REVISTA SALUS
JOURNAL OF HEALTH SCIENCES

REVIEW ARTICLE

Effects of mercury exposure on conductance and resistance vessels

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.

Article received on September 2, 2016

Article approved on October 3, 2016

Keywords

Mercury; Condutance Artery; Aorta; Resistance artery

Abstract

Exposure to mercury is a pro-inflammatory factor and causes oxidative stress. One of the main sites affected by oxidative stress, due to the development of atherosclerosis, is the aorta. In addition, changes in the reactivity of resistance arteries greatly influence blood pressure. This work aims to show the effects of mercury, in low concentrations, close to those found in environmental or occupationally exposed individuals, in conductance and resistance arteries. These low concentrations of mercury, for 30 days, caused increased vascular reactivity, oxidative stress and inflammation, as well as the reduction of NO bioavailability in both resistance and conductance arteries. Exposure to mercury has an important deleterious effect on vascular function, mainly because it induces endothelial dysfunction and vascular remodeling. This impact can be compared to those produced by traditional cardiovascular risk factors such as hypertension, diabetes and hypercholesterolemia.

*Corresponding author:

lorafurieri@yahoo.com.br

Introduction

Mercury in organic, inorganic and elemental forms is used in various human activities and this causes man to be frequently exposed to this metal. Reports of the toxic effects of mercury are dating from the nineteenth century, however, only after the disasters in Japan (Minamata Bay) and

Iraq in the 70s that more attention has been given to these effects.[1,2]

The toxic effect of this metal is directly related to the type, time and route of exposure, and human exposure often occurs through the consumption of contaminated fish with organic mercury, administration of thimerosal in vaccines and inhalation of mercury vapor from dental amalgams.[3,4]

Initially, it was observed that the renal and central nervous system had their functions affected by the exposure to mercury, however, in the last two decades also alterations in the cardiovascular system have been noticed, among which are highlighted arterial hypertension, carotid atherosclerosis, coronary artery disease and acute myocardial infarction.[5-9] The toxic effect of mercury on these systems is related to the higher generation of reactive oxygen species.[9-11]

In experimental studies, our group has documented that direct infusion of mercury in rat caudal arteries produced a vasoconstriction associated with changes in endothelial function. These changes are evidenced by the reduction of the mediated endothelium-dependent relaxation and the increased production of COX-derived vasoconstricting prostanoids, increased free radical production with consequent reduction of NO bioavailability.[12] In this same arterial bed, nanomolar concentrations of mercury have already promoted increased reactivity to phenylephrine by increasing ACE activity and stimulation of Angiotensin II.[13]

A study conducted by Bastos et al. with the amazonian riverside population showed that almost all the habitants of the 40 cities studied have blood mercury concentrations above the reference values, indicating that human exposure to mercury is chronic and at low doses.[14]

Considering that humans are chronically exposed to mercury and little was known about the effect of this metal on the vascular system, our group developed an experimental model where the rats were exposed for 30 days to low doses of mercury mimecking human exposure to mercury and allowing the toxic effect of mercury on the vascular system to be evaluated.[15]

In the experimental model of chronic exposure to low doses of mercury developed by Wiggers et al,[15] it was observed that at the end of treatment the animal had a blood concentration of mercury of approximately 8 ng/ml (29nmol/L), a concentration similar to that observed in the human population exposed to this metal.[4,16,17] No alteration of systolic blood pressure levels was observed in this model of exposure, however, there was an increase in the plasma activity of the angiotensin converting enzyme (ACE). With this experimental model it was possible to evaluate the vascular function of resistance and conductance arteries.

