozmieszczenie rtęci w narządach zależy od rodzaju związku wchłoniętego do organizmu i czasu trwania ekspozycji. Główną drogą wchłaniania tego metalu jest układ oddechowy.

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Można wyróżnić dwa rodzaje zatruc rтęcią: ostre i przewlekłe. Narządem krytycznym w zatruciach ostrych parami rтęci są płuca. Gdy do organizmu dostaje się duża ilość rтęci drogą oddechową, może rozwinąć się ostre zapalenie oskrzeli, oskrzelików i zapalenie płuc. Natomiast w przypadku przewlekłego narażenia na pary rтęci układem krytycznym jest ośrodkowy układ nerwowy. Ta postać choroby występuje w przypadku długotrwałego narażenia na niskie stężenia par rтęci.

Rтęć jest uznana za czynnik przyczynowy różnego rodzaju zaburzeń, w tym neurologicznych, nefrologicznych, immunologicznych, kardiologicznych, rozrodczych, a nawet genetycznych. Badania wykazały korelację między toksycznością rтęci a patogenezą choroby Alzheimera lub choroby Parkinsona, autyzmem i stwardnieniem rozsianym.

Rтęć może być zaangażowana w cztery procesy, które prowadzą do genotoksyczności: wytwarzanie wolnych rodników i stresu oksydacyjnego, działanie na mikrotubule, wpływ na mechanizmy naprawy DNA i bezpośrednią interakcję z cząsteczkami DNA.

Słowa kluczowe: rтęć, metyl ortęć, etyl ortęć, tiomersal, toksyczność.

INTRODUCTION

Mercury is a silver-white metal whose Latin name is *hydrargyrum*, meaning liquid silver, hence its symbol Hg. In its liquid form, mercury is poorly absorbed and poses a low health risk. Its vapours, however, are well absorbed into the respiratory system, thus being the major cause of numerous intoxications. Mercury is considered a serious problem as it accumulates in the environment. Organic compounds are more dangerous due to their toxic effects. Compared to inorganic forms, they are more easily soluble in lipids, more mobile in the human body and are highly likely to cause brain damage because they cross the blood-brain barrier (CLARKSON et al. 2007, MAGOS et al., 2006).

Mercury in pharmaceuticals and utility products

Mercury has long been a popular choice for dental amalgams. In individuals with amalgam fillings, chewing gum for example leads to the release of mercury vapours, which are transported with inspired air to the olfactory bulbs, brain and lungs and permeate into the blood vessels (BAIRD et al. 2004). Thus, the amount of mercury in the brain may be proportional to the number of amalgam fillings. Moreover, individuals with such fillings have 4 to 5-fold higher levels of mercury in urine and blood.

Mercury compounds have antibacterial and antifungal properties, which is why they are used as preservatives or antiseptics in paints, cosmetics, medicines and vaccines. For example, thimerosal is a mercury-containing compound used as a preservative in hepatitis B, diphtheria, pertussis, acellular pertussis and tetanus vaccines. The use of mercury in vaccines has aroused interest due to infant deaths and speculations about its effects (WESTPHAL HALLIER 2003). Skin whitening creams and soaps made in some developing countries are a recognized source of chronic mercury poisoning (HARADA et al. 2001).

Mercury in the human body

Distribution of mercury in organs depends on the type of compound absorbed and duration of exposure. The major route of mercury absorption is via the respiratory system; 80% of mercury absorbed by breathing is retained in the body, mainly in the blood, brain and foetal tissues.

Metallic mercury vapour enters the bloodstream, causing oxidation of red blood cells; 99% of mercury species circulating in plasma are attached to protein-bound thiol groups. Transport of mercury into organs and subsequent organ distribution is determined by the remaining 1% of mercury bound to "diffusible thiols", i.e. low molecular weight thiols that are capable of crossing the cell membranes.

A certain amount of elemental mercury remaining in blood crosses the blood-brain and placental barrier, causing the accumulation of mercury in the brain and foetal tissues. The concentration of mercury in the brain of those occupationally exposed to mercury vapour was found to be several times higher than in other organs (except kidneys). Moreover, in women exposed to mercury during pregnancy, the content of methylmercury in blood was lower compared to foetal blood cells.

In humans, about 95% of alkylmercury compounds are absorbed from the gastrointestinal tract, in contrast to just 7% of inorganic mercury compounds. Methylmercury compounds are also absorbed through the skin. Approximately 90% of inorganic mercury accumulate in kidneys.

The concentration of mercury in urine reflects its level in kidneys. Since kidneys mainly accumulate inorganic fractions of mercury, they may be considered a biomarker of mercury vapours in the entire body (SEŃCZUK 2002).

Much of inorganic mercury is eliminated through the gastrointestinal system, with bile and faeces. High mobility of mercury vapours is associated with its physical properties. It is believed that an atom of mercury crosses the cell membranes by passive diffusion. Mercury passes to the bile as a complex with glutathione. The structure of mercury glutathione complex (Hg-GS-SG) is similar to that of oxidized glutathione (GS-SG) and thus may freely permeate the hepatic cell membranes (CLARKSON et al. 2007, BALLATORI 2005).

