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Editorial

NO and Oxidative Stress in Mercury Exposure: The Tipping Point

Swati Omanwar*

Zebu Research, Dwarka, New Delhi, India

***Corresponding Author:** Swati Omanwar, Zebu Research, Dwarka, New Delhi, India.

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In the first half of the twentieth century amidst Second World War a strange disease afflicted the fishing community of Minamata, Japan. At first it was difficult to understand that the disease could have occurred due to a factory releasing its waste containing methylmercury into Minamata Bay. Mercury (Hg) popularly known as quicksilver, is a chemical element belonging to the transition element series of the periodic table and is liquid at or near standard room temperature. In Minamata Bay, bioaccumulation (accumulation of a toxic chemical in the tissue) and biomagnification (increased concentration of a toxic chemical as we go up in the food chain) occurred in fish and when this fish was eaten by the local population, it caused the largest case of mercury poisoning known, which brought forward the effect of mercury on public health. Today mercury exposure is the second-most common heavy metal poisoning and is an occupational hazard and epidemiological studies have correlated mercury exposure with cardiovascular disease (CVD) [1].

As with any other pollutant when mercury enters the body, it reaches the various organs through the circulatory system therefore blood vessels are the primary site of exposure. On mercury exposure the layer of the blood vessel in direct contact with mercury will be the vascular endothelium which is a regulator of vascular tone as it releases various vasoactive substances. The endothelium maintains the balance between vasorelaxation and vasoconstriction and disturbing this tightly regulated equilibrium leads to endothelial dysfunction i.e. functional disruption of the vascular endothelium which is one of the factors that triggers development of CVD. The disruption of the L-arginine-nitric oxide (NO) pathway is thought to be the most important indicator of endothelial dysfunction. NO is formed from substrate L-arginine when eNOS (endothelial nitric oxide synthase) in endothelial cell is stimulated. NO relaxes the vascular smooth muscle by activating soluble guanylate cyclase to form cyclic GMP (cGMP) which via cGMP -dependent protein kinase increases extrusion of Ca^{2+} from the cytosol in vascular smooth cells muscle and phosphorylates K^+ATP channels causing hyperpolarization and inhibition of vasoconstriction producing vasorelaxation. NO release from vascular endothelium is affected by mercury exposure was first reported by Golpon and co-workers [2] further studies from our group on isolated aortic rings validated that mercury produces a dual response: vasoconstriction at high concentration and vasorelaxation at lower concentrations [3]. As vasorelaxation produced at low concentrations of mercury is blocked by L-NAME (eNOS inhibitor) and glybenclamide (K^+ ATP inhibitor) it means when endothelial cells come in contact with low dose of mercury, eNOS is stimulated forming NO which causes vasorelaxation by cGMP induced extrusion of Ca^{2+} from the cytosol in vascular smooth muscle and also by directly phosphorylating K^+ ATP channels which also causes vasorelaxation [3]. At higher concentrations of mercury vasoconstriction is observed due to oxidative stress and formation of a potent vasoconstrictor peroxynitrite (a combination of NO with free radicals). This interaction of NO and oxidative stress in mercury exposure is better understood from studies on animal models where both oxidative stress and an increase in serum NO levels have been noted. Enhanced endothelial function is observed on acute exposure of methylmercury despite oxidative stress, suggesting a tipping towards NO [4]. A converse interface between NO and oxidative stress is observed in chronic exposure to mercury chloride where endothelial dysfunction is observed though oxidative stress is accompanied with increased NO levels along with up-regulation of K^+ ATP channels as a compensatory mechanism for the attenuated NO-mediated vasodilatation [5]. A delicate balance exists between free radicals and NO released by endothelial cells on mercury

exposure. When there is an increase in NO release, enhanced endothelial function is observed. When the balance is tipped in favor of oxidative stress, endothelial dysfunction is observed. Therefore, balance of NO signaling mechanism and oxidative stress is the tipping point in the mercury-induced cardiovascular diseases in the populations exposed to mercury.

Conflict of Interest

There is no conflict of interest.

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