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Review

Metals, oxidative stress and neurodegeneration: A focus on iron, manganese and mercury

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ABSTRACT

Essential metals are crucial for the maintenance of cell homeostasis. Among the 23 elements that have known physiological functions in humans, 12 are metals, including iron (Fe) and manganese (Mn). Nevertheless, excessive exposure to these metals may lead to pathological conditions, including neurodegeneration. Similarly, exposure to metals that do not have known biological functions, such as mercury (Hg), also present great health concerns. This review focuses on the neurodegenerative mechanisms and effects of Fe, Mn and Hg. Oxidative stress (OS), particularly in mitochondria, is a common feature of Fe, Mn and Hg toxicity. However, the primary molecular targets triggering OS are distinct. Free cationic iron is a potent pro-oxidant and can initiate a set of reactions that form extremely reactive products, such as $OH^{\cdot}$. Mn can oxidize dopamine (DA), generating reactive species and also affect mitochondrial function, leading to accumulation of metabolites and culminating with OS. Cationic Hg forms have strong affinity for nucleophiles, such as –SH and –SeH. Therefore, they target critical thiol- and selenol-molecules with antioxidant properties. Finally, we address the main sources of exposure to these metals, their transport mechanisms into the brain, and therapeutic modalities to mitigate their neurotoxic effects.

1. Introduction

Analogous to carbon-based molecules, metals are crucial for the maintenance of cell homeostasis and preservation of life. They display important structural, regulatory and catalytic functions in different types of proteins, such as enzymes, receptors and transporters (Phipps, 2002). Among the 23 elements with known physiological functions, 12 are metals (sodium, magnesium, potassium, calcium, vanadium, chromium, *manganese (Mn)*, *iron (Fe)*, cobalt, copper, zinc, and molybdenum) (for a review, see Fraga, 2005). Nutritional deficiencies in specific trace-element metals [Fe (Cook et al., 1994; Goodnough, 2012), zinc (Chasapis et al., 2012) and Mn (Takeda, 2003)], as well as genetic disorders leading to altered metal homeostasis (Kodama et al., 2012; Nandar and Connor, 2011), culminate in human diseases. At the other spectrum, exposures to toxic levels of essential metals, such as Mn (Racette et al., 2001), Fe (Schumann, 2001) and zinc (El Safty et al., 2008), may lead to pathological conditions. Of particular importance, *oxidative stress* and *neurodegeneration* have been reported as consequences of toxic exposures to essential metals, along with dyshomeostasis in essential metal metabolism (Bowman et al., 2011; Brewer, 2012; Jaiser and Winston, 2010).

Xenobiotic metals with no physiological functions, such as aluminum, cadmium, lead and *mercury*, are present in measurable concentrations in living organisms (Fraga, 2005). Such metals often enter organisms by molecular mimicry, utilizing inherent transporters for essential metals (Martinez-Finley et al., 2012). Environmental, occupational or intentional exposures to xenobiotic metals are frequently related to the development of toxicity and pathological conditions (Goyer, 1995; Valko et al., 2005). Notably, exposures to toxic metals, such as mercury (Clarkson et al., 2003), lead (Fox et al., 2012) and aluminum (Bondy, 2010), have been related to the development of neuropathological conditions.

Among the aforementioned essential and non-essential metals, Fe, Mn and Hg have received considerable attention due to their ability to induce oxidative damage and neurodegeneration. Notably, the etiologies of neurodegenerative disease such as Parkinson's disease (PD) and Alzheimer's disease (AD) seem to be greatly dependent on environmental factors or on environmental/genetic interactions (Marras and Goldman, 2011). Of particular importance, specific metals have pro-oxidative properties and can perturb neurodegenerative genes by epigenetic events, leading to altered gene expression and late-onset neurodegenerative diseases (Kwok, 2010). Due to its ability to assume two oxidation states in

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biological systems [ferric (3+) and ferrous (2+)], Fe is an intrinsic producer of reactive oxygen species (ROS), leading to neuronal oxidative stress and neurodegeneration (Nunez et al., 2012). Fe dyshomeostasis has been reported as an important event mediating the physiopathogeny of PD and AD (Bartzokis et al., 2000; Jellinger, 1999). Analogous to Fe, Mn is also of concern due to its ability to cause manganism, an extrapyramidal syndrome resembling idiopathic PD (Benedetto et al., 2009). In contrast to Fe and Mn, Hg is a non-essential metal, whose neurotoxicological properties have been reported several decades ago secondary to environmental epidemic outbreaks (Bakir et al., 1973; Harada, 1978). Humans are continuously exposed to environmental and occupational mercury. Early-life exposures to this metal have been associated with long-lasting and enduring neurobehavioral and neurochemical deficits (Yorifuji et al., 2011). Moreover, *in vitro* experimental studies with neural cells have shown that mercury induces glial cell reactivity (a hallmark of brain inflammation), increases the expression of the amyloid precursor protein and stimulates the formation of insoluble beta-amyloid, which plays a crucial role in the pathogenesis of AD (Monnet-Tschudi et al., 2006). This review provides a synopsis on the chemical properties of Fe, manganese and mercury, as well as on their biological and toxicological aspects, highlighting oxidative stress as a pivotal event in mediating their toxicity. Particular emphasis is directed to their effects on the central nervous system (CNS).

2. Iron

2.1. Properties, chemical forms and human exposure

Iron (Fe) belongs to group VIII of periodic table and is one of the most abundant elements in the earth's crust (Weber et al., 2006) and the most abundant of the transition metals in the periodic table (Wachtershauser, 2007). Therefore, Fe availability to living organism is high, which, added to its redox chemical properties (Bleackley and Macgillivray, 2011), likely contributes to its selection as a central element in mediating energy-related processes in living organisms (Turrens, 2003; Wachtershauser, 2007; Weber et al., 2006). Fe can exist in different oxidation states, varying from −2 to +6; however, within biological systems, it is bound to specific metalloproteins and is found in the +2 or +3 oxidation states; such change in its redox state is crucial to oxidative metabolism (Levi and Rovida, 2009). However, subtle changes in the folding of Fe-containing proteins can modify its coordination bond properties, which changes the physiological and/or pathological role played by the protein in cell biology (Patriarca et al., 2012). In the catalytic cycle of cytochrome P450, which is an important class of enzymes involved in the oxidative transformation and degradation of different xenobiotics and endogenous substrates, Fe is postulated to assume an Fe(IV)oxo (or ferryl) oxidation state (Rittle and Green, 2010). In contrast, the transport and storage of oxygen by hemoglobin and myoglobin in vertebrates does not involve change in the oxidation state of Fe^{2+} (Shikama, 2006).

In view of its widespread distribution in the earth's crust, we are constantly exposed to Fe mainly via food intake. Normally, Fe absorption is physiologically regulated to avoid Fe toxicity (see bellow in Section 2.2.). Sporadic accidental, intentional suicidal or occupational exposure to Fe may occur, but rarely has it been linked to neurotoxicity (Andersen, 2004; Anderson, 1994; Carlsson et al., 2008; Howland, 1996; Jang and Hoffman, 2011; Magdalan et al., 2011; Siew et al., 2008; Sipahi et al., 2002; Tseng et al., 2011). Within the context of neurodegeneration, there is no longitudinal study supporting that a single episode of exposure to toxic Fe levels results in delayed neurodegeneration. With respect to neurodegeneration, limited epidemiological evidence indicates that co-exposure to Fe and other toxic metals (Pb and Cu) present a risk factor for PD (Gorell et al., 1997, 1999).

Biochemically, Fe^{2+} can be easily oxidized to Fe^{3+} and reduced back to Fe^{2+} after interaction with different oxidizing or reducing agents (Levi and Rovida, 2009). These changes in the oxidation state of Fe are crucial for energy production by many living organisms. In aerobic cells, Fe plays a vital role in the transport of electrons derived from food oxidation to molecular oxygen (O_2) located at the end of respiratory chain (Levi and Rovida, 2009). Paradoxically, the redox properties of Fe determine its participation in potentially cytotoxic reactions. In fact, Fe^{2+}can catalyze the decomposition of H_2O_2 with the formation of hydroxyl radical ($OH^{\cdot}$) (Fig. 1), which is normally considered the most reactive and damaging intermediate formed during cellular metabolism (Gutteridge, 1984; Halliwell, 1984, 1992; Halliwell and Turrens, 2003 – Fig. 1). Fe^{3+} can also be reduced back to Fe^{2+} after reacting with superoxide anion ($O_2^{\cdot-}$) (Haber and Weiss, 1932). Consequently, in a pro-oxidant intracellular environment (particularly in mitochondria), the formation of $O_2^{\cdot-}$ can stimulate Fe^{2+}-mediated H_2O_2 decomposition even in the presence of small catalytic amounts of free Fe (the coupling of these two reactions are depicted in Fig. 1) (Halliwell, 1984, 1992; Halliwell and Gutteridge, 1984). Fe^{2+}/Fe^{3+} are also involved in the propagation of lipid peroxidation, by a complex mechanism which has yet to be fully understood; however, it likely involves the direct interaction of Fe with molecular oxygen and ROS, such as organic peroxides (ROOH) formed in biological membranes (Minotti and Aust, 1989, 1992; Tadolini and Hakim, 1996).

Importantly, mitochondrial dysfunction elicited by different environmental or endogenous toxic agents (including Fe itself) can either initiate or propagate Fe release from non-toxic sites (i.e. Fe binding proteins), which may trigger and/or accelerate the progression of degenerative diseases (Beal, 1998; Horowitz and Greenamyre, 2010; Kumar et al., 2012; Mesquita et al., 2012; Sebastiani and Pantopoulos, 2011; Zecca et al., 2004). In mitochondria, the iron–sulfur clusters ([Fe–S]) found in complexes I and III of the electron transport chain (ETC.) can be attacked by ROS, releasing free Fe to participate in the Fenton Reaction and other oxidative processes (Fig. 1). Thus, Fe is an important player in cell toxicity and it can either initiate by itself a set of extremely oxidative toxic reactions, or nourish oxidative stress provoked by xenobiotics or endogenous metabolites. Of particular importance, Fe-mediated oxidative stress has been classically linked to apoptotic cell death (Ott et al., 2007; Wallace, 1999) and more recently to ferropoptosis, which represents a Fe-dependent form of non-apoptotic cell death (Dixon et al., 2012).

2.2. Transport, metabolism and excretion

As detailed above, Fe is highly abundant in the environment and its requirement for the proper human body functioning is normally exceeded after ingestion of western diets. In order to avoid Fe overload, the absorption of dietary Fe is tightly regulated by a complex and not yet fully understood interplay between Fe body burden and gastrointestinal absorptive mechanisms (De Domenico et al., 2008; Nunez, 2010). Fe transport into the enterocyte is adjusted to fulfill the body requirements of this element. The fine regulation of Fe absorption is extremely important because there are no cellular regulated processes for Fe excretion (De Domenico et al., 2008; Finberg, 2011; Fleming and Ponka, 2012; Mesquita et al., 2012).

