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The toxicology of mercury: Current research and emerging trends

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ABSTRACT

Mercury (Hg) is a persistent bio-accumulative toxic metal with unique physicochemical properties of public health concern since their natural and anthropogenic diffusions still induce high risk to human and environmental health. The goal of this review was to analyze scientific literature evaluating the role of global concerns over Hg exposure due to human exposure to ingestion of contaminated seafood (methyl-Hg) as well as elemental Hg levels of dental amalgam fillings (metallic Hg), vaccines (ethyl-Hg) and contaminated water and air (Hg chloride). Mercury has been recognized as a neurotoxicant as well as immunotoxic and designated by the World Health Organization as one of the ten most dangerous chemicals to public health. It has been shown that the half-life of inorganic Hg in human brains is several years to several decades. Mercury occurs in the environment under different chemical forms as elemental Hg (metallic), inorganic and organic Hg. Despite the raising understanding of the Hg toxicokinetics, there is still fully justified to further explore the emerging theories about its bioavailability and adverse effects in humans. In this review, we describe current research and emerging trends in Hg toxicity with the purpose of providing up-to-date information for a better understanding of the kinetics of this metal, presenting comprehensive knowledge on published data analyzing its metabolism, interaction with other metals, distribution, internal doses and targets, and reservoir organs.

1. Introduction

In the human body, only the following trace metals are generally accepted as essential: cobalt (Co), copper (Cu), iron (Fe), manganese (Mn), molybdenum (Mo), selenium (Se), and zinc (Zn). The doses at which deficiencies and, at the upper end of the scale poisonings occur are specific to each of the metals (Nordberg et al., 2000). In nature, toxic metals like lead (Pb), cadmium (Cd), mercury (Hg) and aluminum (Al) are usually bound to other substances. In modern times, metals are extracted from naturally occurring mineral compounds, involving humans as well as animals and plants may be exposed to high concentrations of toxic elements. In humans, these elements tend to deposit in anatomical structures like bones, liver, brain, and kidneys (Glomski et al., 1971; Barregård et al., 1999; Haouem et al., 2007; Antonini et al., 2009).

High concentrations of toxic metals during pregnancy represent a serious concern (Chisolm, 1974; Bowring, 2005; Riess and Halm, 2007; Wang et al., 2009) as the fetus is vulnerable to influences and may accumulate toxic metals. It has been shown that specific windows exist in the prenatal time span in which metals show a particularly high degree of toxicity (Bowring, 2005; Wang et al., 2009). The degree of toxic metal exposure to the unborn can be tested by autophagy of stem cells in cord blood (Di Gioacchino et al., 2008). Already human spermatozoa can be completely immobilized by Cu (Holland and White, 1982).

Metal exposure can arise from occupational exposure (Dounias et al., 2010), water (Mastromonaco et al., 2017; Ramasamy et al., 2017), food (Bernhoft, 2012), household environment (cutlery, cooking pots, skin creams) (Copan et al., 2015) or soil (Aelion and Davis, 2007; Dooyema et al., 2012; Pikula et al., 2013; Xiang et al., 2017). Metal exposure and excess can lead to a variety of pathologies including mental retardation, cognitive impairment, and developmental delay (Aelion and Davis, 2007; Liu et al., 2010; Hsueh et al., 2017). The development of Parkinson's and Alzheimer's diseases (Hegde et al., 2009; Chin-Chan et al., 2015; Chakraborty, 2017), and multiple sclerosis (Siblerud and Kienholz, 1994; Anglen et al., 2015; Kahrizi et al., 2016) appear also to be expedited by toxic metal exposure. The toxic effects involve structural and functional impairment of various organs, including the nervous system (Milioni et al., 2016; Bakar et al., 2017), the lungs (Lilis et al., 1985; Hirano, 1996), the cardiovascular

