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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).

5. Interaction of mercury with sulfhydryl groups

The most important motif with which Hg compounds attaches in neuroglia and neurons are thiol groups. The capacity for blocking essential thiol groups in cellular enzymes and membranes leads to neurotoxic effects of mercurials (Syversen and Kaur, 2012). Analogs mechanisms also contribute to the toxicity of other thiophilic metals, e.g., arsenic (As), Pb, and Cu (Aaseth et al., 2016a). Neuronal microtubules are the brain macromolecules making up the neuronal cytoskeleton, and these macromolecules are also essential components for intracellular transport (Bjørklund et al., 2017a). Microtubules are tubulin polymers, which comprise tubulin monomer with 15 SH-groups and may be attacked by mercurials (Syversen and Kaur, 2012). Also, neuroinflammation, including microglial activation could be induced by Hg compounds (Dewi et al., 2012). Different cellular SH-levels and localizations may be involved in the selective toxicity of Hg compounds (EFSA, 2012). The phenomenon of "molecular mimicry" indicates that low molecular weight thiols such as e.g. cysteine have an important role in the circulation and transport of Hg compounds through the body. Thus, CH_3Hg-cysteine resembles the essential amino acid methionine, and MeHg appears to be absorbed and imported into cells bound to cysteine by the same mechanism. On the other hand, chelating thiols such as dimethylcysteine (penicillamine) as well as *meso* − 2,3-dimercaptosuccinic acid (DMSA) and sodium 2,3-dimercaptopropanesulfonate (DMPS) inhibit cellular uptake of mercurials (Aaseth et al., 1981). And the two latter antidotal agents are considered to be drugs of choice in treatment for Hg toxicity (Rooney, 2007; Aaseth et al., 2016a). Other chelation agents such as alpha-lipoic acid (ALA), a disulfide, and its metabolite dihydrolipoic acid (DHLA), the corresponding dithiol, have also been reported to possess chelation properties (Ou et al., 1995).

Unlike MeHg elemental Hg vapor (Hg^0) is taken up by diffusion into neurons and glia, and subsequently oxidized to inorganic Hg through the action of catalase. The oxidized Hg^{2+}-ions can link to the thiol groups in most proteins as well as to the tripeptide glutathione (Clarkson, 2002). Supplements that have been proven to be efficient in mitigating metal toxicity include sulfur containing amino acids like taurine (Agha et al., 2014), cysteine, and methionine. They can assist the excretion and can reduce the associated oxidative stress. Also, it has been suggested the protective effect of taurine is related to its antioxidative action and anti-inflammatory efficacy (Agha et al., 2014).