In the human intestine, Fe is absorbed by different (at least three) molecular mechanisms into the enterocyte, depending upon its chemical form and dietary source (Theil, 2011; West and Oates, 2008). There is a system that absorbs heme-Fe (normally derived from myoglobin from red meat or blood hemoglobin), which was formerly called heme carrier protein 1 (HCP1) due to its role in

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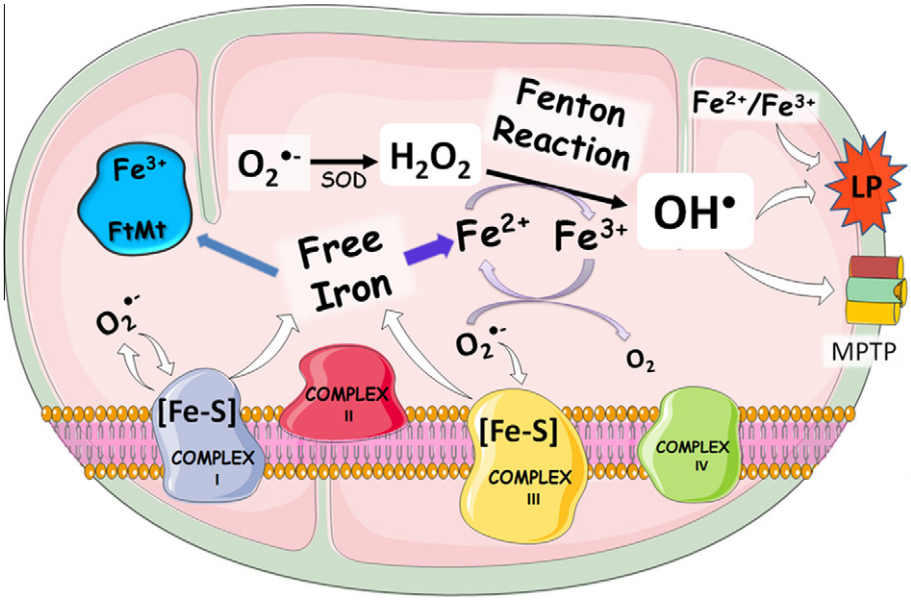

Fig. 1. Fe and mitochondria oxidative stress: Fenton reaction and hydroxyl radical formation are critical factors in Fe-induced mitochondrial toxicity; this type of reaction is thought to be central in neurodegeneration. Fe can start mitochondrial oxidative stress via interaction with different reactive oxygen species (ROS). Free Fe can be released from mitonchondrial Fe–sulfur clusters in complexes I and III upon interaction with ROS (in the figure it is shown the release of superoxide anion by these complexes and the potential oxidation of Fe–S cluster by $O_2^{\bullet-}$; the oxidation of the Fe–sulfur clusters can increase the free Fe in the mitochondrial matrix. This can facilitate the operation of the toxic Haber–Weiss and Fenton reactions, feeding a general pro-oxidant cycle). The redox pair Fe^{2+}–Fe^{3+} can also directly stimulate lipid peroxidation, which can intensify the oxidative stress and contribute to mitochondrial and cellular demise via mPTP formation. Free cationic Fe (regardless of the redox state) is the critical element for neurotoxicity and it can be buffered by intramitochondrial ferritin (FtMt), which acts as an antioxidant protein in the mitochondrial matrix.

heme-Fe transport and absorption (Shayeghi et al., 2005). Experimental details on the modulation of heme-Fe absorption by these heme-transporters are poorly understood (Theil, 2011; West and Oates, 2008), but it is thought that the primary physiological role of the heme-transporters involves folate transport (Le Blanc et al., 2012). For this reason, the transporter involved in intestinal heme-Fe absorption is now named proton-coupled folate transport or PCFT/HCP1.

The literature also corroborates the existence of a clathrin-dependent, receptor-mediated endocytosis mechanism for mineralized Fe^{3+} in ferritin found in legume seeds, such as soybean (San Martin et al., 2008; Theil, 2011). There is a third system involved in non-heme Fe^{2+} derived from salts or chelators from supplements that is mediated by the divalent metal transporter 1 (DMT1), which works jointly with an Fe oxireductase (Dcytb, duodenal cytochrome b; (McKie et al., 2001). The Dcytb protein reduces Fe^{3+} to Fe^{2+} in the apical part of enterocytes (Fig. 2, left), which allows absorption via DMT1. DMT1 mRNA transcripts have been found in a variety of tissues, indicating a universal role for this transport in Fe distribution in mammals (Mims and Prchal, 2005).

The export of absorbed Fe from enterocyte to the plasma is mediated by ferroportin (FPT), which is regulated by hepcidin and plays a crucial role in regulating plasma Fe levels (Nemeth and Ganz, 2006). In plasma, Fe^{2+} is oxidized to Fe^{3+} by ceruloplasmin or hephaestin and then binds to transferrin, which can distribute Fe to cells throughout the body. Fe^{3+}-transferrin complex can interact with transferrin receptor 1, resulting in endocytosis and uptake of the transferrin-bound metal. Fe can then be transported to mitochondria and incorporated in heme prosthetic groups or into Fe–sulfur clusters (Finberg, 2011; Fleming and Ponka, 2012; Wang and Pantopoulos, 2011). Intramitochondrial free Fe can also be buffered by a specific mitochondrial ferritin (FtMt; Fig. 1), which has an important physiological role as an antioxidant (Campanella et al., 2009; Santambrogio et al., 2007) (Fig. 1).

The central role of mitochondria in heme biosynthesis highlights the importance of this organelle in Fe fate and metabolism. Physiologically, mitochondria have adapted to cope with Fe and to circumvent the potential toxicity of free cationic Fe forms (Levi and Rovida, 2009; Ott et al., 2007; Richardson et al., 2010). Since mitochondria are also important intracellular sites for ROS production (i.e. $O_2^{\bullet-}$ and H_2O_2) (Halliwell, 1992; Ott et al., 2007), the continued presence of Fe inside the mitochondrial matrix renders these organelles susceptible to damage by extremely reactive intermediates that can be formed after interaction of ROS with transitory free Fe^{2+} and Fe^{3+} (see Fig. 1). In effect, mitochondrial Fe seems to play a fundamental role in neurodegeneration associated with several brain pathologies (Beal, 1998; Galaris and Pantopoulos, 2008; Horowitz and Greenamyre, 2010).

If the body burden of Fe is adequate and there is no requirement for this micronutrient, its absorption is negatively modulated by different mechanisms. As previously mentioned, the peptide hepcidin, which is synthesized as pro-hormone in the hepatocytes, is released into the blood in response to Fe intake. Hepcidin inhibits the intestinal absorption of Fe and its export from enterocytes (and also that derived from heme from red blood cells phagocytized by macrophages in the reticuloendothelial system). Hepcidin binds to ferroportin and stimulates its phosphorylation and degradation, modulating in this way the body burden of Fe and its availability for heme synthesis and erythropoiesis (Finberg, 2011; Nemeth and Ganz, 2006; Sebastiani and Pantopoulos, 2011; Wang and Pantopoulos, 2011). The absorption, distribution and storage of Fe are also regulated by the concerted interaction of Fe regulatory proteins (IRPs) and Fe responsive elements (IREs). IREs are located in the untranslated regions of mRNAs encoding protein involved in Fe handling and can interact with IRPs (Wang and Pantopoulos, 2011). For instance, the synthesis of Fe trafficking and storage proteins (DMT1, transferrin receptor and ferritin, etc.) is finely coordinated by IRPs and IREs in order to increase or decrease Fe absorption, depending upon the physiological requirements for Fe (Theil, 2011; Wang and Pantopoulos, 2011).

One important (but not fully explored) aspect on Fe homeostasis is how dietary or genetic Fe loading can modify the metabolism of proteins involved in Fe absorption, trafficking and storage in

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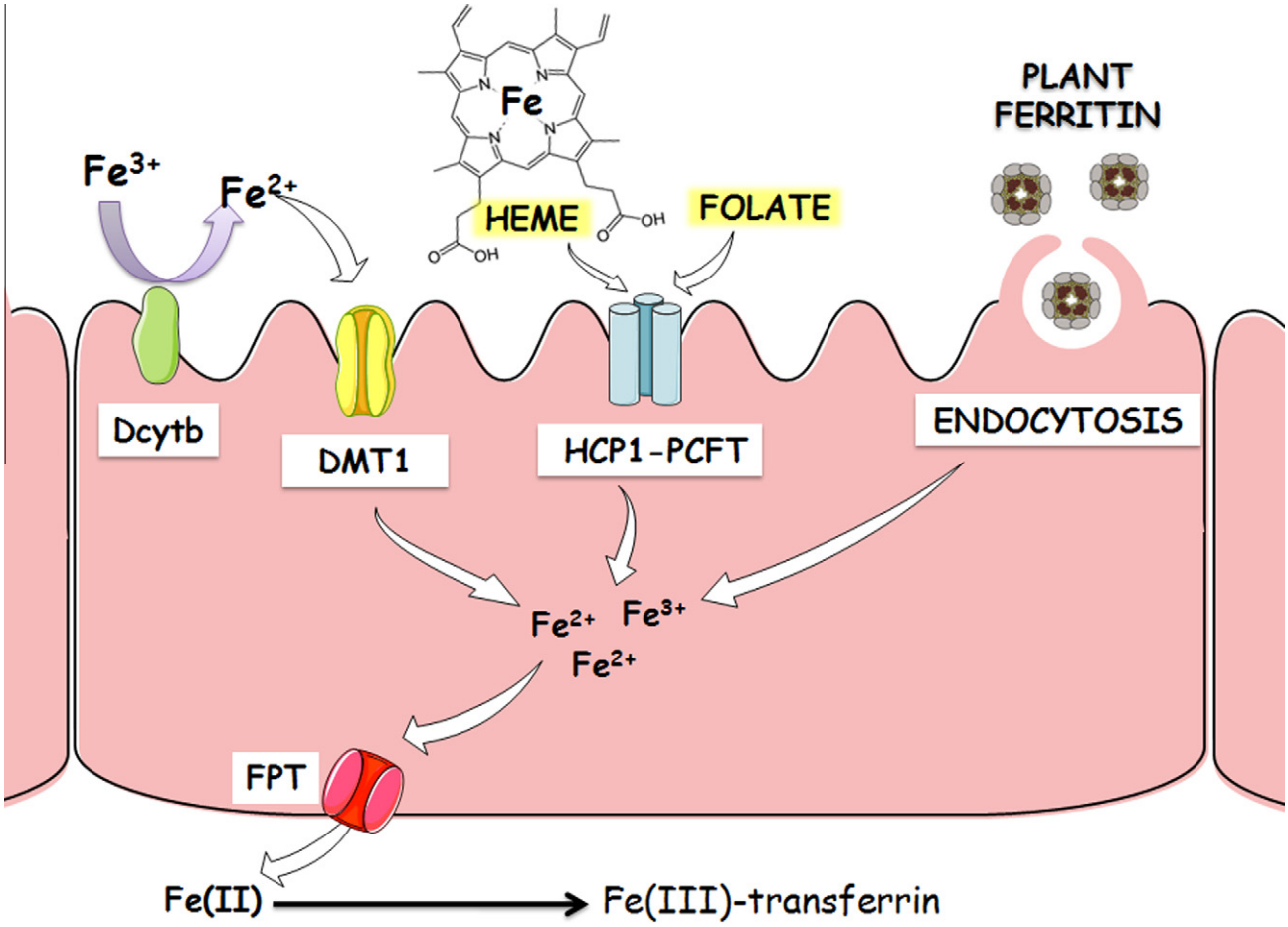

Fig. 2. Mechanisms of intestinal Fe uptake. Fe can be absorbed in the enterocyte via distinct mechanisms: (1) Divalent Metal Transporter 1 (DMT1) and duodenal cytochrome b (Dcytb) Fe oxireductase system, which is involved in the absorption of free divalent Fe (Fe^{2+}); (2) HCP1/PCFT or heme carrier protein 1 (HCP1)/proton-coupled folate transporter, which is involved in the absorption of heme–Fe and folate, and (3) a clathrin-dependent, receptor-mediated system that is involved in the absorption of vegetable-ferritin-bound Fe via endocytosis. After absorption, all forms of Fe are transformed to cationic Fe that can be exported from enterocytes by ferroportin (FTN). In the plasma, Fe^{2+} is oxidized by ceruloplasmin or hephaestin and binds to transferrin. Tranferrin can distribute Fe to all tissues of the body, including brain where Fe overloading contributes to neurodegeneration.

brain tissues. Clarifying such aspects would contribute on understanding how Fe participates in neurodegenerative processes; such knowledge may improve treatment options in a range of neurodegenerative disorders (Johnstone and Milward, 2010a,b).

