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REVIEW ARTICLE

Effects of chronic exposure to mercury in special circulations

Lorena Barros Furieri[1]; Franck Maciel Peçanha[2]; Giulia Alessandra Wiggers[3]

[1]PhD, Professor of Departament of Nursing, Federal University of Espírito Santo, Vitória, ES, Brazil.

[2,3] Doctor, Professor of Federal University of Pampa, Uruguaiana, RS, Brazil.

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Abstract

It is well established that exposure to mercury, whether organic or inorganic, is a cardiovascular risk factor. Chronic exposure to mercury is considered a risk factor for the development of different kinds of diseases, and more recently, it was noted that significant deleterious effect that such exposure causes in the vascular system. In this paper we will discuss the effects on coronary, cerebral and superior mesenteric vascular beds.

Exposure 30 days to HgCl2 promotes endothelial dysfunction in coronary arteries, evidenced by reduced bioavailability of NO related to the increased oxidative stress. Cerebral arteries in the same model of exposure to a low concentration of mercury leads to a reduction in bradikinin-induced relaxation and increased serotonin (5-HT) - induced contraction also by reducing the bioavailability of NO. The metal exposure participates for the development of vasospasms in basilar arteries. In addition to changes in vasoconstrictor and vasodilator activity induced by drugs, treatment with mercury also increases the vasoconstrictor response to electrical stimulation. And this change is due to changes in nitrergic and adrenergic modulation in superior mesenteric arteries by reducing the release and bioavailability of NO via nNOS and increased release of superoxide anion and NA.

Occupational or environmental exposure to mercury is an important risk factor for cardiovascular diseases such as hypertension, myocardial infarction and stroke.

*Corresponding author:
lorafurieri@yahoo.com.br

Introduction

Mercury is an environmental contaminant that affects human health.[1]The effects on human health depends on its chemical form, since the sources of exposure, the target organs, toxicity and metabolism are very different.[2]

Occupational exposure to mercury usually results from exposure to inorganic mercury and elemental mercury as vapor. Dentists, dental offices technicians, chlorine and soda industrial workers, miners, measuring and fluorescent lamps equipment industries workers are the main subjects exposed.[3-5]

The concentration of vapor mercury considered safe for chronic inhalation of steam by the WHO is 0.2 g/m3/kg/day. The concentration should not exceed 1 g/m3 in the air per year.[6]

Exposure to organic mercury occurs primarily by ingestion of contaminated fish (methylmercury) and exposure to ethylmercury contained in cosmetics and vaccines containing the preservative thimerosal.[7,8] Brazil is one of the few developing countries that still allow and provide for the population vaccines containing thimerosal.[9] Intrauterine exposure and children have been shown to alter neurodevelopment.[8]

In The Joint FAO/ WHO Expert Committee on Food Additives (2010) has argued that the beneficial effects on child neurodevelopment of fish consumption is reduced when there is contamination with methylmercury.[10]

According to the WHO, people who consume fish and seafood one or more times a day may have mercury concentrations in the hair reaching up to 10 µg/g. However, in individuals who do not normally consume fish, concentrations cannot exceed 1 to 2 µg/g.[11] In Brazil, the recommendation of the Ministry of Health is the intake up to 400 g of fish with a concentration of 0.5 ug/g of mercury consumed per adult weekly.[12]

The cases of severe mercury exposure occurred in Iraq and Minamata (Japan). In Minamata, between the decades of 20 and 60, a Japanese company specializing in the production of acetaldehyde and PVC dumped methylmercury directly on the bay of the city. It is estimated that in four decades were disposed about 150 tons of methyl mercury in the bay, leading to contamination of fish and the contamination of people who eat these contaminated fish. In total, two million people were exposed, 900 people died and 3,000 people suffered "Minamata Disease", which is characterized by severe seizures, psychosis outbreaks, loss of consciousness and coma.[3,13]