6. Immune activation and autoimmunity

A group of systemic autoimmune disorders known as connective tissue disease (CTD), which are composed of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Sjögren's syndrome (SS) are characterized by a broad spectrum of clinical features and multisystem involvement (Iaccarino et al., 2013; Stejskal et al., 2015b). Autoimmune diseases could be induced by an interaction between genetic susceptibility and different factors, which stimulate the onset of diseases such as gender, ethnicity, age, and environment (Crowe et al., 2017). Environmental factors such as mineral oils, drugs and toxic metals including Pb, gold (Au), and Hg induce autoimmune diseases in animal models, and analogs observations have been reported in occupationally exposed humans (Jha et al., 2014). All Hg salts analyzed have immunomodulatory potential (Shenker et al., 1992) as well as allergenic properties (Stejskal et al., 1996). Mercury has been revealed to stimulate autoimmunity in genetically susceptible animals (Pelletier et al., 1988; Goldman et al., 1991; Stejskal, 2015a) and can induce or promote the development of autoimmunity in humans (Stejskal and Stejskal, 1999; Prochazkova et al., 2004). In the other hand, Hg-containing compounds can deeply induce immunostimulation, immunosuppression, immunomodulation, delayed-type hypersensitivity (type 4 allergy), and autoimmunity, through the pathways that involve altering the immune cytokines production (Kern et al., 2014; Berlin et al., 2015). Moreover, a toxic metal such as Hg could act as a hapten, producing a complex with one or more biological macromolecules, which together act as an antigen (Vas and Monestier, 2008; Kern et al., 2014). Mercury is a low-molecular hapten and only rarely produce antibodies (Stejskal, 2015a). Genetic factors such as major histocompatibility complex genes could influence on these effects that they are widely variable among individuals (Vas and Monestier, 2008). Numerous studies revealed that the responses of the immune system to Hg could be a factor in the development of various autoimmune diseases (Sterzl et al., 1999; Hybenova et al., 2010). Also, remarkable overexpression of pro-inflammatory cytokines like interferon (IFN)-gamma was reported in the multiple chemical sensitivity individuals (De Luca et al., 2010), indicating metal-induced inflammation could be a critical risk factor in the majority of metal-sensitized patients (Stejskal et al., 2013). It has been suggested that Hg-induced autoimmunity could result from the generation of autoreactive T cells and a defect at the T suppressor level in $HgCl_2$-injected Brown-Norway (BN) rats (Pelletier et al., 1988). Also, Hg has been found to induce autoimmune diseases in exposed animals with pathophysiologic signs of the lupus-like syndrome and specific autoantibody overproduction (Silbergeld et al., 2005). Mice exposed to MeHg (organic Hg) may also suffer from autoimmunity but without any immune complex formation (Crowe et al., 2017). Another study using murine models reported that the exposure to subtoxic levels of Hg in genetically susceptible strains of mice provoked an autoimmune disease characterized by the production of highly specific anti-nucleolar autoantibodies, hyperglobulinemia, and nephritis (Jha et al., 2014). Moreover, a wide range of clinical observations revealed that Hg exposure could induce multiple sclerosis and other autoimmune diseases (Stejskal, 2015a). Furthermore, in a study, 72% of patients with oral lichen planus, another kind of autoimmune disease, demonstrated a significant response to Hg in vitro (Stejskal et al., 1996). After removal of dental amalgams, local and systemic symptoms remarkably decreased. However, a mixed population analysis comprising metal-allergic patients, and patients with oral problems, or skin hypersensitivity revealed that oral exposure to palladium (Pd), Au or Hg did not influence autoimmune disease development (Rachmawati et al., 2015). Cathepsin B appears to regulate the severity of Hg-induced autoimmune and inflammatory responses, which is important when following adaptive autoimmune response to environmental factors (Toomey et al., 2014). Data provided by National Health and Nutrition Examination Survey, 2009–2012 revealed that celiac disease (CD), also an autoimmune disease, was related to relatively low contents of blood Pb and Hg in children but not in adults, indicating that low levels of toxic metals in blood may represent outcomes of CD in the US children (Kamycheva et al., 2017). In sum, it is proposed that inorganic Hg precipitates markers of autoimmunity to a greater extent than organic Hg, although its effects on human clinical outcomes need to be clarified.

7. Effects on DNA, RNA and protein synthesis

Interaction of MeHg with the synthesis of DNA, RNA, and protein are documented in several studies (Yoshino et al., 1966; Gruenwedel, 1970; Sarafian and Verity, 1983; Syversen and Kaur, 2012; Basu et al., 2014). It is proposed that the attachment of Hg to SH-groups has a significant role in secondary changes in DNA and RNA and structural modifications in ribosomal proteins. The exposure to Hg compounds may be associated with epigenetic changes such as DNA methylation (Goodrich et al., 2013). A role of Hg exposure was attested in the hypermethylation of Rnd2 gene in Hg-treated mouse embryonic stem cells (Yoshikazu et al., 2011). On the other hand, Hg exposure could be linked with DNA hypomethylation as assessed in brain tissue of the polar bear (Richard Pilsner et al., 2010). A significant decrease in cerebellar and cerebral synaptosomes and brain protein synthesis was found during the neurotoxic phase of MeHg exposure (Verity et al., 1977). It has been reported that Hg can be concentrated in the smooth

endoplasmic reticulum of small Indian mongoose (*Herpestes auropunctatus*) (Horai et al., 2014) and induce degenerative modifications in rough endoplasmic reticulum, resulting in biochemical changes (Syversen, 1981). Numerous researchers have reported reduced protein synthesis resulting from Hg exposure both in vivo and in vitro (Yoshino et al., 1966; Cavanagh and Chen, 1971; Syversen, 1981). The inhibitory activity on protein synthesis of inorganic Hg was reported approximately ten times stronger than of MeHg in the cell-free systems prepared from mouse glioma, rabbit reticulocytes and Yoshida ascites sarcoma cells (Nakada et al., 1980).