2.3. Fe and neurodegeneration

As discussed above, free cationic Fe can be extremely toxic via disruption of mitochondrial function, and theoretically, $Fe^{2+} \leftrightarrow Fe^{3+}$ redox changes can be coupled with formation of extremely reactive species, such as hydroxyl radical ($OH^{\cdot}$). This molecule is highly reactive and its free existence is limited to its diffusion coefficient. In fact, $OH^{\cdot}$ is expected to be found only close to its site of formation and in close proximity to Fe ions (Gutteridge, 1984). The formation of $OH^{\cdot}$ can damage different biomolecules and start a vicious cycle of cellular damage (Fig. 1). Furthermore, the redox pair Fe^{2+}/Fe^{3+}serves as an *in vivo* initiator of cytotoxic reactions, particularly, lipid peroxidation (Ryan and Aust, 1992; Welch et al., 2002).

With respect to neurodegeneration, a vast amount of literature data indicates that Fe is an important etiologic factor associated with oxidative stress induction and cell demise in pathological situations (Johnstone and Milward, 2010b; Jomova and Valko, 2011; Mesquita et al., 2012; Wu et al., 2012). Recently, it has been proposed that Fe could be a primary and unifying factor involved in the progression of different chronic neurodegenerative diseases, such as PD, Alzheimer's and Huntington's disease (Kell, 2010). In fact, there are numerous observations to support an early role for brain Fe overloading in the progression of neurodegenerative diseases (Rosas et al., 2012). However, temporal aspects on Fe-mediated initiation or progression of neuropathological conditions, as well as the exact role played by activation of Fe-triggered toxicological pathway(s), remain unknown (Andersen, 2004; Johnstone and Milward, 2010b; Kumar et al., 2012).

It is noteworthy that Fe deposition has been observed only in specific brain regions in patients with chronic degenerative diseases (Kell, 2010; Kumar et al., 2012; Rosas et al., 2012; Sian-Hulsmann et al., 2011). The basal ganglia represent a preferential site of Fe deposition in neurodegenerative diseases (Akatsu et al., 2012; Berg et al., 2001; Gregory and Hayflick, 2011). A similar phenomenon is also observed in a wide range of genetic diseases collectively named neurodegeneration with brain Fe accumulation (NBIA, such as Friedreich ataxia, pantothenate kinase 2-associated neurodegeneration, PLA2G6-associated neurodegeneration, FA2H-associated neurodegeneration, Kufor-Rakeb disease, aceruloplasminemia, and neuroferritinopathy (Gregory et al., 2009; McNeill et al., 2008; Schipper, 2012). These genetic diseases are characterized by Fe accumulation in basal ganglia and associated with mutations in proteins involved in Fe traffic or metabolism (Prohaska et al., 2012). However, as stated for the case of chronic Fe-associated

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degenerative brain diseases, little is known about the mechanisms that lead to brain Fe accumulation (Prohaska et al., 2012). Nevertheless, the study and understanding of the neuropathological modifications associated with the wide spectrum of NBIA diseases have indicated the existence of clinical, morphological and molecular features similar to those seen in chronic neurodegenerative diseases such as PD, Huntington's and Alzheimer's disease (Berg et al., 2001; Schneider et al., 2012).

As briefly noted above, the temporal relationship between Fe deposition and neurodegeneration has yet to be clearly established. Thus, in some diseases, Fe deposition can be the consequence and not the cause of neurodegeneration. Here we have a gap in knowledge, which indicates the need of mechanistic studies to determine the primary, secondary and tertiary factors involved in the initiation and progression of neurodegeneration in different Fe-associated brain pathologies. Most importantly, from a therapeutic point of view, the identification of a potential non-returning point of Fe neurotoxicity would be of great value in developing therapeutic and other interventional procedures that could delay the attainment of this point of cell demise. In short, although Fe (as Fe^{2+}) is a central factor in Fenton reaction and, consequently, in $OH^{\cdot}$ production, which is expected to damage biomolecules and contribute to neurodegeneration, there is no a direct or even an indirect method to accurately follow the chronology of Fenton's reaction in a representative living model system of neurodegeneration. The assertion for the central role of Fe^{2+}–Fe^{3+} (either as participants in Fenton reaction or as direct inductors of lipid peroxidation) in neurodegeneration is based largely on reactivity parameters derived from classical indirect procedures that are used to determine their occurrence in chemical pure systems. Thus, experimental *in vitro* and *in vivo* models designed to determine with precision the temporal role of Fenton reaction in neurodegeneration are highly needed. Furthermore, the role played by Fenton chemistry in the activation or inhibition of specific molecular and subcellular pathways that participate in Fe neurotoxicity is not fully understood. The ability of Fe (Fe^{2+}:Fe^{3+}) to initiate and propagate membrane lipid peroxidation adds an additional factor to these complex issues. In fact, we have no experimental indication on the proportional contribution of these specific reactions (Haber and Weiss, 1932; Halliwell and Gutteridge, 1984) either in simple or complex chemico-biological system(s).

2.3.1. Acute brain Fe overload

High amount of Fe can be acutely released in specific brain regions after local hemorrhage caused by brain trauma or after stroke episodes resulting from different etiologies (Carbonell and Rama, 2007; Halliwell, 1992; Raz et al., 2011; Wagner et al., 2003). After the hemorrhagic episode, erythrocytes are released inside the brain parenchyma, followed by hemolysis. Hemoglobin, heme and Fe are then released in the extracellular space, causing local Fe overloading (Halliwell, 1992). Although little is known about the fate of heme released from hemoglobin after brain hemorrhage, a recent study has indicated that hemoglobin and heme uptake was higher in neurons than in glial cells (Lara et al., 2009). Consequently, heme uptake by neurons after brain trauma or stroke contributes to Fe-associated neurodegeneration (Aronowski and Zhao, 2011).

2.3.2. Fe and cell death

At the molecular level, the primary toxicity of free Fe is associated with its redox properties, which can culminate in the production of ROS that will initiate a cascade of cytotoxic events. For instance, $OH^{\cdot}$ can oxidize a variety of biomolecules, including thiol-containing proteins, and in the case of mitochondria this can lead to the formation of mitochondrial permeability transition pore (mPTP). mPTP formation will collapse membrane mitochondrial potential, increase intramitochondrial Ca^{2+}, decrease ATP synthesis and in extreme cases result in cell death (Halestrap, 2009). The formation of mPTP can also trigger less dramatic changes in mitochondrial metabolism that can be associated with delayed apoptosis and/or necrosis (Kinnally et al., 2011). However, our knowledge on the role of Fe-induced oxidative stress on the activation of (a) particular cascade(s) of cellular or mitochondrial events that result in cell death is superficial. Recently, it was demonstrated that Fe is a key element involved in mitochondrial-induced oxidative stress and cell death (Dixon et al., 2012). This form of cell death, which was named ferroptosis, is morphologically, biochemically and genetically distinct from apoptosis, necrosis or autophagy, and can be activated by glutamate (Dixon et al., 2012). Accordingly, Fe can contribute to neurodegeneration by activating different cell death pathways.

2.4. Antidotal strategies

Therapeutic approaches to treat neurodegeneration associated with Fe overload is limited and involve the use of chelating agents (Heli et al., 2011; Jomova and Valko, 2011; Miyajima et al., 1997; Molina-Holgado et al., 2007; Selim et al., 2011). However, treatment with these agents (including desferoxamine) may cause toxicity (Gassen and Youdim, 1997; Heli et al., 2011). Natural products, such as catechin and other polyphenols have been indicated as potential therapeutic agents against Fe toxicity, because of their simultaneous antioxidant and Fe-chelating properties (Mandel and Youdim, 2004; Reznichenko et al., 2006). The therapeutic efficacy of polyphenol compounds found in natural preparations used in folk medicine can be linked to these two general properties (Fibach and Rachmilewitz, 2010; Perron and Brumaghim, 2009).

3. Manganese

3.1. Properties and chemical forms and human exposure

Manganese (Mn) is one of the most abundant naturally occurring elements in the earth's crust; it does not occur naturally in a pure state. Oxides, carbonates and silicates are the most important Mn-containing minerals. Mn exists in various chemical forms, oxidation states (Mn^{2+}, Mn^{3+}, Mn^{4+}, Mn^{6+}, Mn^{7+}), salts (sulfate, chloride and gluconate) and chelates (aspartate, fumarate, succinate). More than 25 million tons are mined yearly, representing 5 million tons of the metal (Emsley, 2001). The versatile chemical properties of Mn have enabled its industrial usage in glass and ceramics, adhesives, welding, paint, gasoline anti-knock additives (methylcyclopentadienyl manganese tricarbonyl, MMT), just to name a few. Manganese dioxide is also used as a catalyst (Su et al., 2012). Mn is used to decolorize glass and make violet colored glass. Potassium permanganate is a potent oxidizer and used as a disinfectant. Other compounds with commercial applications are Mn oxide (MnO) and Mn carbonate ($MnCO_3$), which have been present in fertilizers and ceramics, as well as in materials for making other Mn compounds. Mn is a paramagnetic metal, meaning that it has an unpaired electron in the outer shell and that it can be detected with MRI, Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) (Aschner et al., 2007a; Inoue et al., 2011). These techniques allow for the tracking of Mn dynamics repeatedly in the same subject *in vivo* (Aschner et al., 2007a; Newland, 1999). Mn can also chemically interact with fluorophore fura-2, by quenching it and increasing its fluorescence, representing a new methodological approach for *in vitro* kinetic studies (Kwakye et al., 2011).

There are several sources of exposure to Mn, as follows:

3.1.1. Dietary exposure

The primary source of Mn for the general human population is diet. Adult dietary intake of Mn has been estimated to range from

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0.9 to 10 mg Mn/day (ATSDR, 2000; Finley and Davis, 1999). Foods with Mn levels in excess of 30 mg/kg include grains, rice and nuts. A cup of tea contains as much as 0.4–1.3 mg Mn (ATSDR, 2000). Another important source of Mn intake is the consumption of Mn-containing dietary supplements; tablets may contain 5–20 mg of Mn (NAS, 2001). Water concentrations of Mn typically range from 1 to 100 μg/L, with most values below 10 μg/L. Nevertheless, in some countries, such as Sweden, Mn concentrations in drinking water reach an average of 150 μg/L (Ljung and Vahter, 2007). Such elevated values pose the greatest potential risk to infants, in particular, as they have a higher retention of Mn and a more sensitive CNS than adults (Wasserman et al., 2006). Mn intake in milk is low; however, in formula-fed infants is much higher than that observed in their breast milk-fed counterparts, since levels of Mn in infant formulas may be substantially higher than those found in human milk (Krachler et al., 2000).