- Effects in resistance arteries

Peripheral vascular resistance is inversely proportional to the vessel radius to the fourth power and therefore decreases inthe size of these arteries can produce significant increases in peripheral resistance and therefore increased blood pressure.[18] The luminous diameter is determined by the active and passive properties of the vessel. That is, by its morphological and functional alterations.[19]

Wiggers et al, have shown that treatment with low mercury concentration for 30 days induces endothelial dysfunction in resistance mesenteric arteries possibly by increasing oxidative stress, reducing NO bioavailability, and increasing superoxide anion production derived from NADPH oxidase. Among the main results of the functional evaluation, it is highlighted that the chronic exposure to mercury caused: 1) increased vasoconstricting response to phenylephrine and reduced endothelial NO modulation of this response; 2) reduction of ACh-induced endothelium-dependent vasodilatory response; 3) increased superoxide anion production, plasma

malondialdehyde and total antioxidant status; 4) restoration of NO endothelial modulation in the contractile response to phenylephrine and ACh-induced vasodilation in the presence of SOD (superoxide anion scavenger) and apocynin (NADPH oxidase inhibitor).[15]

It is known that cardiovascular changes, such as hypertension, in addition to having oxidative stress and endothelial dysfunction, are accompanied by structural changes in resistance vessels, a process known as vascular remodeling, usually associated to decreases in its diameter.[20-23] Vascular remodeling is a complex process that may involve an increase (hypertrophy), decrease (hypotrophy) or rearrangement (eutrophy) of vascular wall material.[21,24] In the literature, there was no experimental evidence that chronic treatment with HgCl2 could be associated with structural or mechanical changes of resistance vessels. Our study evaluated for the first time the structural and mechanical properties of third order mesenteric arteries of Control rats and treated with HgCl2 in a system for pressurized arteries, which represents one of the most appropriate current methods for this type of study for its approach to in vivo conditions.[25]

The mercury treatment produced a reduction in wall thickness and in the media: lumen ratio of the vessels, as well as an increase in internal diameter, which could be a consequence of a decrease in vascular wall thickness.[15] These parameters correspond to the definition of outward hypotrophic remodeling.[26]

- Conductance arteries

Exposure to mercury, as demonstrated in resistance arteries and other biological systems, is known to be an important cause of oxidative stress and inflammation.[9,11,15,27] Oxidative stress and inflammation are important factors that generate LDL cholesterol which, in conductance arteries, will lead to atherosclerosis.[28,29] Thus, the effects on conductance arteries, such as the aorta, together with the changes observed in resistance arteries are important for the study of metal exposure, since endothelial dysfunction in both are added as factors of cardiovascular risk.

This same experimental model was used to evaluate the effect of mercury on the conductance arteries and, for this, experiments of vascular reactivity were developed in segments of the thoracic aorta. In this vascular bed, it was also observed that exposure to low doses of mercury during 30 days caused an increase in the contractile response to phenylephrine and a lower participation of NO in this response, reduction of the vasodilator response to acetylcholine, increase in superoxide anion production and malondialdehyde levels (MDA). In addition, it was observed that in the presence of apocynin (NADPH oxidase inhibitor) and SOD (superoxide anion scavenger), there was an improvement of the endothelial NO modulation in the contractile response to phenylephrine and an increase in the vasodilator response to acetylcholine. These results suggest that exposure to mercury promoted endothelial dysfunction due to the reduction of NO bioavailability due to the increase in the production of reactive oxygen species by NADPH oxidase.[15]

The participation of the angiotensin II pathway in the vascular alterations caused by mercury had already been observed by our group.[13] Subsequently, other authors have demonstrated that angiotensin II was able to induce COX-2 expression, to increase prostanoid production[30,31] and that contractile prostanoids derived from the COX-2 pathway caused endothelial dysfunction.[32-34] To elucidate the role of angiotensin II and contractile prostanoids derived from the COX-2 pathway in the vascular reactivity of rats exposed to mercury Peçanha et al, conducted experiments on aortic artery segments.

