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Occurrence, use and potential toxic effects of metals and metal compounds

Ana-Maria Florea & Dietrich Büsselberg*
*Institut für Physiologie Universitätsklinium Essen, Universität Duisburg-Essen, Hufelandstrasse 55, 45122, Essen, Germany; *Author for correspondence (Phone: +49-0-201-723-4627; E-mail: Dietrich.Bberg@uni-essen.de)*

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Abstract

Metals and metal compounds are constituents of our natural environment. Their distribution depends on the existence of natural sources (e.g. volcanoes or erosion) and their use in human's activity. They are transformed naturally (e.g. by bacterial activity) with formation of organic species that influence their mobility and accumulation in abiotic as well as biotic systems. Up to date metal species are released into the environment questioning their influence on human health. Due to their widespread use in human activities such as industry, agriculture and even as medicine (e.g. As, Se, Pt), numerous health risks may be associated with exposure to these substances. Different reports on metal intoxication are documented and studies especially on neurotoxicity, genotoxicity, or carcinogenicity, are previously published in numerous articles. This mini-review gives an overview on the use and the actions of selected metal species of actual scientific concern, with a focus on neuronal cells.

Introduction

Metals and metal compounds are natural constituents of all ecosystems, moving between atmosphere, hydrosphere, lithosphere, and biosphere (Bargagli 2000). Their distribution in the environment is a result of natural processes (volcanoes, erosion, spring water, bacterial activity) and anthropogenic activities (fossil fuel combustion, industrial and agricultural processes) (for review see Florea *et al*. 2004; Florea 2005). While, compounds containing Cd, Cu, Cr, Hg, Ni, Pb, and Zn are industrially produced, metallic derivatives containing Cu, Co, As, Sb, Zn, Cd, Au, Cl, C and Pb, are also used in home activities (Fergusson & Kim 1991; Abdulla & Chmielnicka 1990). Therefore, metal compounds are also increasingly introduced in the environment and could finally accumulate in a/biotic systems (Nordberg *et al*. 1985; Han *et al*. 2002). In addition, acidification (e.g. upon acid rain fall) may increase their bioavailability and possibly raise their toxic potential (Nordberg *et al*. 1985; Wood *et al*. 1978; Bryan & Langston 1992; Han *et al*. 2002).

Exposure to heavy metals is potentially harmful especially for those metal-compounds, which do not have any physiological role in the metabolism of cells. The ingestion of metals via food or water could modify the metabolism of other essential elements such as Zn, Cu, Fe and Se (Abdulla & Chmielnicka 1990). Furthermore, most metals are capable of forming covalent bonds with carbon, resulting in metal-organic compounds. Such a transformation (by methylation or alkylation) influences their mobility, accumulation as well as their toxicity (e.g. Pb, Zn, Cu, Cd, As, Sb, Cr, Ca, Na, Au, Cl, Br (Fergusson & Kim 1991)) (reviewed in: Büsselberg 1995, 2004; Florea *et al*. 2004; Cook *et al*. 2005; Florea 2005). Prolonged exposure to metals and metal compounds could result in dysregulation of cellular pathways causing subsequent toxicity (Fitsanakis & Aschner 2005). Metals and metal compounds interfere with functions of the central nervous system (CNS),

the haematopoietic system, liver and kidneys. Recently, more attention and concern is given to metal compounds that have toxic effects at low levels of exposure than those that produce overt clinical and pathological signs and symptoms (Kalia & Flora 2005).

In general, the toxic properties of metal-organic compounds differ from those of the inorganic forms. Due to their ability to reabsorb and accumulate metals, kidneys are one of the first target organs of metal toxicity (Barbier *et al.* 2005). Furthermore, numerous authors described induction of genotoxicity and cytotoxicity by metallic species (for review see Florea *et al.* 2004; Florea 2005; Florea *et al.* 2005a, Florea & Büsselberg 2005). Cell signalling components affected by metals include growth factor receptors, G-proteins, MAP kinases, and nuclear transcription factors (Harris & Shi 2003). The neurotoxicity of metals is associated with their ability to penetrate the blood-brain barrier (Clarkson 1997, 1990). Therefore they are able to produce severe damage and impair higher cognitive functions (e.g. lead, aluminium, tetraethyllead, triethyltin, trimethylbismuth and methylmercury) (Akila *et al.* 1999; Torrente *et al.* 2005).