3.1.2. Airborne exposure

Inorganic Mn compounds are not volatile; however, they can exists as fumes, aerosols or suspended particulate matter (ATSDR, 2000). Atmospheric Mn derives from both anthropogenic and natural sources. Industries associated to Mn emissions include ferroalloy production, iron and steel foundries, metal fumes from welding, battery production and power plant and coke oven combustion (Aschner et al., 2005). Mn is also found in methylcyclopentadienyl manganese tricarbonyl (MMT), a fuel additive used in some unleaded gasoline (Davis, 1998). The use of this additive has been subject of much debate by regulatory agencies (Davis et al., 1998; Kaiser, 2003).

3.1.3. Parenteral nutrition

Due to Mn essentiality, parenteral nutrition (PN) generally contains significant amounts of this trace element. However, many products contain Mn as ubiquitous contaminant (Hardy, 2009). There are several case reports of PN users that developed Mn neurotoxicity and showed high MRI intensity in the brain (Hardy, 2009). In PN patients, the normal intestinal regulatory mechanism is bypassed and the amount of Mn delivered via the intravenous route is 100% bioavailable. In addition, the normal pathway of elimination via the hepatobiliary system frequently is impaired because of PN-associated biliary stasis and obstructive jaundice. This may be especially important for parenterally fed infants who pass little or no stool and often show evidence of hepatic dysfunction and cholestasis (Aschner and Aschner, 2005). It also predisposes long-term PN patients to tissue accumulation and/or brain deposition of Mn, resulting in neurologic symptoms. However, a clear cause–effect relationship between PN-associated cholestasis and neurotoxicity has not been established and data about the temporal relationship between the dose and duration of Mn supplementation and increased Mn levels have been contradictory (Siepler et al., 2003).

3.1.4. Mn-containing drugs

A relatively new form of presumed Mn poisoning has been reported in drug-addicted subjects from Eastern Europe and the Baltic states who have intravenously injected self-prepared methcathinone hydrochloride (ephedrone), which is synthesized from pseudoephedrine hydrochloride using potassium permanganate as the oxidant (Zhingel et al., 1991). Ephedrone is relatively easily accessible for abuse. Its users develop an extrapyramidal syndrome and it is not known if this is caused by methcathinone itself, by side-ingredients (Mn), or both (Sikk et al., 2011). Neuroimaging studies with MRI have demonstrated Mn accumulation in the basal ganglia of these addicts (Sikk et al., 2010).

3.2. Transport, metabolism and excretion

As previously mentioned, the major source of Mn in humans is via dietary ingestion (Au et al., 2009). Approximately 3–5% of ingested Mn is absorbed, and the rest is excreted in the feces. Its uptake is tightly regulated and any excess of ingested Mn is readily excreted via the bile. In contrast, both pulmonary uptake and particulate transport via the olfactory bulb can lead to Mn deposition in the striatum and cerebellum and inflammation of the nasal epithelium (Roth, 2009).

Mn ions (Mn^{3+}) bind to the same location as ferric ions (Fe^{3+}) on the large glycoprotein molecule mucin, which is known to stabilize the ions preventing precipitation in the lumen of the gastro intestinal tract (Powell et al., 1999). Both metals are known to have an affinity for the intercellular metal binding molecule mobilferrin (Conrad et al., 1992). Absorption of metal ions into enterocytes is known to take place via transmembrane transporters. Gunshin et al. (1997) cloned the Divalent Metal Transporter1 (DMT1) from proximal small bowel, which avidly binds Fe^{2+} ions, but also has an affinity for Mn^{2+} and other cations. In this regard, it is important to mention that dietary Fe^{3+} is firstly reduced to Fe^{2+} by ascorbate or surface ferrireductases before being transported via DMT1 into the enterocytes (Mackenzie and Garrick, 2005). During Fe deficiency the number of transporters in enterocyte membranes is increased in order to maximize Fe absorption (Gunshin et al., 1997). This will inevitably result in increased Mn absorption, particularly in the absence of Fe. Fe has a strong influence on Mn homeostasis as both metals share the transporter, transferrin (Tf), binding and uptake via the Tf transporter and the divalent metal transporter, DMT1/NRAMP2. In rodents, Fe deficiency is associated with increased Mn absorption across the gastrointestinal tract, as well increased Mn brain deposition (Fitsanakis et al., 2008; Freeland-Graves and Lin, 1991; Garcia et al., 2007).

The exact identity of the carrier(s) involved in Mn transport into the brain is still controversial. In general, it is believed that at normal plasma concentrations, Mn enters into the CNS primarily across the capillary endothelium, whereas at high plasma concentrations, transport across the choroid plexus predominates (Murphy et al., 1991). How, and in what chemical form Mn is transported across the blood–brain barrier (BBB) has been addressed in a series of studies. Mn is absorbed in the GI tract as Mn^{2+}, is oxidized to Mn^{3+} by liver and plasma ceruloplasmin and transported through the blood by transferrin (Tf) (Aschner and Gannon, 1994; Takeda et al., 1995). Although Tf-dependent Mn transport across the BBB has been documented (Aschner and Gannon, 1994), the majority of BBB transport occurs via the DMT1.

A critical regulator of brain Mn levels is the divalent metal transporter, DMT-1/NRAMP-2. DMT-1 (also referred to as the DCT, or divalent cation transporter) is known to shuttle both Mn and Fe ions in the (+2) valence, as well as other divalent metals. Disruption of the orthologous DMT-1 gene in the rat or mouse results in significantly lower tissue levels and uptake of Mn and Fe in the brain (Chua and Morgan, 1997; Fleming et al., 1998). Notably, a recent study (Salazar et al., 2008) has shown that DMT1 contributes to neurodegeneration in an experimental model of PD. These authors observed an increased expression of a specific DMT1 isoform (DMT1/Nramp2/Slc11a2) in the substantia nigra of Parkinson's disease patients. Moreover, the authors also showed that the administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, a dopaminergic toxin used in experimental models of Parkinson's disease) increased DMT1 expression in the ventral mesencephalon of mice, which was concomitant with iron accumulation, oxidative stress, and dopaminergic cell loss (Salazar et al., 2008).

Additional brain Mn transporters include the Mn-citrate transporters (MCT) and the Mn-bicarbonate symporters (Crossgrove

et al., 2003). However, the relevance of these proteins to Mn transport *in vivo* is not completed understood. The Mn-bicarbonate symporters, ZIP-8 and ZIP-14, have been identified as members of the solute carrier-39, and are expressed on brain capillaries (He et al., 2006). These symporters utilize a HCO_3^- gradient as the driving force for Mn uptake across the plasma membrane.

Other possible mechanisms for Mn transport include the dopamine transporter (DAT). It is believed that DAT facilitates Mn transport into dopaminergic (DAergic) striatal neurons and that Mn accumulates in the *globus pallidus* via axonal transport (Anderson et al., 2007). As a result, blockage of the DAT in the striatum should attenuate Mn accumulation in striatal neurons and cause decreased Mn concentrations in the *globus pallidus* (Anderson et al., 2007). Finally, Mn transport via voltage regulated channels (Lucaciu et al., 1997), store-operated channels (Riccio et al., 2002), ionotropic glutamate receptor channels (Kannurpatti et al., 2000) (all Ca^{2+} channels) and choline transporters (Lockman et al., 2001) has also been described.

3.3. Mn and neurodegeneration

It has been known for more than 150 years that Mn can be a neurotoxic agent; its toxicity has been predominantly observed in occupational settings, following the accidental ingestion of large quantities or after chronic inhalation of high levels (Mergler et al., 1994). The brain is particularly susceptible to excess of this metal, but the mechanisms of toxicity are poorly understood. In humans, it has been postulated that there is a spectrum of neurobehavioral and neurophysiological effects associated with Mn toxicity, including subclinical and clinical symptoms (Mergler et al., 1994).

Mn neurotoxicity, or *locura manganica*, also referred to as manganism, is a neurologic disorder characterized by psychological and neurological abnormalities, which resemble Parkinson's disease (Barbeau, 1984; Huang et al., 1989; Mena et al., 1967). Mn also damages brain areas distinct from those that are affected in PD (Calne et al., 1994; Olanow, 2004). The similarities between the clinical manifestations of PD and manganism include the presence of generalized bradykinesia and widespread rigidity and a characteristic "cock-walk" (Calne et al., 1994). There are also differences with respect to treatment response – although there may be an initial response to levodopa, the primary treatment option for PD, there is typically a failure to achieve a sustained therapeutic response in patients with manganism (Aschner et al., 2009; Calne et al., 1994). The similarities between the two disorders can be partially explained by the fact that the basal ganglia accumulate most of the excess Mn compared with other brain regions, and dysfunction in the basal ganglia is also involved in PD (Dobson et al., 2004).

Mn has also been linked to the etiology of other neurodegenerative diseases, such as Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, as well reviewed by other authors (Aschner et al., 2009; Benedetto et al., 2009; Bowman et al., 2011; Zatta et al., 2003). Mechanisms mediating Mn-induced neurotoxicity, as well as their relationship with neurodegenerative diseases, are detailed as follows.

3.3.1. Dopamine oxidation

DA is one of the most abundant catecholamine within the brain. Chronic exposure to Mn has been shown to cause the degeneration of nigrostriatal DAergic neurons (Barbeau, 1984). Postnatal Mn exposure causes a decline in pre-synaptic DAergic functioning, reduced DA transporter expression and DA uptake in the striatum, and a long-lasting decrease in DA efflux (Huang et al., 2003; McDougall et al., 2008). In adult animal models, exposure to Mn inhibits DA neurotransmission and depletes striatal DA (Barceloux, 1999; Calne et al., 1994; Chen et al., 2006; Pal et al., 1999), thereby resulting in motor deficits (Guilarte, 2010).

Although it is generally accepted that free radicals play a key role in mediating Mn-induced DAergic neurodegeneration (Erikson et al., 2007), the precise mechanism of Mn-induced neurotoxicity remains unknown. One hypothesis invokes the ability of Mn to enhance ROS generation via quinone formation (Fig. 3) (Graham, 1978). Indeed, the Mn-catalyzed autoxidation of DA involves redox cycling of Mn^{2+} and Mn^{3+} in a reaction that generates ROS and DA-*o*-quinone, thereby leading to oxidative damage (Donaldson et al., 1982; Reaney and Smith, 2005). Thus, elevated rate of autoxidation of cytoplasmic DA induced by Mn may contribute to DAergic cell death secondary to the formation of cytotoxic quinones and ROS (Graham, 1978).

Mn-induced DA oxidation is a complex process involving several steps in which semi-quinone, aminochrome intermediates, L-cysteine or copper (Cu) and NADH are implicated (Segura-Aguilar, 1996; Segura-Aguilar and Lind, 1989). Mechanisms underlying semi-quinone and aminochrome-induced damage in the Mn-induced neurodegenerative process likely include: (i) NADH or NADPH depletion; (ii) inactivation of enzymes by oxidizing thiol groups or essential amino acids; (iii) formation of ROS and (iv) lipid peroxidation. It is noteworthy that neither Mn^{2+} nor Mn^{3+} can generate hydroxyl radicals from hydrogen peroxide and/or superoxide via Fenton-type or Haber–Weiss-type reactions, while Mn^{2+} can scavenge and detoxify superoxide radicals (Archibald and Tyree, 1987; Donaldson et al., 1982).