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(Bottino et al., 2016; Takahashi et al., 2017) and the renal systems (Lin et al., 2014; Li et al., 2015). Autism spectrum disorder (ASD) has been demonstrated to be accompanied by distorted metal homeostasis (Yau et al., 2014; Khaled et al., 2016; Mostafa et al., 2016; El-Ansary et al., 2017; Skalny et al., 2017; Wozniak et al., 2017). The degree to which people are affected by the metals seems to be largely influenced by the individual genetic makeup (Gundacker et al., 2010; Andreoli and Sprovieri, 2017). Especially Hg exposure has become a suspected causative factor for many pathological conditions, and several sources of exposure to Hg compounds can be listed, including dental amalgam fillings (Corsello et al., 2009; Mutter, 2011; Bernhoft, 2012; Bengtsson and Hylander, 2017; Sun et al., 2015; Kall et al., 2016), seafood (Dadar et al., 2016; Kuras et al., 2017), vaccines (Mitkus et al., 2014) and increasingly from energy saving light bulbs as well. The aim of the present article is to give an updated review of current research and emerging insights in the toxicology of Hg.

2. Forms of mercury

There are several environmental sources of different chemical forms of Hg including elemental Hg (metallic), inorganic and organic Hg (Bjørklund et al., 2017a). Elemental Hg (Hg^0) originates from thermostats, thermometers, dental amalgams, and Hg added to latex paint, to some extent entering the atmosphere in a vaporized state (Patrick, 2002). This zero oxidation state, Hg° represents the only metal that occurs in liquid form at room temperatures. It plays a critical role in serious occupational health problems as well as in global cycling of Hg and can be quickly absorbed by inhalation. Mercury can cross the blood-brain barrier and is rapidly oxidized to ionic Hg^{2+} intracellularly (Clarkson and Magos, 2006), which is retained in the brain cells for years (Berlin et al., 2015). In large parts of the world, dentists still use dental amalgam fillings that contain elemental Hg as a main component.

Inorganic Hg (Hg salts) has been found in laxatives, cosmetic products, teething powders, diuretics, and antiseptics. It can also be induced from the elemental Hg vapor or methylmercury (MeHg) metabolism (Ozuah, 2000).

Organic Hg is considered as the most hazardous and most frequent form of Hg exposure, which is frequently detected as MeHg, and ethylmercury (EtHg) (Crowe et al., 2017). It has been found in various sources e.g. fish, poultry, insecticides, fungicides, pesticides, and thimerosal-containing vaccines. The most frequent exposure occurs from fish consumption holding MeHg (CH_3Hg^+) as well as the prophylactics used of vaccines containing the preservative thimerosal that is quickly metabolized to EtHg ($C_2H_5Hg^+$). Thimerosal-containing vaccines (T-CVs) elevate the risk of cumulative exposure to co-occurring EtHg with MeHg from fish, which in some cases may result in neurological effects (Dórea, 2017). Numerous studies have indicated a link between organic-Hg exposure and increased risks of neurodevelopmental disorders, such as tic disorder, ASD, attention-deficit/hyperactivity disorder (ADHD), and delayed language/speech skills (Hviid et al., 2003; Young et al., 2008). During the time the organic Hg forms deposited in the brain are metabolized to mercuric Hg (Hg^{2+}) (Berlin et al., 2015), and mercurials may also evoke immunological reactions.

3. Neurotoxicity of toxic metals

One way metals exhibit toxic effects in the body is by blocking calcium (Ca)-binding proteins including calmodulin. Thus, toxic metals can interfere with cellular processes by substituting Ca on essential constituents (Habermann et al., 1983; Kursula et al., 2007). Toxic metals can also induce neuroinflammatory changes (Ray and Lahiri, 2009; Cao et al., 2016). An example is aluminum chloride ($AlCl_3$), which was found to induce neuroinflammation in the hippocampus, characterized by loss of dendritic spines and elevated mRNA levels of IL-1β, IL-6, and TNF-α. These changes were accompanied by impaired learning and memory in the studies on developing rats (Cao et al., 2016).