8. Interaction of mercury with microtubules

Microtubules are filamentous intracellular structures that are responsible for the maintenance of the three-dimensional cellular structure as well as different movements in all eukaryotic cells. Microtubules are composed of polymers of tubulin and various kinds of microtubule-associated proteins (MAPs) which is attached to their surfaces (Syversen and Kaur, 2012). There are at least 13 free SH-groups per tubulin monomer. Presumably, microtubules can be protected by selenoproteins in the neuronal cytosol (Aaseth et al., 2016b). Various kind of cellular functions such as axonal and dendritic transport (Kreutzberg, 1981; Lasek, 1981) neuronal growth and differentiation (Solomon et al., 1981; Sarma et al., 2015), structural maintenance (Burkhardt, 1998) and cellular migration (Ridley et al., 2003; Bartolini et al., 2016) are attributed to the microtubules. Methylmercury reveals a high affinity for SH-groups of tubulin (Vogel et al., 1985), which may lead to the depolymerization and derangement of cerebral microtubules (Carratù and Signorile, 2015). Also, exposure to MeHg could be a potential risk factor for neuropsychiatric and neurodegenerative diseases, presumably because this mercurial can attenuate expression of microtubule-associated protein-2 (MAP-2) in neurons and lead to hyperphosphorylation of tau. Also, it could induce deficits in hippocampus-dependent spatial learning and memory during adolescence apparently due to inhibited development of dentate gyrus neurons (Tian et al., 2016). In sum, MeHg could induce adverse effects on cytoskeletal proteins (microtubules) and cytoskeleton-regulating proteins (Rho family proteins), causing disturbances in neuronal migration and differentiation (dos Santos et al., 2016).

9. Mercury and membrane transport

Depending on the Hg species, the uptake into the cells can be active, energy-dependent (e.g. MeHg-cysteine) as well as passive (e.g. MeHgCl in cell cultures) (Heggland et al., 2009; Aschner and Clarkson, 1988). It has been revealed that inhibition of the glutamine/amino acid (ASCT2) transporter could be induced by MeHg (Oppedisano et al., 2010). The studies indicated that the inhibition resulted from a coordinative binding of the mercuric compounds to the Cys residue(s) of the transporter (Oppedisano et al., 2010).

The ASCT2 is an ASC (alanine-, serine-, cysteine-preferring) neutral amino acid exchanger that has a physiological function in the transport of amino acid substrates such as L-serine, L-glutamine, L-cysteine and/or L-glutamate and D-serine (Gliddon et al., 2009), thereby playing an essential role in intracellular glutathione synthesis.

It has been presumed that the ASCT2 transporter has an important function in clearing excitotoxic L-glutamate levels from the extracellular space quickly around Purkinje cells as compared to the clearance around cerebellar granule cells and that MeHg could inhibit this clearance. Also, it was found that chloride concentration and pH influenced the diffusion of inorganic Hg (Hg^{2+}) through planar lipid bilayer membranes (Gutknecht, 1981). Moreover, acute exposure to minute submicromolar concentrations of MeHg could inhibit barium (Ba^{2+}) transport carried out by multiple Ca^{2+} channel subtypes in primary cultures of cerebellar granule cells (Sirois and Atchison, 2000).

Simultaneous incubation with organic methylmercury chloride (MeHgCl) and Thimerosal allowed Hg to cross the blood-brain barrier in both directions, but with a slight accumulation in the brain facing compartment, while, for inorganic $HgCl_2$, the blood-brain barrier cells transfers Hg out of the brain (Lohren et al., 2016).