3.3.2. Mitochondrial dysfunction

Intracellular Mn preferentially accumulates in the mitochondria, mainly as Mn^{2+} via the Ca^{2+} uniporter (Gavin et al., 1992; Gunter and Pfeiffer, 1990). Elevated intramitochondrial Mn interferes with oxidative respiration, leading to excessive production of ROS and consequently mitochondrial dysfunction (Gavin et al., 1992; Gunter and Pfeiffer, 1990). The ability of Mn to enhance oxidative stress is due to the transition of its oxidative state +2 to +3, which increases its pro-oxidant capacity (HaMai et al., 2001; Reaney and Smith, 2005). Superoxide produced in the mitochondrial electron transport chain (ETC.) may catalyze this transition through a set of reactions similar to those mediated by SOD and thus lead to the increased oxidant capacity of the metal (Archibald and Tyree, 1987; Gunter and Pfeiffer, 1990). Superoxide radical can also form hydrogen peroxide (H_2O_2) by superoxide dismutase. This reaction is catalyzed by manganese (Mn)-superoxide dismutase (Mn-SOD) in the mitochondrial matrix. It also needs to be considered that Mn^{3+} has greater pro-oxidant potential than Mn^{2+}, and its production in the mitochondria may also accentuate oxidative damage (Ali et al., 1995).

Mn can directly impair mitochondrial function by inhibiting the ETC. (Gavin et al., 1992), resulting in reduced ATP production, increased leakage of electrons and increased $O_2^{\cdot-}$ production (Scholte, 1988). Although Mn^{3+} is more potent at inhibiting complex I (Archibald and Tyree, 1987), Mn^{2+} is the predominant species within cells and is largely bound to ATP (Gunter and Pfeiffer, 1990).

Mn interferes with calcium (Ca^{2+}) homeostasis in mitochondria by inhibiting its efflux (Gavin et al., 1990; Spadoni et al., 2000). Oxidative stress generated by high Mn concentrations leads to the induction and opening of the mitochondrial permeability pore (MPT) pore, a Ca^{2+}-dependent process, resulting in increased solubility to protons, ions and solutes, loss of the mitochondrial inner membrane potential ($\Delta\psi m$), impairment of oxidative phosphorylation and ATP synthesis and mitochondrial swelling (Gavin et al., 1990; Yin et al., 2008a; Zoratti and Szabo, 1995).

3.3.3. Astrocytosis

Astrocytes make up approximately 50% of the human brain volume (Chen et al., 2006) and assume many critical pathophysiological roles essential for normal neuronal activity, including

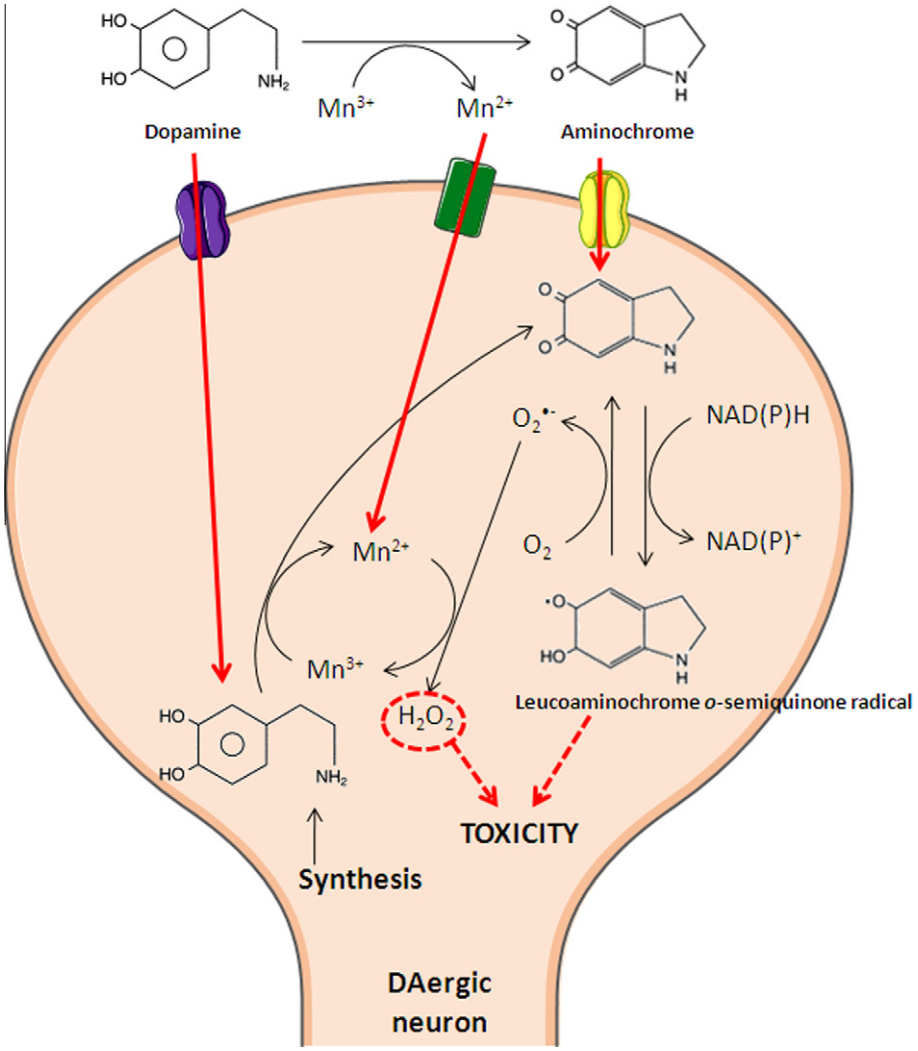

Fig. 3. Mn-induced dopamine (DA) oxidation: primary reactions involved in reactive oxygen species (ROS) and *o*-quinones radical generation. Mn-catalyzes the autoxidation of DA, involving the redox cycling of Mn^{2+} and Mn^{3+} in a reaction that generates ROS and DA-*o*-quinone or catalyzes the production of H_2O_2 inside the neurons, thereby leading to oxidative damage in DAergic neurons.

glutamate uptake, glutamine release, K^+ and H^+ buffering, volume regulation and membrane–membrane mediated trophic cell signaling (Aschner and Gannon, 1994; Aschner et al., 2007a; Chen et al., 2006). Unlike neurons, astrocytes concentrate Mn to levels at least 50-fold higher than the culture media, thus functioning as the major homeostatic regulators and storage site for Mn (Aschner et al., 2009, 2007a; Aschner and Gannon, 1994). Primate models of Mn toxicity have shown astrocytic pathological alterations (*Alzheimer type II*) (Olanow et al., 1996; Pentschew et al., 1963; Yamada et al., 1986), and exposure of cultured astrocytes to pathophysiologically relevant concentrations of Mn leads to a concentration- and time-dependent cell swelling, which appears to be a consequence of oxidative stress and changes in MPT (Rao and Norenberg, 2004). Increased accumulation of Mn in astrocytes has also been shown to alter glutamate homeostasis and elicit excitatory neurotoxicity (Erikson and Aschner, 2003). Thus, Mn decreases astrocytic glutamate uptake (Hazell and Butterworth, 1999; Hazell and Norenberg, 1998) and reduces the expression of the astrocytic glutamate:aspartate transporter (GLAST) (Erikson and Aschner, 2002), leading to increased extracellular glutamate levels, and neuronal excitability.

Mn has been implicated in the impairment of the glutamate-glutamine cycling, by deregulation of their turnover in astrocytes (Sidoryk-Wegrzynowicz et al., 2009). The functioning of this cycle is critical for normal brain function, once glutamine is the precursor of glutamate and GABA as well (Sidoryk-Wegrzynowicz et al., 2012). Expression of glutamine transporters was downregulated in Mn-exposed cultured astrocytes (Sidoryk-Wegrzynowicz et al., 2009), thus reducing glutamine uptake. As a consequence of this deregulation in glutamine transport, there is impairment in glutamine shuttling between neurons and astrocytes, altering the synthesis of glutamate and GABA (Sidoryk-Wegrzynowicz et al., 2009). Furthermore, Mn induces protein kinase C δ (PKC-isoform δ) activation, causing a decrease in glutamine uptake through two particular systems: SNAT3 and ASCT2 (Sidoryk-Wegrzynowicz et al., 2010). This process putatively promotes the initiation of the down-regulation of these transporters in astrocytes by the ubiquitin-mediated proteolytic system (Sidoryk-Wegrzynowicz et al., 2010). PKC activation by Mn exposure leads to reduced glutamate uptake, and inhibition of PKC reverses Mn-dependent down-regulation of glutamate influx, as well as increases GLT-1 and GLAST protein level in astrocytes (Sidoryk-Wegrzynowicz et al., 2011). Transfection of astrocytes with shRNA against PKCδ showed decreased sensitivity to Mn, corroborating the involvement of the PKCδ signaling (Sidoryk-Wegrzynowicz et al., 2011).

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3.3.4. Interaction with Fe-containing enzymes

It is known that certain proteins have a degree of "promiscuity" in metal binding. However, most of these enzymes are active with only one metal as cofactor, although both metals can bind *in vitro* and *in vivo*. Fe(II) and Mn(II) bind weakly to most proteins and possess similar coordination preferences (Cotruvo and Stubbe, 2012). There are cases where enzymes, such as epimerases, are thought to use Fe^{2+} as a Lewis acid under normal growth conditions but switch to Mn^{2+} under oxidative stress. Estradiol dioxygenases have been found to use both Fe^{2+} and Mn^{2+} (Farquhar et al., 2011). Notably, a specific class of I ribonucleotide reductases (RNRs), which convert nucleotides in deoxynucleotides, have evolved unique biosynthetic pathways to control metallation (Stubbe and Cotruvo, 2011). For instance, Fe- and Mn-dependent superoxide dismutases (SODs) catalyze the disproportionation of superoxide using highly similar protein scaffolds and nearly identical active sites (Cotruvo and Stubbe, 2012). Despite the extensive homology between the isoforms, Mn- and Fe-SODs are only active with their cognate metal (Vance and Miller, 2001). Misincorporation of Fe into Mn-SOD or *vice versa* alters the redox potential of the enzyme's active site and inhibits superoxide disproportionation (Beyer and Fridovich, 1991). Nevertheless, misincorporation of Fe into Mn-SOD does occur *in vivo*, as observed in *Escherichia coli* (Yang et al., 2006). Using mitochondria from *Saccharomyces cerevisae*, Naranuntarat and coworkers verified that Fe binds to SOD-2 when cells are starved for Mn, inactivating the enzyme (Naranuntarat et al., 2009).

Furthermore, *in vivo* chronic Mn exposure in rats receiving intraperitoneal injection of 6 mg/kg Mn as $MnCl_2$ daily for 30 consecutive days led to a region-specific alteration in total aconitase in frontal cortex, striatum and *substantia nigra* (Zheng et al., 1998). Aconitase is an enzyme from the tricarboxylic acid cycle that possesses an iron–sulfur cluster. When the cellular Fe level is insufficient, cytoplasmic aconitase loses the fourth labile Fe and assumes a [3Fe–4S] configuration. In this state, the coordination chemistry of Mn closely resembles that of Fe, possibly allowing Mn to interact with Fe in both mitochondrial and cytoplasmic aconitases, thus altering cellular energy metabolism and Fe regulation (Zheng et al., 1998). Unzai et al. prepared a series of hybrid hemoglobins in which Fe from heme was replaced by different metals, Mn included, in the α or β subunits. None of the substituted hemoglobins reacted with dioxygen or carbon monoxide, suggesting that the putative substitution of Fe by Mn during ferropenic anemia would impair hemoglobin function (Unzai et al., 1998).