The use, benefits, sources of human exposure and potential (neuro)toxicity of selected inorganic as well as organic forms of metals are described in this mini-review. We focus on arsenic, lead, mercury, platinum, and tin because these are environmental relevant metal species to which humans could easily get exposed. Furthermore, the scientific interest increased on those metal compounds over the last years since human exposure could result in health problems.

The occurrence, use and toxic neuro-potential of metals and metal compounds

Arsenic

Occurrence/use/sources of human exposure

Arsenic (As) is a common environmental contaminant and human exposure comes from contaminated water and soil as well as from food rich in arsenic species (e.g. garlic, marine food). Another source of arsenic exposure is related to occupational activities (Hughes 2002; Rodriguez *et al.* 2003), since arsenic is used in pesticides, wood preservatives, and in the production of glass, paper, and semiconductors. In spite of its high toxicity, arsenic is a common contaminant in pharmaceuticals (Bohrer *et al.* 2005) and is used for therapeutic purposes, e.g. for the treatment of chronic myelogenous leukaemia, leishmaniosis and trypanosomiasis (for review see Florea 2005; Florea *et al.* 2005a). Arsenic trioxide has been proven to be effective in the treatment of various types of cancers by inducing G(2)/M arrest (Akay *et al.* 2004). Accidentally, the presence of arsenite and arsenate species in solutions of amino acids, salts, vitamins, and lipids commercialized for i.v. administration was documented (Bohrer *et al.* 2005).

Potential (neuro-)toxic effects

While there is evidence that exposure to arsenic is toxic in the nervous system, there are only few studies analysing neuronal aspects at the cellular level. Polyneuropathies, EEG abnormalities up to hallucinations, disorientation and agitation have been described by Rodriguez and co-workers (2003). Arsenic at a non-lethal level in drinking water consumed over a longer period of time has been reported to produce chronic toxicity and various types of health problems ranging from skin cancer to disturbance in memory. Neurotoxic effects have been reported in clinical cases with chronic exposure to arsenic.

Arsenic and its methylated derivatives are found to be distributed in different organs and systems. Arsenic toxicity induces damage to brain cells prior to more visible clinical conditions. The deleterious effects also pass from the maternal to foetal tissue across the transplacental barrier (Chattopadhyay *et al.* 2002b). Human foetal brain explants exposed to arsenic in culture showed disturbance in lipid peroxidation, generation of nitric oxide (NO), reactive oxygen species (ROS) and apoptosis (Chattopadhyay *et al.* 2002a; Milton *et al.* 2004). In addition, human exposure to arsenic causes cancer, liver damage and dermatosis. As a possible mechanism of action of inorganic arsenic in the pentavalent state a replacement of phosphate is discussed. In the trivalent state arsenic may react with critical thiols in proteins and inhibit their activity. Its role in the induction of cancer is not well understood. Potential mechanisms include

genotoxicity, altered DNA methylation, oxidative stress, altered cell proliferation, co-carcinogenesis, and tumour promotion (Hughes 2002). In addition, arsenic has been shown to activate/inhibit a variety of cellular signalling pathways such cell growth, differentiation and apoptosis, e.g. arsenite and arsenate activate the EGFR-Shc-Grb2-MEK1/2-ERK1/2 signalling cascade in NHEK cells (Tanaka-Kagawa *et al*., 2003; Milton *et al*. 2004).

In humans, inorganic arsenic is metabolically methylated to mono-, di-, and tri- methylated forms, and toxicological studies show this process as a toxification pathway (Florea 2005; Florea *et al*. 2005a). Trivalent forms of arsenic have been found as inductors of apoptosis in several cellular systems, and involvement of membrane bound cell death receptors, caspases, calcium stores and intracellular glutathione level have been described (Florea *et al*. 2005a).