The hypothesis that exposure to mercury promotes a greater participation of the angiotensin II pathway in vascular reactivity was was reinforced because in rats exposed to mercury it was observed: a) increased plasma ACE activity; B) reduction of the contractile response to phenylephrine in the presence of Losartan (AT 1 receptor antagonist). In addition, the presence of indomethacin (non-selective COX inhibitor), NS 398 (COX-2 inhibitor), SQ 29,548 (TP receptor antagonist), furegrelate (TXA2 synthase inhibitor), SC 19,220 (EP 1 receptor antagonist) reduced the contractile response to phenylephrine in aortic segments of rats exposed to mercury and promoted increased gene expression of COX-2 in the aortas of these animals. These results indicate the involvement of the angiotensin II pathway and the COX-2 pathway, especially TXA2 and PGE2, in the vascular alterations (vascular reactivity) caused by mercury contamination.[35]

Later, in a study where chronically exposed rats at low doses of mercury were co-treated with apocynin (nonspecific NADPH oxidase inhibitor), it was demonstrated for the first time that apocynin improved the endothelial function of the aorta from rats chronically exposed to mercury.[31] This effect is due to the prevention of increased oxidative stress, reduction of lipid peroxidation, changes in defense mechanisms and consequent improvement of NO bioavailability. It is noteworthy that treatment with apocynin did not reduce the participation of COX-2-derived prostanoids in the contractile response to phenylephrine. These results reinforce the hypothesis that chronic exposure to mercury promotes a greater participation of these prostanoids and reactive oxygen species in the contractile response of the rat aorta to phenylephrine. In addition, they indicate that mercury acts via two different pathways, COX-2 and NADPH oxidase pathways, independently.[36]

A more recent study from our group showed that the effects of mercury exposure on vascular reactivity is concentration dependent. Since exposure to a concentration 2.5 times greater than the experimental model proposed by Wiggers et al,[15] causes an increase in vascular reactivity of the aorta, but half of the concentration promotes a reduction in the contractile response to phenylephrine. This reduction is probably due to an increase in NO bioavailability as reinforced by the protein expression data of the phosphorylated fraction of eNOS in aortic segments.[37]

However, when mercury (6nM) was added directly to the perfusion medium of aortic arteries, it was observed that there was still an increase in reactivity to phenylephrine due to increased oxidative stress and consequent reduction of NO bioavailability.[38] This concentration is much lower than the plasma concentration achieved by the treatment proposed by our group previously (29nM or 8ng/mL).[15]

That is, the effects shown by Azevedo et al,[37] were surprising, suggesting that chronic and controlled exposure of mercury at concentrations that do not lead to endothelial dysfunction promotes adaptive and protective responses of the arterial vasculature.[37]

These results show the deleterious effects of mercury on the vascular system, even at low concentrations, help to clarify the mechanisms by which this metal exerts its effects and already suggest possible therapeutic pathways.

Exposure to low concentrations of mercury has a negative effect on vascular function, mainly because it induces endothelial dysfunction and vascular remodeling. This impact can be compared to those produced by traditional cardiovascular risk factors such as hypertension, diabetes and hypercholesterolemia. Therefore, mercury can be considered an important risk factor for cardiovascular disease that can participate in the development of cardio and cerebrovascular events. Whether these effects increase the consequences of

traditional risk factors or play a primary role in patients with low cardiovascular risk still needs to be better studied.

References

1. Bakir F, Damluji SF, Amin-Zaki L, Murtadha M, Khalidi A, Al-Rawi NY, et al. Methylmercury poisoning in Iraq. Science. 1973;181(96):230-241.

2. Eto K. Minamata disease. Neuropathology. 2000;20:14-19.

3. Clarkson TW, Magos L. The toxicology of mercury and its chemical compounds. Crit Rev Toxicol. 2006;36(8):609-62.

4. McKelvey W, Gwynn RC, Jeffery N, Kass D, Thorpe LE, Garg RK, et al. A biomonitoring study of lead, cadmium, and mercury in the blood of New York city adults. Environ Health Perspect. 2007;115(10):1435-41.

5. Yoshizawa K, Rimm EB, Morris JS, Spate VL, Hsieh CC, Spiegelman D, et al. Mercury and the risk of coronary heart disease in men. N Engl J Med. 2002;347(22):1755-60.