3.4. Antidotal strategies

It remains controversial as to whether manganism, a Parkinsonian-like syndrome, can be treated with levodopa (Lucchini et al., 2009; Racette et al., 2001). Accordingly, other therapeutic approaches using drugs and genomic evaluations have been investigated.

Because oxidative stress plays a crucial role in Mn-induced neurotoxicity, antioxidant compounds have been of great interest. It has been demonstrated that synthetic compounds such as organochalcogens 2-phenyl-1,2-benzisoselenazol-3[2H]-one (ebselen) and diethyl-2-phenyl-2 tellurophenyl vinylphosphonate (DPTVP) (Avila et al., 2010; Santos et al., 2012) mitigate Mn-induced neurotoxicity. These compounds, which possess strong antioxidant properties, caused improvement in motor activity in rats and attenuated Mn-induced brain ROS generation (Avila et al., 2010; Santos et al., 2012). In the nematode *Caenorhabditis elegans*, these compounds protected against Mn-induced oxidative stress, decreasing ROS levels and increasing the life-span of Mn-exposed worms (Avila et al., 2012). Another important antioxidant, lycopene, strongly inhibited lipid peroxidation induced by Mn in brain and liver by acting as an efficient chain-breaking antioxidant, trapping lipid radicals (Lebda et al., 2012).

In rodents, anti-inflammatory agents, such as indomethacin and para-aminosalicilic acid, reduced Mn-induced increase in oxidative stress (isoprostanes) and neuroinflammation (prostaglandin E2) (Milatovic et al., 2011; Santos et al., 2012). Notably, indomethacin protected against progressive spine degeneration and dendritic damage in striatal medium spiny neurons of mice exposed to Mn (Milatovic et al., 2011). This protection is probably mediated by the transcription factor NF-κB (Moreno et al., 2011). Using transgenic mice expressing a transcription factor fused to a green fluorescent protein (GFP), Moreno and co-workers showed that Mn exposure increased NF-κB reporter activity and nitric oxide synthase 2 (NOS2) expression in both microglia and astrocytes, and that these effects were prevented by supplementation with steroid 17β-estradiol. This steroid is one of the most active estrogen hormones possessing neuroprotective effects in both *in vivo* and *in vitro* models, and it has been shown to enhance astrocytic glutamate transporter function (Liang et al., 2002). Estrogen also decreased neuronal protein nitration in treated mice and inhibited apoptosis in striatal neurons cocultured with Mn-treated astrocytes *in vitro* (Moreno et al., 2011). Furthermore, tamoxifen, an estrogen related compound, effectively reversed glutamate transport inhibition in a Mn-induced model of glutamatergic deregulation, suggesting a potential therapeutic modality in neurodegenerative disorders which are characterized by altered glutamate homeostasis (Lee et al., 2012). In agreement with this study, Xu et al. showed that the pretreatment of rats with the NMDA (*N*-methyl-D-aspartate) antagonist MK801 protected neurons from Mn-induced glutamate excitotoxicity (Xu et al., 2010). Several studies have addressed genetic factors that mediate of Mn toxicity. Streifel and co-workers used mice lacking NOS, postulating that they would be protected from the neurotoxic effects of Mn. They found that loss of NOS2 reduced NO-induced peroxynitrite formation, thus attenuating Mn-related peroxynitrite adduct formation in the striatal-pallidum and substantia nigra pars reticulate. These mice showed attenuated alterations in neurobehavioral function and neurochemistry *in vivo* and also loss of NOS2 also prevented astrocyte-mediated neuronal apoptosis *in vitro* (Streifel et al., 2012). *In C. elegans,* Benedetto et al. observed that Mn-induced DAergic neurotoxicity requires the NADPH dual-oxidase BLI-3, suggesting that *in vivo* BLI-3 activity promotes the conversion of extracellular DA into toxic reactive species, which, in turn, can be taken up by DAT-1 in DAergic neurons, thus leading to oxidative stress and cell degeneration (Benedetto et al., 2010). BLI-3 knockout or inhibition may represent a novel strategy for mitigating Mn neurotoxicity. Expression of parkin, an E3 ubiquitin ligase also linked to PD, protects against Mn toxicity, as observed in SH-SY5Y cells (Roth, 2009). Conversely, deletion of parkin leads to increase in DMT-1 levels, thus causing increase in Mn uptake (Roth, 2009). Furthermore, it was reported in yeast that expression of PARK9, a gene linked to PD, protected cells from Mn toxicity (Gitler et al., 2009).

4. Mercury

4.1. Properties, chemical forms and human exposure

Mercury is a transition metal commonly named quicksilver due to its liquid and silvery characteristics. It is recognized by the symbol Hg, which comes from the Latin term *hydrargyrum,* meaning "watery silver". It is present in the environment due to both natural (earth's surface evaporation and volcanic eruptions) and anthropogenic (emissions from coal-burning power stations and incinerators) sources. As a result of specific reactions (i.e.

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oxidation, methylation), different chemical forms of Hg are present, such as elemental mercury (Hg^0), inorganic (divalent and monovalent cationic forms; Hg^{2+} and Hg^+) and organic (i.e. methylmercury; MeHg) mercury compounds. While human exposures to all environmentally existing forms of Hg have been documented, exposure to MeHg represents a major concern. Exposures to MeHg, which is present at high concentrations in seafood diets, are common and ubiquitous; MeHg has a higher entry rate into the CNS compared with inorganic mercurials, rendering it an important neurotoxicant (Aschner et al., 2007b; Debes et al., 2006). Occupational exposures to Hg (mainly in the form of elemental mercury, Hg^0), due to its use in industry (Neghab et al., 2012) and artisanal gold mining (Lubick, 2010), are also of toxicological relevance. In addition, iatrogenic exposures to Hg continue to represent a concern. For example, dental amalgams (important source of Hg^0) are still used (for a review, see Clarkson and Magos, 2006).

The toxic properties and target organs of Hg are dependent upon its chemical speciation. This review focuses on forms of Hg with major neurotoxicological relevance: (i) primary focus is directed at *MeHg*, which occurs mainly from contaminated seafood; (ii) because of its efficient transport through the BBB, the neurotoxicological significance of *mercury vapor*, secondary to exposures from occupational settings and dental amalgam, is also discussed.

4.2. Transport, metabolism and excretion

4.2.1. Methylmercury

Methylmercury (MeHg; CH_3Hg^+) is an organic mercury compound found in the aquatic environment (Ullrich et al., 2007). The majority of MeHg is derived from the methylation of inorganic mercury, carried out mostly by aquatic microorganisms (Compeau and Bartha, 1985). MeHg is biomagnified in the aquatic food chain, reaching concentrations as high as 1 ppm in predatory fish (Hintelmann, 2010). Accordingly, populations that rely on fish diets can be exposed to high MeHg levels (Clarkson et al., 2003). MeHg is well absorbed by the gastrointestinal tract (around 95%) (Miettinen, 1973). After absorption, more than 90% of MeHg in the blood is intracellular (bound to erythrocyte hemoglobin); the fraction present in the blood is about 6%, upon complete equilibrium between blood and tissues is reached (Kershaw et al., 1980). In humans orally exposed to MeHg, the percentage (of total) of inorganic Hg in the blood, breast milk and urine is 7%, 39% and 73%, respectively (IPCS, 1990), suggesting that inorganic Hg is an important excretable metabolite of MeHg. Additionally, experimental evidence shows that MeHg can also be excreted via the biliary route, likely complexed to glutathione (GSH), as a GSH mercaptide (CH_3Hg-SG) (Ballatori et al., 1995).

The CNS represents the main target organ of MeHg toxicity reflecting its efficient transport into the brain. MeHg transport across the BBB, as well as its uptake by neural cells, occurs via a MeHg-L-cysteine complex, which is transported by the L-type neutral amino acid transporter (Kerper et al., 1992; Yin et al., 2008b). Of note, a high percentage of inorganic Hg (above 80%) was found in the brain of a 30 year old individual who was exposed to MeHg at 8 years of age (22 years before) (Davis et al., 1994). Neurohistological outcomes were cortical atrophy, neuronal loss and gliosis, most pronounced in the paracentral and parietooccipital regions. Before death, the most evident neurological signs were cortical blindness, diminished hand proprioception, choreoathetosis, and attention deficits. In this patient, the total Hg level (more that 80% as inorganic Hg) in the left occipital cortex was more that 50-fold the levels found in control individuals (Davis et al., 1994), indicating a high persistence of Hg in the brain after MeHg exposure. Although MeHg is well recognized as a neurotoxicant by acting at specific biomolecular sites (for a review, see Farina et al., 2011a,b), the dealkylation of MeHg into inorganic Hg likely accounts for Hg's persistence in the brain, and potentially long-lasting neurological outcomes (Grandjean et al., 1997a; Ninomiya et al., 2005).

MeHg is transferred from the pregnant mother to the fetus, reaching the fetal brain. In an experimental study where pregnant mice were directly exposed to MeHg, Watanabe and collaborators (1999) detected higher levels of the metal in the fetuses brain when compared to the dams, indicating a high transplacental transport of MeHg, as well as a great retention in the fetus brain. MeHg seems to be actively transported from the maternal to the fetal blood as its cysteine conjugate via the neutral amino acid carrier system (Kajiwara et al., 1996). Its high entry in the developing brain is related, at least in part, to the lack of functional BBB (Costa et al., 2004; Manfroi et al., 2004).

There are epidemiological studies showing that maternal exposure to MeHg during pregnancy causes neurological deficits in their offspring (Grandjean et al., 1997b; Murata et al., 2004). Interestingly, exposure to MeHg during early fetal development is linked to subtle brain injury at levels much lower than those affecting the mature brain (Grandjean and Landrigan, 2006), most likely because it affects cell differentiation, migration and synaptogenesis (Theunissen et al., 2011; Zimmer et al., 2011).

4.2.2. Mercury vapor

The major sources of elemental mercury vapor (Hg^0) exposure are occupational and dental amalgams. Hg^0 is still used in industry in the production of caustic soda and chlorine, and in the manufacture of thermometers, thermostats, fluorescent light bulbs, batteries and manometers (for a review, see Clarkson and Magos, 2006). Artisanal miners are also exposed to Hg^0 by inhaling vapors when they burn off the Hg that is used to amalgamate gold (Lubick, 2010). Dental amalgams have also been reported as an important source of Hg^0 (Hursh et al., 1976), although it may also be ingested in a particulate form.

Once absorbed (mainly through the respiratory tract), Hg^0 is oxidized mainly by erythrocyte catalase to mercurous (Hg^+) and mercuric (Hg^{2+}) ions, which are toxic to several organs (particularly the kidneys), but have limited access to the CNS. Conversely, a certain amount of blood Hg^0 (not oxidized by blood catalase) passes through the BBB, reaching the CNS. Data on the distribution of brain Hg after Hg^0 exposure are scarce. In an experimental study with squirrel monkeys, the profile of distribution was not homogeneous within the different encephalic structures; Hg was found in both glial cells and neurons mainly in the cortical areas and in the fiber systems (Warfvinge et al., 1994). After Hg^0 exposure in man, urine and feces are the main pathways of Hg excretion (Tejning and Ohman, 1966). Because of the fast oxidation of Hg^0 into Hg^{2+}, the mercury excreted in feces is probably in the form of mercuric mercury (for a detailed review on Hg^0 toxicokinetics, see Clarkson and Magos, 2006).