Another study revealed that the lipodepsipeptide syringomycin E (SR-E), a member of the lipodepsipeptide family, interplays with two Hg-supported biomimetic membranes, which contain a self-assembled phospholipid monolayer (SAM) in addition to a tethered bilayer lipid membrane (tBLM. These structures which were separated from the Hg surface by a hydrophilic tetra ethylene oxy (TEO) spacer appeared to act as a reservoir of Hg^{2+}-ions (Becucci et al., 2015).

Given that Hg species disturb amino acid transport and energy metabolisms and also may induce phospholipid breakdown, it is important to investigate further how MeHg can penetrate across biological membranes, in order to design novel approaches to inhibit its transfer both at the placental border and at the blood–brain barrier.

It is well known that MeHg usually is linked to sulfhydryl-containing molecules including cysteine in the environment to compose a MeHg–cysteine complex (MeHg-S-Cys) acting as a mimic of the neutral amino acid, methionine, that can be transported via the L-type neutral amino acid carrier transport (LAT) system. Methionine is a substrate of the neutral L-amino acid transporter system (Syversen and Kaur, 2012). The effects of MeHg (administrated as MeHg-S-Cys)-induced neurotoxicity in mice, and further investigations revealed that L-Met increases cerebellar Hg deposition in mice exposed to MeHg and that simultaneous exposure to MeHg and L-Met could induce greater motor impairment than MeHg alone in mice (Zimmermann et al., 2014). Also, it was shown that the LAT system regulates MeHg- or EtHg-cysteine complex uptake into C6 rat glioma cell line and that MeHg- or EtHg-cysteine complex could induce reduction of intracellular thiols in C6 cells. (Zimmermann et al., 2013).

10. Interactions of mercury with glutathione and cellular redox balance

The intracellular low-molecular-weight thiol glutathione (GSH) induces protective effects, i.e., through its role as a cofactor for the glutathione peroxidase (GPx) selenoenzymes. Astrocytes, notably the cortical astrocytes of brain cells, have a high capacity for GSH synthesis that may explain their relative resistance against Hg toxicity (Bjørklund et al., 2017a). Moreover, brain GSH levels influence the uptake of *elemental* Hg in brain tissue as a 20% decline in brain GSH levels will lead to a substantial increase in brain Hg levels (Eide and Syversen, 1983). One of the most important mechanisms of MeHg-induced toxicity is through the reactive oxygen species (ROS) production and GSH reduction (Farina et al., 2011a). The outcomes of MeHg-induced neurotoxicity appear to be mediated by a disturbed balance between the oxidative and reductive cellular processes. Usually, after MeHg exposure decreased GSH contents coordinate with elevated ROS contents (Sarafian and Verity, 1990; Sarafian et al., 1994; Stringari et al., 2008). However, an epidemiological investigation indicated that both an increase and a decrease in GSH levels could result from MeHg exposure (Grotto et al., 2010). Another study showed that the medicinal herb Bacopa (also called Brahmi) could normalize MeHg-induced reduction of GSH levels, an effect which was attributed to chelating or antioxidant properties of the herbal drug (Ayyathan et al., 2015). Moreover, a protective effect of a diet enriched with the Amazon fruit Euterpe oleracea against MeHg toxicity has been reported, which might be related to the antioxidative polyphenols identified in an extract from this fruit (Brasil et al., 2016). It has been shown that Apocynin, an NADPH oxidase inhibitor (Chandasana et al., 2015) and antioxidant (Heumüller et al., 2008), inhibits mitochondrial damage and oxidative stress induced by MeHg in cultured bovine aortic endothelial cells, indicating a contribution of NADPH oxidase in the MeHg-induced toxicity (Ghizoni et al., 2017). An experimental study on MeHg-exposed neuronal cells revealed that the exposure inhibited the natural phosphorylation of

cofilin, a family of actin-binding proteins which disassembles actin filaments, an effect which was attributed to oxidative deteriorations promoted by MeHg (Caballero et al., 2016). The same authors also reported reduced expression of phosphorylated cofilin in human placentas of individuals exposed to MeHg above the reference dose.