6. Guallar E, Sanz-Gallardo MI, van't Veer P, Bode P, Aro A, Gómez-Aracena J, et al. Mercury, fish oils, and the risk of myocardial infarction. N Engl J Med. 2002;347(22):1747-54.

7. Virtanen JK, Voutilainen S, Rissanen TH, Mursu J, Tuomainen TP, Korhonen MJ, et al. Mercury, fish oils,and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland. Arterioscler Thromb Vasc Biol. 2005;25(1):228-33.

8. Fillion M, Mergler D, Sousa Passos CJ, Larribe F, Lemire M; Guimarães JR. A preliminary study of mercury exposure and blood pressure in the Brazilian Amazon. Environ Health. 2006: 5:29.

9. Houston MC. The role of mercury and cadmium heavy metals in vascular disease, hypertension, coronary heart disease, and myocardial infarction. Altern Ther Health Med. 2007;13(2):128-33.

10. Kishimoto T, Oguri T, Tada M. Effect of methylmercury (CH3HgCl) injury on nitric oxide synthase (NOS) activity in cultured human umbilical vascular endothelial cells. Toxicology. 1995;103(1):1-7.

11. Wolf MB, Baynes JW. Cadmium and mercury cause an oxidative stress-induced endothelial dysfunction. Biometals. 2007;20(1):73-81.

12. da Cunha V, Souza HP, Rossoni LV, França AS, Vassallo DV. Effects of mercury on the isolated perfused rat tail vascular bed are endothelium-dependent. Arch Environ Contam Toxicol. 2000;39(1):124-30.

13. Wiggers GA, Stefanon I, Padilha AS, Peçanha FM, Vassallo DV, Oliveira EM. Low nanomolar concentration of mercury chloride increases vascular reactivity to phenylephrine and local angiotensin production in rats.Comp Biochem Physiol C Toxicol Pharmacol. 2008;147(2):252-60

14. Bastos WR, Gomes JP, Oliveira RC, Almeida R, Nascimento EL, Bernardi JV, et al. Mercury in the environment and riverside population in the Madeira River Basin, Amazon, Brazil. Sci Total Environ. 2006;368(1):344-51.

15. Wiggers GA, Peçanha FM, Briones AM, Pérez-Girón JV, Miguel M, Vassallo DV, et al. Low mercury concentration cause oxidative stress and endothelial dysfunction in conductance and resistance arteries. Am J Physiol Heart Circ Physiol. 2008;295(3):1033-1043.

16. Gupta M1, Bansal JK, Khanna CM. Blood mercury in workers exposed to the preparation of mercury cadmium telluride layers on cadmium telluride base. Ind Health. 1996;34(4):421-5.

17. Chen C, Qu L, Li B, Xing L, Jia G, Wang T, Gao Y, Zhang P, Li M, Chen W,

Chai Z. Increased oxidative DNA damage, as assessed by urinary 8-hydroxy-2'-deoxyguanosine concentrations, and serum redox status in persons exposed to mercury. Clin Chem. 2005;51(4):759-67.

18. Mulvany MJ1, Aalkjaer C. Structure and function of small arteries. Physiol Rev. 1990;70(4):921-61.

19. Mulvany MJ. Determinants of vascular hemodynamic characteristics. Hypertension. 1984;6(2):13-8.

20. Schiffrin EL, Deng LY, Larochelle P. Blunted effects of endothelin upon small subcutaneous resistance arteries of mild essential hypertensive patients. J Hypertens. 1992;10(5):437-44.

21. Mulvany MJ. Small artery remodeling and significance in the development of hypertension. News Physiol Sci. 2002; 17:105-9.

22. Schiffrin EL, Touyz RM. From bedside to bench to bedside: role of renin-angiotensinaldosterone system in remodeling of resistance arteries in hypertension. Am J Physiol Heart Circ Physiol. 2004;287(2):435-46.

23. Mulvany MJ. Small artery remodelling in hypertension: causes, consequences and therapeutic implications. Med Biol Eng Comput. 2008.