Lead

Occurrence/use/sources of human exposure

Lead was widely used for more than 5000 years because this metal is corrosion resistant, dense, ductile and malleable. Therefore it was deployed for building materials, pigments to glaze ceramics, water pipes, ammunition, ceramics glazers, glass and crystals, paints, protective coatings, acid storage batteries, gasoline additives, cosmetics (face powders, lipstick, mascara, etc.), spermicidal (e.g. for birth control), and as a wine preservative (stops fermentation). Due to its wide use, humans are exposed to lead derivatives and have a daily lead intake by food, drinking water and by inhalation.

Lead is one of the oldest known and most widely studied occupational and environmental toxins (Gidlow 2004). Deteriorated leaded paint in old houses remains the most common source of lead exposure for children; however, other lead sources are known, particularly among certain racial/ethnic populations. For example in 2003, the Rhode Island Department of Health recognized litargirio (lead monoxide), used as an antiperspirant/deodorant and a folk remedy in the Hispanic community, as a potential source of lead exposure (Nordberg *et al*. 1985; Centers for Disease Control and Prevention 2005a).

Potential (neuro-)toxic effects

Lead can damage the neurologic, hematologic, and renal systems (Centers for Disease Control and Prevention 2005a). Human exposure to lead has reached levels that result in adverse health effects in certain sensitive segments of the general population in several countries (Nordberg *et al*. 1985). Memory and learning deficits could be clearly correlated to blood lead levels measured in the population (Needleman & Landrigan 1981). Medical treatment of acute and chronic lead and arsenic toxicity is furnished by chelating agents that function by linking together metal ions to form complex ring-like structures called chelates, being used clinically as antidotes for acute and chronic poisoning (e.g. 2, 3-dimercaprol, Meso 2, 3, -dimercapto succinic acid) (Stangle *et al*. 2004; Kalia & Flora 2005).

It was emphasised that occupational lead exposure results in a decline in cognitive function over time having an (1) acute effect on neurobehavioral test scores as a function of recent dose and a (2) longer-term effect on cognitive decline as a function of cumulative dose (Schwartz *et al*. 2004). Chronic lead exposure affects encoding as well as storage and retrieval of verbal information (Marchetti 2003; Bleecker *et al*. 2005). The neurotoxicity of lead has been well established through numerous studies but the cellular processes of lead neurotoxicity remain unknown, thus, oxidative stress plays a primary role in lead-induced neurotoxicity (Reddy *et al*. 2002; Marchetti 2003; Aykin-Burns *et al*. 2005). Recent findings recognized that both calcium dependent proteins and neurotransmitters receptors represent significant targets for lead (Büsselberg *et al*. 1994; Marchetti 2003; Büsselberg 2004) as well as alterations in transcription of genes that are essential for growth and differentiation (Atkins *et al*. 2003). Lead-exposure perturbs the aminergic system in the cerebral cortex, cerebellum and hippocampus and may contribute to the cognitive and behavioural impairments (Devi *et al*. 2005).

Chronic lead nephropathy occurs as a result of years of lead exposure (Brewster & Perazella 2004). Lead is a potent neurotoxin, causing brain damage and cognitive deficits in children even at low exposure levels and lead neurotoxicity can occur after prenatal or postnatal exposure (Huang & Schneider 2004). Dietary calcium supplement has been suggested to children and pregnant

women for prevention of lead toxicity, because of lead-calcium interaction which might have an effect to protect lead peripheral neurotoxicity. However, reduction of occupational lead exposure is the essential way to protect against lead induced neuropathy (Canfield *et al*. 2004; Chuang *et al*. 2004; Needleman 2004). A review on the toxicology of *organolead* has been published by Grandjean and Nielsen (1979). The main chemical among organoleads is tetraethyllead (TEL) and tetramethyllead (TML). TML was used as an additive in motor fuels. These tetra-ethylated or methylated forms are degenerated in the body to the trivalent organic forms, which are also highly toxic. Both forms occurred as environmentally relevant metal(loid)organic compounds. Most of the knowledge about organolead toxicity was obtained by accidental cases of acute fatal poisoning.