In sum, recent literature suggests that MeHg leads to elevated generation of ROS that may either reduce GSH levels or initiate an adaptive response to oxidative stress by increasing GSH levels.

11. Metallothioneins and mercury

Metallothioneins (MTs) are a family of cysteine-rich, small, low-molecular-weight proteins (6–7 kDa) with 61–68 amino acids which are the most common intracellular metal-binding proteins due to their many SH groups (Aschner, 1996; Andrews, 2000; Malekzadeh and Shahpiri, 2017). For the first time, they were isolated from horse kidney by Margoshes and Vallee (1957). MTs have high affinity to seven divalent and 20 monovalent toxic metal ion species. These interactions have been comprehensively investigated due to their roles in metal detoxification and their involvement in scavenging of free radicals (Krizkova et al., 2016). MTs could protect the brain and gastrointestinal tract against overload by toxic metals. Metals such as Cd and Zn are strongly bound to metallothionein, and they are commonly also potent inducers of apo-metallothionein synthesis (Bjørklund, 2013). In comparison with Zn, Cu is known as a potent apo-metallothionein inducer. However, Zn is the most abundant of the MT-inducing elements (Park et al., 2001), while Cu is also very significant as an MT-inducing metal. In spite of the lower abundance of some toxic metals such as Cd and Hg, they could lead to significant disturbance of Zn and Cu metabolism because of their potency as MT inducers (Underwood, 1977).

Human MTs are the results of a gene cluster at a single locus on chromosome 16q13, and human MTs include four isoforms, MT1, MT2, MT3, and MT4, which differ only by minor structural variations (Miles et al., 2000). Individual MT isoforms could also be expressed and have been detected in various intracellular levels such as cytosol, nucleus, lysosomes, and mitochondria and individual tissues. MT1 and MT2 are the most widely expressed isoforms in most tissues such as the brain, kidney, liver, intestine, and pancreas, while MT3 is mainly expressed in the brain, although it in trace amounts is also expressed in heart, kidney, and stomach. MT4 can be detected in certain stratified squamous epithelia (Aschner et al., 2006; Krizkova et al., 2016). In human, eight members of MT1 (MT-1A, 1B, 1E, 1F, 1G, 1H, 1M, 1X) and one member of MT-2, MT-3 and MT-4 have been identified (Zalewska et al., 2014; Krizkova et al., 2016). The expression of MT1 and MT2 are up-regulated by exposure to metals including Hg, Cd, Cu and Zn, cytokines and ROS, apparently to guard essential cellular functions and elevate survival (Aschner et al., 2006; Tokuda et al., 2007). An experimental study revealed that MT gene deletion could increase the vulnerability to Hg-induced neurocognitive impairment (Eddins et al., 2008). It is also noteworthy that the neuroprotective MT3 isoform is not easily induced by exposure to the agents listed above (Tokuda et al., 2007). The abundance of MTs in the CNS and the recognization of a brain-specific isoform, MT3, indicate important functions of these proteins in the CNS, including neuroprotection, regeneration, and even modulation of cognitive functions (Aschner et al., 2006; West et al., 2008).

The production of MT3 in the hippocampus, amygdala and piriform cortex could be induced by elevated concentrations of vesicular Zn (Faber et al., 2009). Also, Hg-induced elevation in the plasma cytokines could secondarily induce MTs (Yasutake and Nakamura, 2011). Also, the recombinant protein of mouse metallothionein gene (*mt1*) in chloroplasts increases mercury accumulation and phytoremediation capability (Ruiz et al., 2011). Mercury induced toxicity could be regulated by the content of SH-groups such as GSH, MTs, and other SH constituents. Therefore, it is speculated if differences in the cellular SH-levels may be involved in the different sensitivity of various kinds of brain cell and thus the selective localization of Hg toxicity (Bjørklund et al., 2017a). Also, it was found that MTs can modulate various levels of Hg neurotoxicity (Faber et al., 2009). Interestingly, it has been shown that single nucleotide polymorphisms (SNPs) of metallothionein (MT) could increase the susceptibility of children to Hg neurotoxicity (Woods et al., 2013).