Although Hg^0 exposure can cause toxicity to several organs (Clarkson and Magos, 2006; Goldwater, 1972), neurotoxicological signs are prevalent. In humans, common symptoms observed after occupational exposure to Hg^0 include decreased strength and coordination, and increased tremor (Albers et al., 1988). Corroborating these findings, experimental data have reported motor-related neurological impairments in monkeys (Newland et al., 1996) and mice exposed to Hg^0 (Yoshida et al., 2005).

4.3. Mercury and neurodegeneration

4.3.1. Methylmercury

Although not completely understood, the molecular mechanisms mediating MeHg-induced neurotoxicity and neurodegeneration are better known when compared with those of elemental Hg. Because MeHg is a monoalkylmercurial, its Hg atom is a monocation

(CH_3-Hg^+), which possess electrophilic properties. As an electrophilic compound, MeHg interacts with and oxidizes nucleophilic groups of several biomolecules; sulfhydryl (thiol/thiolate; –SH/–S^-) groups are important and relevant targets of MeHg in the biological systems. Accordingly, the interactions of MeHg with sulfhydryl-containing proteins (i.e. neurotransmitter receptors, transporters, antioxidant enzymes, etc.), as well as with nonprotein thiols (i.e. glutathione, cysteine), are crucial events in mediating its neurotoxicity (Clarkson et al., 2003; Sumi, 2008). By direct interaction with thiols, as well as indirect mechanisms (discussed latter), MeHg can modify the oxidation state of the –SH groups on proteins, modulating their functions (Kim et al., 2002). Consequently, the activities of several –SH-containing proteins whose roles are decisive for proper homeostasis of neuronal and glial cells [i.e. creatine kinase (Glaser et al., 2010), GSH reductase (Stringari et al., 2008), Ca^{2+}-ATPase (Freitas et al., 1996), thioredoxin reductase (Branco et al., 2012), choline acetyltransferase and enolase (Kung et al., 1987)] are perturbed after MeHg exposure. Altered protein function has been posited as a causative factor in MeHg-induced neurotoxicity and neurodegeneration (Farina et al., 2012, 2011b).

In addition to –SH-containing proteins, nonprotein thiols (represented mainly by GSH, the major low-molecular-weight thiol) are also important molecular targets involved in MeHg-induced neurotoxicity. Knowledge on the direct chemical interaction between MeHg and GSH, as well as its importance in mercurial toxicity, dates several decades (Neville and Drakenberg, 1974). Such an interaction affects the deposition of MeHg in tissues (Richardson and Murphy, 1975) and modifies Hg excretion in the bile of MeHg-exposed rats (Osawa and Magos, 1974), indicating that this low-molecular-weight thiol compound modulates its toxicity. Based on these observations (Neville and Drakenberg, 1974; Osawa and Magos, 1974; Richardson and Murphy, 1975), studies on the toxicological relevance of MeHg × GSH interaction have shown that strategies to increase GSH levels are protective against MeHg-induced neurotoxicity (Kaur et al., 2006, 2011; Shanker et al., 2005). Moreover, several *in vitro* studies with isolated organelles or cultured cells (Franco et al., 2007; Ni et al., 2011), as well as *in vivo* studies in mice (Franco et al., 2006; Stringari et al., 2008), have shown that MeHg exposure causes GSH depletion. Because of the crucial role of GSH in maintaining redox homeostasis (Dringen et al., 2005), several aspects of MeHg-induced neurotoxicity have been ascribed to GSH depletion (for a review, see Farina et al., 2011a).

Based on the direct chemical interaction between GSH and MeHg, GSH depletion upon MeHg exposure (Franco et al., 2006; Stringari et al., 2008) represents an expected phenomenon. However, intracellular GSH concentrations in the mammalian cerebrum and cerebellum are in the millimolar (mM) range. Because decreased GSH levels have been reported in the cortices (cerebral and cerebellar) of MeHg-exposed animals whose cortical mercury levels were in the low micromolar (μM) range (Franco et al., 2006; Stringari et al., 2008), it is reasonable to assume that the simple MeHg–GSH interaction is not the only cause of MeHg-induced GSH oxidation. MeHg seems to induce the formation of ROS by GSH-independent mechanisms as well, leading to subsequent GSH oxidation (Franco et al., 2007; Mori et al., 2007). This event seems to be also important in terms of protein oxidation, where ROS generated from MeHg can modulate the redox state of proteins, thus affecting their function. A classical example of such phenomenon was described by Allen et al. (2001), who showed that MeHg induces the generation of hydrogen peroxide (a common endogenous ROS), which down regulates the activity of astrocytic glutamate transporters, culminating in excitotoxicity (Lockman et al., 2001).

In addition to –SH groups (from both protein and low-molecular weight sources), selenohydryl (selenol/selenolate; –SeH/–Se^-) groups have also been reported as important targets mediating MeHg-induced neurotoxicity/neurodegeneration. From a molecular point of view, it is important to note that selenols are more nucleophilic than thiols, which could render selenoproteins preferential molecular targets of MeHg compared with –SH-containing proteins (Farina et al., 2012). Accordingly, a recent and growing body of evidence points to selenoproteins, such as GSH peroxidase and thioredoxin reductase, as critical and primary targets in mediating MeHg-induced neurotoxicity (Branco et al., 2012; Carvalho et al., 2008; Farina et al., 2009; Franco et al., 2009; Usuki et al., 2011). This is based on the higher affinity of Hg for selenols compared with thiols (Sugiura et al., 1976). Such affinity allows for the transference of MeHg from a thiol to a selenol biomolecule (MeHg–SR + RSeH ⇒ MeHg–SeR + RSH). This higher affinity of Hg for selenols also renders the selenium–mercury linkage relatively stable, even in the presence of high (i.e. mM) thiol concentrations. In agreement, nM concentrations of MeHg significantly decreased the activity of the selenoprotein GSH peroxidase-1 in cultured neurons (Farina et al., 2009), whose cytosolic GSH concentrations are in the mM range.

Based on the aforementioned, it is reasonable to assume that any selenoprotein can represent a potential molecular target for MeHg. Interestingly, GSH peroxidase-1 (Farina et al., 2009; Franco et al., 2009), GSH peroxidase-4 (Zemolin et al., 2012), thioredoxin reductase (Branco et al., 2012; Wagner et al., 2010), selenoprotein W (Kim et al., 2005) and 5′-deiodinase (Watanabe et al., 2007) are examples of selenoproteins whose activities were down-regulated by MeHg. Because of the crucial role of such selenoproteins in the maintenance of the cellular homeostasis (Lu and Holmgren, 2009), one might posit that the selenium–mercury interaction plays a pivotal role in MeHg-induced neurodegeneration. Although the complete understanding on this scheme has yet to be resolved, this hypothesis is reinforced by the fact that inorganic and organic selenium compounds mitigate MeHg-induced neurotoxicity (Farina et al., 2003a; Glaser et al., 2010; Kaur et al., 2009; Yin et al., 2011).

As already mentioned, the neurotoxicity induced by MeHg is related, at least in part, to changes in the redox state of nucleophilic groups (mainly thiols and selenols) from protein sources. These changes are likely responsible for two important events that occur in the CNS of MeHg-exposed animals, namely, oxidative stress (reviewed by Farina et al., 2011a) and glutamate dyshomeostasis (see below). From a mechanistic point of view, the altered redox state may represent a consequence of the direct interaction of the nucleophilic groups with MeHg, as well as a resultant from the pro-oxidative effects of ROS generated during MeHg exposure. Table 1 depicts several enzymes, transporters and receptors (most of them are sulfhydryl- or selenohydryl-containing proteins) as potential molecular targets of MeHg-induced neurotoxicity/neurodegeneration.

An established event in MeHg-induced neurotoxicity, which seems to result from the primary interaction of the electrophilic toxicant with nucleophilic groups, is glutamate dyshomeostasis (reviewed by Aschner et al., 2007b). Glutamate is the most important excitatory neurotransmitter in the mammalian CNS, serving crucial roles on development, learning, memory and response to injury (Fonnum, 1984). Due to its direct and indirect pro-oxidative properties, MeHg increases extracellular glutamate levels, which result from both inhibition of glutamate uptake (Aschner et al., 2000; Brookes and Kristt, 1989) and stimulation of its release into the synaptic cleft (Reynolds and Racz, 1987), culminating in excitotoxic events (Aschner et al., 2007b). Over-activation of the NMDA subtype glutamate receptors leads to an increased Na^+ and Ca^{2+} influx, which is associated with the generation of oxidative stress and neurotoxicity (Lafon-Cazal et al., 1993). Indeed, glutamate-mediated increased intracellular Ca^{2+} concentrations leads to increased nitric oxide production (due to activation of neuronal nitric oxide synthase), as well as to mitochondrial collapse (Farina et al.,

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Table 1
Potential proteins mediating MeHg-induced neurotoxicity.

Protein	Effect	Functions	References
3-Ketoacid-coenzyme A transferase I	⇓∗	Ketone body metabolism	Vendrell et al. (2007)
5′-Deiodinase	⇓#	Thyroid hormone metabolism	Watanabe et al. (2007)
ASC cysteine transporter	⇓#	Cysteine uptake	Shanker et al. (2001)
Astrocytic glutamine transporter	⇓#	Glutamine uptake from synaptic cleft	Yin et al. (2011)
Choline acetyl transferase	⇓#	Acetylcholine synthesis	Kung et al. (1987)
Creatine kinase	⇓#	Energetic metabolism	Glaser et al. (2010)
Cytosolic phospholipase A2	⇑#∗	Hydrolysis of membrane phospholipids (arachidonic acid releasing)	Shanker et al. (2004)
Enolase	⇓#	Glycolitic pathway	Kung et al. (1987)
Glutamate transporters	⇓#	Glutamate uptake	Aschner et al. (1990), Manfroi et al. (2004) and Farina et al. (2003a)
Glutathione peroxidase 1	⇓#	Peroxide detoxification	Farina et al. (2009)
Glutathione peroxidase 4	⇓#∗	Peroxide detoxification	Zamolin et al. (2012)
Glutathione reductase	⇓⇑#	Reduction of GSSG to GSH	Farina et al. (2005) and Stringari et al. (2008)
Monoamine oxidase	⇓#	Dopamine, serotonin, and noradrenaline metabolism	Beyrouty et al. (2006)
Nitric oxide synthase	⇑#	Nitric oxide synthesis	Herculano et al. (2006)
Nrf2 transcription factor	⇑∗	Modulation of antioxidant and phase 2 enzyme expression	Ni et al. (2011)
Phosphorylated-cofilin	⇓∗	Reorganization of actin filaments	Vendrell et al. (2010)
Non-phosphorylated-cofilin	⇑∗		
Selenoprotein W	⇓∗	Not well-identified (antioxidant, response to stress, immunity)	Kim et al. (2005)
Thioredoxin reductase	⇓#	Reduction of thioredoxin (antioxidant effect)	Wagner et al. (2010) and Branco et al. (2012)
X(AG(-)) cysteine transporter	⇓#	Cysteine uptake	Shanker et al. (2001)

In vitro and *in vivo* experimental evidences indicate that the activities of several proteins (from neuronal, astrocytic and/or microglial source) are modulated after MeHg exposure, suggesting their role in MeHg-neurotoxicity. The arrows ⇑ or ⇓ mean positive or negative modulator effects, respectively. # indicates that the variable was measured at functional level (i.e. enzyme activity, transporter activity). ∗ indicates that the variable was measured at expression level (protein or mRNA).