Ninety percent of methylmercury compounds are excreted in faeces. Elimination half-life of methylmercury is over 70 days, compared to 40 days for most inorganic salts and 60 days for mercury vapour. Mercury is excreted with urine in the form of metallothionein. In tissues, methylmercury occurs in the form of macromolecular complexes with proteins; small molecular complexes predominate in blood whereas the brain contains mostly methylmercury glutathione.

MERCURY POISONING

Acute poisoning

The critical organs of acute poisoning with mercury vapour are the lungs. Acute poisoning develops when large amounts of mercury are inhaled, which may lead to acute bronchitis, bronchiolitis and pneumonia. Patients die due to respiratory failure. Moreover, inflammatory bowel disease, with dehydration acute heart failure, oral inflammation, drooling and signs of kidney damage have been observed. Ingestion of inorganic salts is followed by salivation, burning sensation in the throat, vomiting, bloody diarrhoea, necrosis of the intestinal mucosa and kidney damage, leading to anuria and uraemia (SEŃCZUK 2002).

Chronic poisoning

In chronic exposure to mercury vapour, the central nervous system is primarily affected. Abnormalities develop with prolonged exposure to low concentrations of mercury vapour. The earliest symptoms include weakness, headache and limb pain. Salivation, inflammation of the mucous membrane and gums, tooth loss, and oral dryness are likely to follow. Moreover, blue-violet plaque on the gums, diarrhoea and symptoms of renal failure are found. Over time, the CNS damage develops, including sleep disorders, impaired concentration or memory, irritability and nervousness, trembling fingers, hands and legs (SEŃCZUK 2002, YILMAZ et al. 2010).

Toxic effects of mercury on organs

Intracellular mercury attaches to thiol residues of proteins, particularly glutathione and cysteine, resulting in inactivation of sulphur and blocking of the related enzymes, cofactors and hormones. Its molecular interactions with sulfhydryl groups in molecules of albumin, metallothionein, glutathione, and cysteine have been implicated in the mechanisms involved in renal and neuronal toxicity (JAMES et al. 2005, FONNUM, LOCK, 2004). Moreover, it blocks the immune function of Mn and Zn leading to deficiency of a principal antioxidant enzyme, superoxide dismutase, involved in various diseases, including Alzheimer's disease, Parkinson's disease, cancer, Down's syndrome, Dengue, etc. (NOOR et al. 2002). Furthermore, in cultured cerebellar granule cells, low concentration of mercury causes a rise in $[Ca^{2+}]$, which may trigger a cascade of events leading to impairment of mitochondrial energy metabolism and generation of reactive oxygen species. By inhibiting the glutamic acid uptake, mercury magnifies the sensitivity of neurones to excitotoxic injury (FONNUM, LOCK 2004). The combination of these mercury-triggered events enhances free radical stress, which is a key factor of disease progression, ageing and degenerative disorders (NAGY 2001).

Central nervous system

The central nervous system starts to develop in the embryonic period and continues through adolescence. During its development, the CNS is sensitive to is exposed to environmental hazards as it is dependent on developmental processes (i.e. proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis).

Comparison of foetuses and adult organisms shows that the former are more susceptible to mercury toxicity. Maternal consumption of methylmercury-contaminated fish or bread during pregnancy may cause psychomotor retardation in the offspring. The common symptoms in children exposed to maternal mercury include impaired motor function, memory, and language, particularly if exposed in the second trimester. Autism is a disorder that can lead to life-long disability. There is a potential link between mercury toxicity and autism in children (LEE et al. 2003).

Low concentrations of some metals, including mercury, can directly induce α -synuclein fibril formation which is the major constituent of intracellular protein inclusions (Lewy bodies and Lewy neurites) in neurons leading to Parkinson's disease (UVERSKY et al. 2001). Moreover, low concentrations of mercury are able to induce oxidative stress, cytotoxicity and increased secretion of β -amyloid, which may result in neurodegenerative diseases (OLIVIERI et al. 2002). Mercury binds sulfhydryl groups of proteins and disulfide groups in amino acids, which inactivates the related enzymes, co-factors, hormones. By binding sulfhydryl groups, it also alters the cellular membrane permeability. Blocked or inhibited sulphur oxidation on cellular levels has been observed in many chronic neurodegenerative disorders, including Parkinson's disease, Alzheimer's disease, ALS, lupus, rheumatoid arthritis, autism, etc. (WILKINSON, WARING 2002).

Furthermore, mercury can induce decreased manual dexterity, increased muscular fatigue, decreased muscular strength, disrupted attention, impaired motor function and verbal memory. The other concerns include tiredness, memory disturbances, finger tremor, abnormal findings of computerised EEG analysis and impaired performance in neurobehavioral or neuropsychological tests (FARHANA et al. 2005).

Urinary system

Kidneys accumulate the highest levels of mercury compared to the brain and liver. Mercuric ion (Hg^{2+}), one of the best-known thiol-binding agents, impairs the NF-KB activation and DNA binding in renal epithelial cells leading to apoptosis (DIEGUEZ-ACUNA et al. 2004).