12. The role of zinc and copper metabolism, and the redox regulation

The abnormal metabolism of metal ions is involved in health and disease conditions: For example, Hg compounds could replace Zn in the metal binding sites of MTs, indicating a detoxification mechanism by preventing the Hg binding to the active sites of enzymes (Faber et al., 2009). An experimental study revealed that intravenously administered mercuric acetate (Hg^{2+}) along with either cadmium sulfate (Cd^{2+}) or zinc sulfate (Zn^{2+}) for pregnant golden hamsters had different effects upon embryogenesis, and the negative effects of the Hg + Cd combinations are much more severe than those of the Hg + Zn combinations (Gale, 1973). Zinc plays a critical role for the metal-responsive transcription factor 1 (MTF-1) that increases the expression of MT genes in response to toxic metal load. Up- and down-regulations of many genes and enzymes responsible for toxic metals elimination could be affected by MTF-1 (Wang et al., 2004; Wimmer et al., 2005). Also, bioaccumulation of silver (Ag^{+}) is notably influenced by the presence of Zn, Cu, and Se in the water. This fact reflects the complex interactions occurring between elements (Ribeyre et al., 1995). Also, Cu plays an important role in the regulation of MT synthesis. These proteins have a high affinity for Cu, and the synthesis of MTs rise as a result of Cu overloads (Arredondo and Núñez, 2005; Faber et al., 2009). MT could retain Cu within intestinal cells and thereby inhibit its systemic absorption (Russo and deVito, 2011). Zinc absorption is also inhibited by MT, suggesting the reasons why overloads of Cu hinders the intestinal absorption of Zn and vice versa (Bjørklund, 2013). It is critical to follow the values for both Zn and Cu during Zn therapy due to the mutual antagonism of these two trace elements, both of them essential for living cells (Bjørklund, 2013).

The expression of MTs appears to be metal regulated as well as redox-regulated (Andrews, 2000) so that elevated oxidative stress heighten the MT expression, which presumably lowers the availability of Zn and Cu as cofactors in enzymes or other proteins. Also, Hg can interact with Zn and Cu availability through its binding to DNA and redox-regulating transcription factors (Qian et al., 2001).

13. Selenium and mercury

Selenium is a chemical element with atomic number 34 that was discovered in 1817 by the Swedish chemist Jöns Jakob Berzelius (1779–1848). The Se structure contains six valence electrons among which two are unpaired. Considering this fact, it can form six covalent bonds due to 4d orbitals. In compounds containing oxygen, it has + 6, + 4, and + 2 oxidation states, such as + 6 in selenium trioxide, + 4 in selenates and + 2 in selenites. Furthermore, it forms binary compounds with an oxidation state of − 2, such as in hydrogen selenide (H_2Se) and organic selenides such as selenomethionine (SeMet) (Bjørklund et al., 2017a). Mercury binds to Se with an extraordinarily high affinity (log K 10^{45}) when compared with the affinity for sulfur (log K 10^{39}) under comparable conditions (Dyrssen and Wedborg, 1991; Berry and Ralston, 2008). The high capability of Se to reduce the toxicity of Hg compounds has been recognized for nearly five decades, and in recent years some aspects of the underlying molecular mechanisms begun to be understood (Bjørklund et al., 2017a). The amino acid selenocysteine differs from cysteine only by one single atom (Se versus Se versus Se versus S), which leads to a higher nucleophilicity and reactivity of the functional Se ligand groups in selenoproteins compared to sulfur proteins. An epidemiological study revealed that small amounts of Hg co-eluted with Se-containing protein such as glutathione peroxidase 3

(GPx3), selenoprotein P (SelP) and selenoalbumin (SeAlb) and up to 50% of plasma Hg was linked to SelP (Achouba et al., 2016). In general, specific selenoproteins include one selenocysteine (SeCys) per molecule, but selenoprotein P, that mainly acts as a selenium transport protein, has ten selenocysteines among which two are involved in seleno–S bridges. Selenoprotein P is also an important extracellular antioxidant, especially in nervous tissue (Driscoll and Copeland, 2003), and this protein appears to be essential for neuronal survival and function (Traulsen et al., 2004).