The toxicity of organolead differs in several regards from inorganic lead compounds depending on alkylation, while the toxic effects of TEL and TML are essentially similar, although the toxicities of these compounds seem to vary by species in animal experiments (Grandjean & Nielsen 1979). TEL poisoning is limited largely to acute or subacute central nervous system signs and symptoms. Early symptoms of insomnia and anorexia are followed by muscle irritability. Agitated encephalopathy resembling delirium tremens occurs in cases of severe poisoning. Increased deep tendon reflexes and cerebellar signs (tremors and ataxia) are also characteristic in severe cases (Landrigan 1994).

Mercury

Occurrence/use/sources of human exposure

Mercury is used as a component of barometers, thermometers, dental products (amalgam), electrical equipment and in control devices, as well as in fungicides. It was also used in gold industry. Mercurous chloride (calomel) is one of the oldest known pharmaceuticals and is continuously used for its antiseptic properties. It prevents seeds from fungus contamination and it is good to amalgamate other metals. Thimerosol is antiseptic containing 49.5% ethyl mercury that has been used for years as a preservative in many infant vaccines and in flu vaccines (James *et al*. 2005). Extensive use of wood from forests results in soil erosion, which contributes to the accumulation of inorganic and alkylated mercury components in the aquatic ecosystem (Webb 2005). This could result in increased methylmercury (MeHg) concentrations in fish that can be of concern in exposed groups of the population, because methylmercury is almost completely absorbed into the bloodstream (Nordberg *et al*. 1985). Any source of environmental mercury represents a potential risk for human MeHg poisoning, because the methylation of inorganic mercury to MeHg in waterways results ultimately in its accumulation in the sea food chain, which represents the most prevalent source for human consumption (Sanfeliu *et al*. 2003; Shanker *et al*. 2003).

Potential (neuro-)toxic effects

The 'Minamata disease' is the most known incident of organic mercury poisoning (Weiss 1996). The pollution with methylmercury has shown the importance of biologically mediated transformation reactions resulting in organometallic compounds (Chang 1977; Tackeucki *et al*. 1978; Annau & Cuomo 1988; Bellama *et al*. 1988; Sanfeliu *et al*. 2003). An extreme example of metalorganic toxicity is the death of Professor Karen E. Wetterhahn in 1997 when she accidentally exposed herself to dimethylmercury by spilling it on her latex gloves that seeped into her skin. She became ill within a few months after the accident and died in less than 1 year after exposure (Zacks 1997; Hanlon 1998; Siegler *et al*. 1999). Generally, human exposure to mercury results in neurologic and kidney disorders (Centers for Disease Control and Prevention 2005b). The kinetics of toxicity induced by mercury differ among species. For example, alkylmercury, is absorbed and accumulated in the central nervous system (CNS). However, in rodents, kidneys and peripheral nerves are damaged at lower concentrations than those that affect the brain (Magos & Butler 1972; Sirois & Atchison 1996; Sanfeliu *et al*. 2003). Lipid solubility of mercury compounds promotes accumulation in lipid-rich compartments such as the brain. Chronic exposure to the lipid-soluble forms of Hg^0 (elemental mercury) and CH_3Hg^+ (methylmercury) perturb neuromotor, behavioral and cognitive functions (Ratcliffe *et al*. 1996; Sanfeliu *et al*. 2003).

The nervous system is the principal target tissue affected by methylmercury in adults – where it also

affects the calcium homeostasis by reducing currents through voltage gated calcium channels (Shafer & Atchison 1991; Pekel *et al.* 1993; Atchison & Hare 1994; Leonhardt *et al.* 1996a, 1996b; Shanker *et al.* 2003). Kidney is the critical organ following the ingestion of mercury salts (Jonnalagadda & Rao 1993). Mercuric chloride as well as methylmercury inhibit lymphocyte functions including proliferation, expression of cell activation markers on cell surface and cytokine production. These cells exhibit a greater sensitivity to the immunotoxic effects of MeHg than to mercuric chloride (Moszczynski 1997). Induction of apoptosis was observed in human lymphocytes after treatment with MeHg. A key event in the induction of apoptosis is the depletion of all thiol reserves, which predisposes cells to ROS damage and at the same time activates death-signalling pathways (Shenker *et al.* 1998). Environmental exposure to mercurials continues to be a public health issue due to their deleterious effects on immune, renal and neurological function. Chronic exposure to methylmercury during fetal and postnatal development had sex-dependent effects on horizontal exploration and on working memory in the modified T maze, and no effects on motor coordination learning and reference memory (Goulet *et al.* 2003).