In Iraq, between the late 60s and early 70s, another case of population mercury poisoning occurred. Soy beans and barley were treated with mercury fungicides and used for direct production of bread and other foods. After this organic mercury intake in foods made from contaminated grains, 6,900 people were hospitalized, 475 people died and 15 children were born with congenital abnormalities.[14]

In Brazil, the Amazon basin is where there is greater mercury contamination. The concern arising from the metal contamination arose in the 80s by the large amount of metal released into the environment by mining activities started in 1979. The population exposure was given by inhalation of mercury vapor by the

miners and the consumption of fish contaminated with methylmercury.[15]

The consumption of mercury-contaminated fish is an important source of exposure in the Amazon basin. The local population has high concentrations of mercury in the hair, and a positive correlation between mercury exposure and arterial blood pressure.[16]

Elemental mercury and its organic and inorganic compounds can cause serious damage to various organs and tissues of the human body, both after acute and chronic exposure.[17] In the renal system it is responsible for glomerular injury, tubular injury, renal failure and apoptosis.[18] In the gastrointestinal tract, inorganic and metallic mercury cause stomatitis, nausea, vomiting, abdominal pain, anorexia, diarrhea, colitis, necrosis of the bowel wall, hematemesis, excessive salivation and even loss of teeth.[19,20]

In the central nervous system (CNS) the most frequent effects of exposure to inorganic mercury are: irritability, fatigue, behavioral changes, tremors, headache, hearing and cognitive impairment, dysarthria, incoordination and hallucinations. Exposure to methylmercury leads to serious changes in CNS development.[20,21]

Chronic exposure to mercury is considered a risk factor for the development of different kinds of diseases, and more recently, it was noted the significant deleterious effect that such exposure causes to the vascular system. Therefore, it is necessary to know which are the effects as well as the mechanisms of action of mercury on the vascular system. In this paper we will discuss the effects on coronary, cerebral and mesenteric vascular beds.

- Coronary arteries

Wiggers et al. have developed an experimental model of 30 days exposure to $HgCl_2$, in which the treated rat reached a concentration equal to 7.97 ± 0.59 ng/mL.[22] The reference value recommended by the North American Enviromental Protection Agency for blood mercury concentrations without adverse health effects is 5.8 ng/mL or ~ 21 nmol/L WHO provides a lower concentration than 6 g/g of mercury as acceptable in human hair.[23]

Furieri and collaborators showed for the first time, the effects of exposure to low concentrations of HgCl2 for 30 days using this experimental model on the reactivity of the coronary arteries of rats. Even in low concentration the treatment with mercury was able to alter the function of this important vascular bed. The coronary arteries showed higher reactivity to serotonin and also a deficit in relaxation to acetylcholine. The data suggest that these observed effects are due to increased production of oxygen-derived free radicals, especially superoxide, leading to reduced NO bioavailability. Also, by increasing the participation of prostanoids vasoconstrictors derivatives of arachidonic acid-cyclooxygenase cascade.[24]

Confirming previous results in coronary vascular reactivity it was also found that local production in septal coronary arteries is impaired, while there is a significant increase in the generation of superoxide anion. The gene expression of two major isoforms of generating free radicals subunities of NADPH oxidase, the NOX-1 and NOX-4 is increased, suggesting that this is the main source of production of reactive species upon exposure to HgCl2. The gene expression of SOD-2, an important enzyme responsible for tmetabolizing the superoxide anion into H2O2 and molecular oxygen is also increased. When evaluating the morphology of the coronary vessels, it was observed that treatment with HgCl2, besides altering the vascular function and to promote vascular endothelial dysfunction, it was still able to reduce the total vessel area and the area of the lumen.[24]