Reproduction

When concentration of methylmercury in mothers is very high they do not conceive; if they do, pregnancy is lost, the foetus aborted or stillborn. In cases of live births, children suffer from serious neurological symptoms. In women exposed to mercury vapour, high incidence rates of menstrual dis-

orders, primary subfecundity and adverse pregnancy outcome are observed. Hg accounts for subfertility of males; both organic and inorganic mercury reduces motility of spermatozoa (FARHANA et al. 2005).

Immune system

The immune system plays an important regulatory role in the host-defence mechanisms. Patients with certain autoimmune and allergic diseases, such as systemic lupus, multiple sclerosis, autoimmune thyroiditis, often show increased lymphocyte stimulation by inorganic mercury (PROCHAZKOVA et al. 2004).

Cardiovascular system

Cardiovascular diseases, including hypertension, are a leading cause of death in developing and developed countries. Mercury can induce hypertension and atherosclerosis in experimental animals and humans. Therefore assessment of its effects on the development of cardiovascular disturbances in the population is essential. Exposure to methylmercury may affect the development of cardiovascular homeostasis in children with low birth weight, systolic and diastolic blood pressure (STERN 2005).

Genome

Human exposure to mercury compounds can induce changes in the genetic material; two processes are mainly involved: teratogenesis and carcinogenesis. The former may manifest itself in progeny in the form of congenital abnormalities, while the latter consists in the direct development of tumours in the exposed individuals.

Methylmercury-induced chromosome damage in cells can give rise to abnormal offspring.

The cytogenetic analysis revealed the effects of mercury on mitotic and meiotic chromosomes (CRESPO-LOPEZA et al. 2009).

MECHANISMS OF MERCURY GENOTOXICITY

Oxidative stress

One of the earliest molecular mechanisms described to explain genotoxic consequences of mercury was oxidative stress (DNA damage caused by action of free radicals generated by the metal). Free radicals are highly reactive chemical species that, in addition to their important physiological role, can also induce DNA damage and consequently, damage to cells leading to carcinogenic processes (HALLIWEL 2007). Free radicals are responsible for initiating the chain reaction resulting in cell proliferation.

Reactive oxygen species (ROS) constitute the main type of free radicals implicated in pathogenic mechanisms. The most important species are: su-

peroxide radical, hydrogen peroxide, hydroxyl radical, oxygen singlet, alkyl radical, peroxy radical and nitric oxide.

Mercury compounds are capable of inducing cellular damage by increasing of ROS levels (ERCAL et al. 2001).

Direct action of free radicals on nucleic acids are likely to cause genetic mutations. Moreover, free radicals may induce conformational changes in proteins responsible for the formation and maintenance of DNA, such as repair of enzymes, DNA-polymerases, even tubulin and kinesin motor proteins, responsible for mitotic spindle and chromosomal segregation (CEBULSKA-WASILEWSKA et al. 2005, STOIBER et al. 2004). Glutathione can act as the main cell defence line against mercury compounds. High levels of intracellular glutathione have a neuroprotective effect against intoxication with mercury (HERCULANO et al. 2006).

Moreover, some other antioxidant substances, e.g. L-ascorbic acid, also demonstrate their protective role against mercury genotoxicity by preventing sister chromatid exchanges and abnormal mitosis.

Microtubules

The influence of mercury species on microtubules has been known since the main proteins constituting microtubules, tubulin and kinesin, were described as preferential targets for mercury binding. However, only recently their potential genotoxic effect has been recognized (THIER et al. 2003, STOIBER et al. 2004). Cytoskeletal proteins are involved in cell movement, mitotic spindle formation, chromosomal segregation and nuclear division, implicating that part of inorganic mercury chromosomal genotoxicity could be due to functional impairment of kinesin and/or microtubules, leading to disturbances in chromosome distribution (BONACKER et al. 2004).

DNA repair mechanisms

Another possible mechanism responsible for mercury genotoxicity is associated with its effect on DNA repair mechanisms, which constitute the defence system designated to protect the genome integrity. The deficient defence system may eventually lead to carcinogenic processes (CEBULSKA-WASILEWSKA et al. 2005, HALLIWEL 2007).

Besides the indirect action on the DNA repair system, mercury can also be directly bound to the “zinc fingers” of DNA repair enzymes, affecting their activity. These “zinc fingers” are sequence-specific DNA-binding proteins, which contain an atom of zinc and four atoms of cysteines and/or histidines. Thus, high affinity of mercury to sulfhydryl groups of these cysteines may severely deform the structural integrity and activity of enzymes (CEBULSKA-WASILEWSKA et al. 2005).

Interaction with DNA molecules

All molecular mechanisms described above as potentially responsible for mercury genotoxicity are primarily associated with mercury-protein

interactions and mercury species affecting these proteins (DNA repair enzymes, antioxidant enzymes, cytoskeleton proteins, etc.) (CRESPO-LOPEZA et al. 2009).

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