Recently the safety of thimerosal, an ethyl mercury-containing preservative used in vaccines, has been questioned due to exposure of infants during immunization. Mercurials have been reported to cause apoptosis in cultured neurons; however, the signalling pathways resulting in cell death have not been well characterized. Cytochrome c was shown to leak from the mitochondria upon organic mercury exposure (thiomersal), followed by caspase 9 cleavage, caspase 3 activation, deleterious effects on the cytoarchitecture and initiation of mitochondrial-mediated apoptosis (Humphrey *et al.* 2005). Because mercury has a high affinity for thiol (sulfhydryl (-SH)) groups, the thiol-containing antioxidant, glutathione (GSH), provides the major intracellular defence against mercury-induced neurotoxicity (James *et al.* 2005). Astrocytes are targeted by MeHg toxicity and they increase neuronal resistance (Shanker *et al.* 2003; Morken *et al.* 2005). It was also shown that skeletal muscle is an important deposit of MeHg (Gonzales *et al.* 2005).

Platinum

Occurrence/use/sources of human exposure

Accumulation of platinum derivatives in the environment has been increased over the last decades. Catalytic converters of cars are one of the main sources of platinum (Pt) compounds in the environment. Studies show that the concentration of these metal species has increased significantly in diverse environmental matrices; like airborne particulate matter, soil, roadside dust and vegetation, river, coastal and oceanic environment. Platinum content in the form of road dust can be soluble; consequently, it contaminates waters, sediments, soil and finally, the food chain. The effect of chronic occupational exposure to platin compounds is well documented, and certain platin species are known to exhibit an allergenic potential (Ravindra *et al.* 2004). Also platin compounds are used in anticancer therapy (Basu *et al.* 2004).

Potential (neuro-)toxic effects

The anti-cancer drug cisplatin has an apoptotic effect in carcinoma cells (Basu *et al.* 2004; Wang *et al.* 2004) by stimulating the Mitochondrial Signalling Pathway (MSP) via an activated caspase 3 and an increase in synthesis of ceramide (Basu *et al.* 2004). Furthermore an application of cisplatin increased the intracellular calcium concentration in human cervix adenocarcinoma cells but not in osteosarcoma cells showing a high specificity of action (Splettstoesser & Büsselberg 2005). Cisplatin inhibits enzymes by a direct interaction with sulfhydryl groups, whereas the zinc-binding sites are only involved with the higher concentrations of cisplatin (Trevisan *et al.* 2004).

The platinum drugs cisplatin, carboplatin and oxaliplatin are the most useful anticancer agents available having also the potential to produce both mild and more serious side effects (Markman 2003; Lehky *et al.* 2004). For example, following oxaliplatin infusion, patients experience cold-induced paresthesias, throat and jaw tightness, and occasionally focal weakness. The acute neurological symptoms reflect a state of peripheral nerve hyperexcitability but chronic treatment causes an axonal neuropathy (Lehky *et al.* 2004).

Chemotherapy-induced peripheral neurotoxicity is a major clinical problem because it represents the dose-limiting side effects of a significant

number of antineoplastic drugs (Cavaletti & Marmiroli 2004; Cavaletti *et al*. 2004; Donzelli *et al*. 2004). Cisplatin also causes apoptosis of dorsal root ganglia (DRG) neurons by binding to neuronal DNA. Disproportionate platinum accumulation may explain why a drug aimed at killing rapidly dividing cells causes sensory neurotoxicity (McDonald *et al*. 2005). The study of the proteins involved in the intracellular transduction pathways that may cause apoptotic death, revealed a very similar pattern of changes after exposure to cisplatin or oxaliplatin e.g. Bcl-2 was significantly reduced, p53 increased, caspases 3 and 7 were activated, p38 protein was activated. The mechanism of action for cisplatin and oxaliplatin induced neurotoxicity are very similar and include DNA damage, and the modulation of specific molecules involved in regulating the cellular equilibrium between apoptotic death and the cell cycle (Donzelli *et al*. 2004).