To elucidate the mechanisms by which occurred endothelial dysfunction, mercury effects were also studied in explanted porcine coronary endothelial cells after exposure for 24 hours to HgCl2. And it was observed that increasing HgCl2 concentration a dependent production of reactive oxygen species took place. After concurrent exposure to some antioxidants known as tempol, apocynin and tiron, a reduction of ROS production occurred suggesting that the main source of these free radicals is the NADPH oxidase. In endothelial cells, increased production of ROS is also related to reduced NO production, as observed after measurement of nitrites and nitrates, the degradation products of NO in cell culture medium. However, the main synthase protein expression responsible for NO production in endothelial cells, eNOS is increased in endothelial cells exposed to HgCl2. This finding seen in conjunction with the reduction of ROS production produced by incubation with L-NAME, a non-selective inhibitor of NOS, shows that besides increasing the expression of eNOS to be compensatory to the reduction of NO, is also contributing to the production of free radicals for uncoupling of eNOS.[24]

- Cerebral arteries

Wiggers et al using the same experimental model of chronic exposure to low concentrations of mercury which mimics human exposure to this metal found in the rat basilar arteries, an increased contractile responses to 5-HT and impaired endothelial-dependent vasodilation. These results suggest that the exposure to this metal causes endothelial dysfunction.[25]

In addition to the endothelial dysfunction the reduced bioavailability of nitric oxide was observed when the concentration response curve to 5-HT was performed in the presence of L-NAME (NOS inhibitor). L-NAME caused a smaller increase the contractile responses to 5-HT in the arteries of rats exposed to mercury when compared to arteries of rats not exposed to the metal featuring reduced bioavailability of nitric oxide. Mercury exposure causes no change in the expression of SOD isoforms.[25]

This study also noted reduction of the contractile response to 5-HT in the presence of Tiron and apocynin (NADPH oxidase inhibitor). In addition, there was improvement in vasodilatory response to bradykinin in the presence of Tiron and SOD. In the presence of indomethacin the contractile response to 5-HT was reduced and improved the vasodilator response to bradykinin. These results suggest the involvement of the increased production of superoxide anion and cyclooxygenase pathway derived prostanoids increasing the contractile response to 5-HT and the worsening of the vasodilator response to bradykinin. This suggests that endothelial dysfunction caused by chronic exposure to mercury chloride, this vascular bed is associated with increased production of reactive oxygen species and products derived from the COX pathway and a consequent reduction of nitric oxide bioavailability.[25]

- Effects on nitrergic and adrenergic innervation in mesenteric arteries

Several studies of our group had shown in many vascular beds, that the chronic exposure affects vascular reactivity. However, there was still a lack in the literature to describe which are the effects of this exposure on vascular innervation. The vascular tone is determined by a balance in the release of many neurotransmitters.[26,27] The mesenteric arteries have nitrergic, adrenergic and sensory innervation, participating in the control of vascular tone in different pathophysiological situations and can be evaluated by electrical stimulation.[28-30]

Blanco-Rivero et al (2011) showed that exposure to low mercury concentration increases the vasoconstrictor response to electrical stimulation in superior mesenteric arteries, as a result of the combined release of noradrenaline, NO and CGRP (calcitonin-related peptide gene). When evaluating the participation of NA in increased vasoconstriction induced by electrical stimulation we observed an increased participation of adrenergic innervation in arteries from treated rats, either by increasing the release and/or change of the response of vascular smooth muscle cells to NA. In addition, there is a reduction of participation nitrergic innervation responsible for the release of NO via nNOS-phosphorylated.[31]

Thus, we can say that in addition to changes in the vasoconstrictor and vasodilator reactivity induced by drugs, the treatment with mercury also increases the vasoconstrictor response to electrical stimulation. And this change is due to changes in nitrergic and adrenergic modulation. It reduces the release and bioavailability of NO, probably by reducing the activity of nNOS, increasing the release of superoxide anion and the release of noradrenaline.[31]

The work of our group showed, for the first time, that exposure to low concentrations of HgCl2, close to that found in individuals who removed dental amalgams, which were exposed to mercury vapor, or routinely consume contaminated fish, was able to cause endothelial dysfunction in coronary and cerebral arteries. And yet change in the participation in nitrergic and adrenergic innervation in superior mesenteric arteries. That is, exposure to this metal, routinely found in the environment and occupational contamination is a major risk factor for cardiovascular diseases such as hypertension, myocardial infarction and stroke.

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