It has been reported that increase of SeMet levels in adult fish and their eggs decreased the toxicity of Hg toxicity (Penglase et al., 2014). Due to the Se antioxidant activity, a diet enriched with this element could lead to maintained antioxidant ability during mercury exposure and also, induce raised excretion of Hg (Copat et al., 2014). Also, a biosynthetic preparation of nano-selenium by a selenite-reducing bacterium, *Citrobacter freundii* Y9, has been proposed as remediation for Hg-contaminated soil, and this product has appeared to be a functional and cost-effective venture for contaminated surface and subsurface soils with Hg (Wang et al., 2017).

Numerous investigations have revealed that Se compounds prevent Hg-induced toxicity through several mechanisms such as Hg sequestration (Magos et al., 1979; Ralston et al., 2008; Chen et al., 2017), antioxidative activity (Kaur et al., 2009; Ralston and Raymond, 2010), GSH synthesis (Burk, 2002), elevated GPx activity (Michalke and Schramel, 1997), increased selenoprotein concentrations (Ralston et al., 2007) as well as facilitated MeHg removal by demethylation (Khan and Wang, 2010). Moreover, an experimental study revealed that pretreatment with Se could decrease Hg content in suckling rat tissues, although an adequate essential element status was preserved (Orct et al., 2015).

Thus, current knowledge indicates that Hg can be detoxified by Se-containing molecules leading to the formation of various complexes such as $(MeHg)_2Se$, MeHg-selenol compounds, inorganic Hg-selenol compounds, HgSe, (HgSe)n-SelP (Khan and Wang, 2009). Despite the common description of Hg(II) as a thiophilic atom, the results of the reviewed studies underscore the "selenophilic" properties of mercurials. More comprehensive information about the direct interaction between Hg and Se could be found in exhaustive reviews published by Khan and Wang (2009), Bjørklund (2015), and Bjørklund et al. (2017a).

14. Concluding remarks

Mercury is known as the 80th element of the periodic table, and its toxicity can be considered a global epidemic, as it may affect approximately everyone on our planet. Mercury toxicity is involved in a variety of neurological deteriorations, including cognitive disorders and autoimmune dysfunctions. Early detection and treatment of Hg burden as well as optimization of nutritional status are critical for effective detoxification and prevention of Hg toxicity (Gerhardsson and Aaseth, 2016).

In particular, the compound MeHg can affect the nervous system, and it concentrates preferentially in cells of glial origin, thereby inducing oxidative stress and neuroinflammation (Farina et al., 2011b). Moreover, MeHg causes disruptions in amino acid metabolism and membrane phospholipid breakdown. Bioaccumulates of MeHg in aquatic food chains and the capacity to cross the blood–brain barrier make this metallic compound more disturbing than inorganic Hg. Recently, epidemiological studies have revealed that pregnant women who ingest a fish-heavy diet with significant amounts of MeHg are at increased risk of giving birth to children with neurological deficits (Julvez et al., 2016). Regarding this issue, the U.S. Environmental Protection Agency expressed a national warning in 2001 recommending that pregnant women and infants limit their intake of fish (US EPA, 2001), which was followed by similar warnings in Japan, U.K., Canada, Australia, and Norway. Thus, the critical effects of MeHg on human health are a worldwide concern.

Occupational exposure to inhaled Hg can be high, e.g., in dentistry (Khwaja and Abbasi, 2014) and chloralkali factories (Ellingsen et al., 2001), causing adverse effects in the lungs as well as on the visuosensory system (Fell et al., 2016).

The toxicity profile of EtHg is different from that of MeHg. However, in real-life scenarios, co-exposure with EtHg and MeHg might induce more adverse neurotoxic effects than each agent alone in developing mammals. Also, there are complex interactions between Hg compounds and other elements, such as i.a. Ag, Pb, Zn, and Cu, resulting in different conditions of metal bioaccumulation in the whole organism and critical organs. Therefore, the present knowledge on this subject is still incomplete, and studies are required to address the predictability of the additive toxicological effects of EtHg and MeHg, as well as other neurotoxicants.

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