It has been shown that the short-term inhalation of Mn caused a significant elevation of proinflammatory chemokines and cytokines in rat brains (Antonini et al., 2009), and it is well known that Mn exposure can lead to neurotoxic effects in children. Also, deficiency of Fe elevates Mn toxicity (Bjørklund et al., 2017b). Moreover, Hg exposure can induce serious injury on the central nervous system (CNS) of humans (Boatti et al., 2017), in addition to its nephrotoxic effects (Bridges et al., 2017).

In pregnancy, it has been shown in rats that Pb produced smaller and lighter fetuses, and the endoplasmic reticulum and the ribosomes showed marked changes (Wang et al., 2009). In rats, mitochondria were shown to be damaged at very low doses of Hg and Cd (Belyaeva et al., 2008). Also, it has been revealed that toxic effects including oxidation of proteins induced by Cd in rats are corrected with elevated antioxidant enzymatic activity (do Carmo Cupertino et al., 2017).

Another problem is the increasing use of metals in nanoparticles in our environment (Baker et al., 2014). Metal ion dissolution from nanoparticles induces oxidative stress at relevant concentrations, resulting in bioaccumulation at all levels in the food chain. As more and more products containing nanoparticles are being released on the market (sun cream, sportswear, cleaning products, etc.), the toxicological research cannot keep pace with the development. Here, it should be underlined that the unborn is particularly vulnerable to influences from toxic compounds. Studies on mouse models have demonstrated neurodevelopmental alterations that may underlie a broad array of neuropsychiatric disorders relevant for human prenatal exposure (Curtis et al., 2010; Stackelberg et al., 2015).

4. Mechanisms of mercury toxicity

Mercury compounds cause toxic action in the body by numerous mechanisms. Molecular and cellular effects of organic Hg in the nervous system have been described in various studies and have suggested that Hg^{2+} may play a role after exposure to EtHg or MeHg, and that occurrence of Hg^{2+} in neurons results from breakdown of organic Hg in glial cells (Hargreaves et al., 1985; Tiffany-Castiglioni and Qian, 2001). Moreover, it was found that the levels of Hg^{2+} after EtHg exposure were higher than after MeHg exposure, while damaged granular layer was observed only after MeHg exposure. Therefore, it was proposed that the demethylation action or Hg^{2+} could not be the basic promoter responsible for MeHg neurotoxicity (Magos et al., 1985). Silver staining also revealed that in the course of the latency period, Hg is present in glial cells, and subsequently could be detected in neurons in the symptomatic phase (Pihl, 1967; Hargreaves et al., 1985). These results suggested that demethylation of MeHg occurred in glial cells and then Hg was moved to neurons and contributed to the MeHg neurotoxicity (Syversen and Kaur, 2012). Also, both CH_3Hg^+ and Hg^{2+} exhibit strong affinity to thiol (-SH) groups that have been demonstrated to play a significant role in the toxic mechanism of Hg and its compounds (Risher and Tucker, 2017a). Many subcellular constituents including the membrane systems require free thiol groups for their proper functioning. Various forms of Hg can attack thiol groups in proteins or membranes. Once Hg links to one or more of the sulfur amino acid residues in proteins or membranes, the physiological, metabolic function may be attenuated or blocked (Ynalvez et al., 2016). Also, oxidative stress (Ou et al., 1999; Garg and Chang, 2006; Yin et al., 2007), damaged Ca homeostasis (Dreiem and Seegal, 2007), as well as the glutamate homeostasis changes (Ou et al., 1999; Farina et al., 2003; Yin et al., 2007) have been reported in numerous studies on mechanisms likely to be involved in the sub-cellular neurotoxicity of MeHg.

Available data indicate that there exist some significant similarities between the neurotoxic mechanisms of MeHg, EtHg and elemental or inorganic Hg. However, there are some differences in metabolic rates of MeHg and EtHg which are summarized in a recent review by Risher and Tucker (2017b).