Tin

Occurrence/use/sources of human exposure

Organotin compounds are ubiquitous in the environment contaminating the sea water and air (White *et al*. 1999, Florea 2005). Alkyltin salts or organotins have been widely used in material sciences and agriculture as antifouling agents and fungicides (Fent 1996). Widespread contamination of harbour sediments occurs globally due to the ongoing use of organotins in antifouling paints on large ships (Fent 2003). Organotins belong to the most toxic pollutants known so far for aquatic life having high toxicity, high environmental persistence, and often high mobility, contaminating the groundwater. In addition, high lipophilicity results in bioaccumulation in food webs (Fent 2003).

Potential (neuro-)toxic effects

Effects of tributyltins from antifouling paints on oysters and neogastropods have been documented and their toxicity has undoubtedly led to environmental degradation (Bryan & Langston 1992). Tin compounds have specific cytotoxicity and therefore they have a limited use as potential anticancer drugs (Gielen *et al*. 2000). In their review Barnes and Stoner (1959) showed the difference in the quantitative and qualitative toxicity of organotin compounds and species differences in susceptibility to particular compounds. The di- and tri-substituted organotin derivatives are the most toxic, tetraalkyltin becomes toxic after the loss of one alkyl group. The acute toxicity of trialkyltins rapidly declines with the length of the alkyl radical, mostly because of their lower gastrointestinal absorption (Stoner *et al*. 1955; Barnes & Stoner 1958). Organotin toxicity in micro-organisms increases with the number and chain length of organic groups bonded to the tin atom. Tetraorganotins and inorganic tin compounds have little toxicity. In general organotins are regarded as membrane permeable because of their lipophilicity. Thus, the site of action of organotins may be at the cytoplasmic membrane and at the intracellular level. Hence, surface adsorption and/or accumulation within the cell might lead to the toxic effects of tin (Florea 2005; White *et al*. 1999).

Snoeij *et al*. (1987) described four different types of target organ toxicity: neurotoxicity, hepatoxicity, immunotoxicity, and cutaneous toxicity. The effects of the organotin compounds on the mitochondrial and cellular level are summarized in relation to the mode of action of these compounds on the central nervous system, the liver and bile duct, the immune system, and the skin (Stahnke & Richter-Landsberg 2004; Todd 2005).

Toxicity of monomethyltin, dimethyltin, dibutyltin and trimethyltin was assessed in neuronal PC12 cells. Dibutyltin was most toxic, followed by trimethyltin whereas monomethyltin was not toxic (Jenkis *et al*. 2004). One of the targets of tributyltin compounds is the central nervous system where they may affect dopamin (Tsunoda *et al*. 2004). It is suggested that IL1alpha/beta expressed in reactive astrocytes participate in TMT neurotoxicity via type II glucocorticoid receptors (Liu *et al*. 2005). Recently, we have demonstrated that also the intracellular calcium signalling is modulated by trimethyltin in a concentration dependent manner (0.25–500 μM) in neuronal and non-neuronal cell lines (Florea *et al*. 2005b, c). Whether such changes of the intracellular calcium signals could be correlated to apoptotic or necrotic cell death is still a matter of discussion (Florea 2005).

Conclusion

Intake of metals occurs by ingestion of food and water and by inhaling contaminated air. While some metals are essential, others are highly toxic, even in very small amounts. While the toxicity could be more pronounced in specific tissues as it is the case for the metal based anti-cancer drugs, this clearly indicated that, there is not a 'common' way in which metals interact with cells or body function. At the cellular level, different (membrane) proteins are targeted and different pathways could be involved, depending on the metal component. This is not only true for the more complex organic components; even the inorganic double charged cations have very specific sites of actions. Therefore, in a case of intoxication, it is of immense importance to determine which metals humans were exposed to. Acute signs of toxicity are not obvious especially when exposed to relatively small amounts. However, contioued exposure over prolonged intervals, as it might occur by chronic uptake of contaminated food or drinking water, toxicity might become apparent.

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