24. Mulvany MJ. Effects of angiotensin converting enzyme inhibition on vascular remodelling of resistance vessels in hypertensive patients. J Hypertens Suppl. 1996;14(6):21-4.

25. Schiffrin EL, Hayoz D. How to assess vascular remodelling in small and mediumsized muscular arteries in humans. J Hypertens. 1997; 15(6):571-84.

26. Briones, A.M.; Gonzalez, J.M.; Somoza, B.; Giraldo, J.; Daly, C.J.; Vila, E.; Gonzalez, M.C.; McGrath, J.C.; Arribas, S.M.. Role of elastin in spontaneously hypertensive rat small mesenteric artery remodelling. Journal of Physiology. 2003; 552:185-95.

27. Mahboob M, Shireen KF, Atkinson A, Khan AT. Lipid peroxidation and antioxidant enzyme activity in different organs of mice exposed to low level of mercury. J Environ Sci Health B. 2001; 36: 687–697.

28. Mitra S, Deshmukh A, Sachdeva R, Lu J, Mehta JL.Oxidized low-density lipoprotein and atherosclerosis implications in antioxidant therapy. Am J Med Sci. 2011; 342: 135–142.

29. Harja E, Bu DX, Hudson BI, Chang JS, Shen X, et al. Vascular and inflammatory stresses mediate atherosclerosis via RAGE and its ligands in apoE2/2 mice. J Clin Invest. 2008; 118: 183–194.

30. Ohnaka K, Numaguchi K, Yamakawa T, Inagami T. Induction of cyclooxygenase-2 by angiotensin II in cultured rat vascular smooth muscle cells. Hypertension 2000; 35: 68-75.

31. Alvarez Y, Perez-Giron JV, Hernanz R, Briones AM, García-Redondo A, Beltrán A, et al. Losartan reduces the increased participation of cyclooxygenase-2- derived products in vascular responses of hypertensive rats. J Pharmacol Exp Ther 2007; 321: 381-388.

32. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol 2003; 42: 1149-1160.

33. Blanco-Rivero J, Cachofeiro V, Lahera V, Aras-Lopez R, Márquez-Rodas I, Salaices M, et al. Participation of prostacyclin in endothelial dysfunction induced by 35 aldosterone in normotensive and hypertensive rats. Hypertension 2005; 46: 107-112.

34. Alvarez Y, Briones AM, Balfagon G, Alonso MJ, Salaices M. Hypertension increases the participation of vasoconstrictor prostanoids from cyclooxygenase-2 in phenylephrine responses. J Hypertens 2005; 23: 767-777.

35. Pecanha FM, Wiggers GA, Briones AM, Perez-Giron JV, Miguel M, Garcia-Redondo AB, et al. The role of cyclooxygenase (COX)-2 derived prostanoids on vasoconstrictor responses to phenylephrine is increased by exposure to low mercury concentration. J Physiol Pharmacol. 2010;61(1):29-36.

36. Rizzetti DA, Torres JG, Escobar AG, Peçanha FM, Santos FW, Puntel RL, et al. Apocynin prevents vascular effects caused by chronic exposure to low concentrations of mercury. PLoS One. 2013; 8(2).

37. Azevedo BF, Simões MR, Fiorim J, Botelho T, Angeli JK, Vieira J, et al. Chronic mercury exposure at different concentrations produces opposed vascular responses in rat aorta. Clin Exp Pharmacol Physiol. 2016;43(7):712-9.

38. Lemos NB, Angeli JK, Faria Tde O, Ribeiro Junior RF, Vassallo DV, Padilha AS, et al. Low mercury concentration produces vasoconstriction, decreases nitric oxide bioavailability and increases oxidative stress in rat conductance artery. PLoS One. 2012;7(11).

How to cite this article:

Furieri LB, Peçanha FM, Wiggers GA. Effects of mercury exposure on conductance and resistance vessels. Salus J Health Sci. [online journal] 2016;2(3):37-43

Available at: http://www.salusjournal.org