2011a). Notably, MeHg-induced Ca^{2+} and glutamate dyshomeostasis, as well as MeHg-induced ROS generation (oxidative stress), are events that contribute independently to neurotoxicity, but also represent inter-connected phenomena affecting each other. Fig. 4 depicts the relationship between glutamate and calcium dyshomeostasis and oxidative stress in MeHg-mediating neurotoxicity.

An interesting aspect of MeHg neurotoxicology is its preferential affinity for specific regions/structures of the CNS, leading to particular histological and behavioral characteristics. Pathological analyses of MeHg-poisoned adult individuals from the Minamata Bay, Japan (where the major MeHg outbreak took place), showed that this mercurial does not uniformly affect the nervous system; commonly, the cerebral and cerebellar cortices are the regions more severely affected (Eto et al., 2010). Indeed, in adult Minamata patients, a significant neurodegeneration has been observed mainly in calcarine, temporal, pre- and postcentral cortices, as well as in the cerebellar hemispheres (Eto et al., 2010). These pathological observations are in agreement with the symptoms observed in Minamata disease patients, characterized by cerebellar ataxia, concentric constriction of their visual fields, and sensory disturbances (Uchino et al., 1995). Experimental studies with MeHg-exposed animals have also pointed to the cerebral and cerebellar cortices as preferential encephalic structures subjected to MeHg-neurodegeneration; moreover, similar symptoms (visual, motor and sensory disturbances) have been observed (Carvalho et al., 2007; Charleston et al., 1995; Dietrich et al., 2005).

The neurodegeneration detected in the cerebral and cerebellar cortices of Minamata patients and MeHg-exposed animals (Carvalho et al., 2007; Eto et al., 2010) is likely consequence of a relative short-term high dose exposure to this mercurial. However, it is noteworthy that fishing communities are commonly exposed to chronic low-dose exposures (Clarkson et al., 2003), which probably induce a more subtle (maybe "undetectable") pattern of neurodegeneration/neurotoxicity. Human health concerns associated with these chronic exposures are of particular relevance taking into account (i) the absence of a factual non-observed adverse effect level (NOAEL) in terms of MeHg-induced neurotoxicity (mainly with respect to developmental toxicity) and (ii) the potential occurrence of a dangerous but silent pandemic of subclinical MeHg neurotoxicity (Grandjean and Landrigan, 2006).

4.3.2. Mercury vapor (elemental mercury)

Data on the molecular mechanisms mediating elemental mercury (Hg^0)-induced neurotoxicity/neurodegeneration are scarce compared with those on MeHg. Hg^0 (in contrast to MeHg) causes general toxicity in several tissues, such as lung, kidney and gastrointestinal tract, among others (Goldwater, 1972; Magos, 1967). Indeed, as previously mentioned, most of the absorbed Hg^0 is oxidized in the blood to Hg^{2+}, and subsequently targets several organs. However, a certain amount of blood Hg^0 (not oxidized to Hg^{2+}) passes through the BBB prior to this oxidation step, thus reaching the CNS. Of note, it is believed that the mercuric ion Hg^{2+} (generated within the CNS from Hg^0 oxidation) is the proximate toxic chemical form because mercury vapor itself is unable to react with tissue ligands. Consequently, the oxidation of Hg^0 to Hg^{2+} (in both blood and CNS) seems to be an important determinant on the degree and pattern of the toxic effects of Hg^0 (Magos, 1967).

From a mechanistic point of view, it is important to note that Hg^{2+} (generated from Hg^0 oxidation within the CNS) binds to –SH-containing ligands (Aschner and Aschner, 1990); this event likely dictates the neurotoxicity observed after Hg^0 exposure. In agreement, an experimental study in Hg^0-exposed mice showed higher susceptibility to Hg^0-induced behavioral changes in metallothionein (MT)-null compared with wild type animals (Yoshida et al., 2005). Based on the high affinity of Hg^{2+} for thiols, as well as on the fact that MTs are cysteine-rich intracellular proteins with great affinity for divalent metals, the results by Yoshida et al. (2005) indicate that the interaction of Hg^{2+} (derived from Hg^0) with –SH-containing ligands in the CNS likely represents an important event mediating toxicity.

In vitro studies aimed on Hg^0-induced neurotoxicity have been carried out with Hg^{2+} (Albrecht and Matyja, 1996; Brookes and Kristt, 1989), as a surrogate of Hg^0 since the latter is rapidly biotransformed to Hg^{2+}. Cell culture-based studies (Brookes and

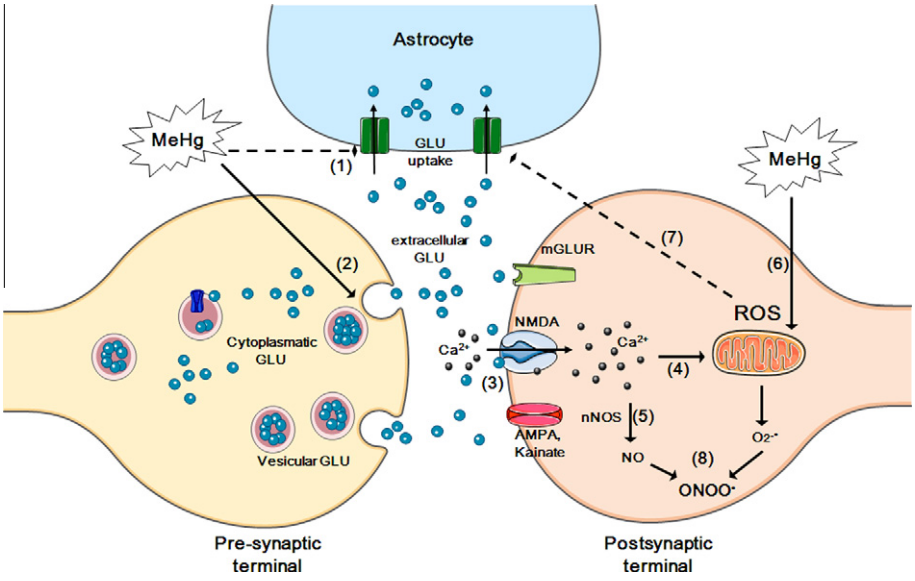

Fig. 4. MeHg-induced glutamate and calcium dyshomeostasis and oxidative stress. MeHg causes increased extracellular glutamate (GLU) levels via the inhibition of astrocytic glutamateuptake (event 1) and the stimulation of glutamate release from pre-synaptic terminals (event 2). Increased extracellular glutamate levels overactivate *N*-methyl D-aspartate (NMDA)-type glutamate receptors, increasing calcium influx into neurons (event 3). Increased levels of intracellular calcium, which can lead to mitochondrial collapse (event 4), activate neuronal nitric oxide synthase (nNOS) (event 5), thus increasing nitric oxide (NO) formation. MeHg affects the mitochondrial electron transfer chain (mainly at the level of complexes II–III) (event 6), leading to increased formation of reactive oxygen species [ROS; superoxide anion ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2)]. H_2O_2 can inhibit astrocyte glutamate transporters (event 7), contributing to the excitotoxic cycle. $O_2^{\cdot-}$ reacts with NO (event 8), generating peroxynitrite ($ONOO^{\cdot}$), a highly oxidative molecule. Adapted from Farina et al., 2011a.

Kristt, 1989) pointed to glutamate dyshomeostasis as a critical event mediating Hg^{2+}-induced toxicity. In fact, sub-μM concentrations of Hg^{2+} inhibited the clearance of extracellular glutamate both in astrocyte and spinal cord cultures, and reduced glutamine content and export in astrocyte cultures (Brookes and Kristt, 1989), indicating that Hg^{2+}-induced neurotoxicity might be mediated by excitotoxic events. In agreement, Albrecht and Matyja (1996) not only observed decreased glutamate uptake, but also increased glutamate release in Hg^{2+}-exposed cultured astrocytes, reinforcing the idea that Hg^0/Hg^{2+}-neurotoxicity may be mediated by excitotoxic activity of glutamate (Albrecht and Matyja, 1996). Interestingly, this study also reported that the inhibition of glutamate uptake was attenuated by addition to the cultures of a cell membrane-penetrating agent dithiothreitol (a dithiol agent), but not of GSH, which is not transported into the cells. These results reinforce that the intracellular thiol status is likely responsible for the effects of Hg^{2+} in mediating astrocyte glutamate dyshomeostasis. This hypothesis is reinforced by the fact that the activity of astrocyte glutamate transporters is sensitive to thiol agents (Volterra et al., 1994).

Although data on the mechanisms mediating Hg^0-neurotoxicity are scarce, existing evidence suggests that changes in the redox state of –SH-containing proteins plays a critical role (Albrecht and Matyja, 1996; Aschner and Aschner, 1990; Brookes and Kristt, 1989; Yoshida et al., 2005). However, based on the high affinity of Hg^{2+} (herein, derived from Hg^0) for selenols, it is reasonable to suggest that selenoproteins could also mediate the neurotoxic effects observed after Hg^0 exposure. This idea is based on the higher affinity of Hg^{2+} for selenols compared with thiols (Sasakura and Suzuki, 1998). Carvalho and coworkers (2008) observed that the selenoprotein thioredoxin reductase (TrxR) is selectively inhibited by Hg^{2+} and concluded that the significant potency of the mercurial to bind to the selenol group in the active site of TrxR represents a major molecular mechanism of its toxicity. Because of the probable interaction between Hg^{2+} (derived from Hg^0) and selenols in the CNS, the potential involvement of selenoproteins in the neurotoxicity elicited by Hg^0 represents an important research field that deserves further attention. This is believed because (i) Hg^{2+} toxicity is antagonized by selenium compounds (Farina et al., 2003b; Yamamoto, 1985), (ii) Hg^{2+}, which is generated in the SNC after Hg^0 oxidation, inhibits the activity of selenoproteins by interacting with their selenol group (Carvalho et al., 2008), and (iii) miners occupationally exposed to Hg^0 had lower levels of plasma selenium when compared with control individuals (Kobal et al., 2004).

4.4. Antidotal strategies

Several compounds have been reported to protect against Hg toxicity in experimental *in vitro* and *in vivo* models. Vitamin E (Shichiri et al., 2007), thiol compounds (Falluel-Morel et al., 2012; Koh et al., 2002), natural products (Farina et al., 2005; Franco et al., 2010; Lapina et al., 2000; Lucena et al., 2007), vitamin K (Sakaue et al., 2011), chelating agents (Carvalho et al., 2007), Ca^{2+}-channel blockers and glutamatergic antagonists (Ramanathan and Atchison, 2011), among others, have shown beneficial effects against mercurial toxicity. Although the aforementioned protective effects have been observed under experimental conditions, unfortunately, the clinical practice with Hg-exposed humans has shown the absence of an effective treatment that completely abolishes the toxic effects. In such cases, supportive care is given when necessary to maintain vital functions and the administration of chelator agents is performed in an attempt to assist the body's ability to eliminate Hg from the tissues. However, these drugs have limited use because of incomplete efficacies in removing Hg from tissues and significant adverse side effects (Tchounwou et al., 2003).

A rapid antidotal intervention is required in high-dose acute exposures, which are commonly observed after occupational or intentional exposures to Hg^0 (Bluhm et al., 1992; De Palma et al., 2008; Eyer et al., 2006). Different chelating agents, including penicillamine, dimercaprol, 2,3-dimercaptopropane-1-sulphonate (DMPS), and meso-2,3-dimercaptosuccinic acid (DMSA), have been administered in these cases (Eyer et al., 2006; Houeto et al., 1994); however, the desired beneficial results are generally not achieved. In fact, even though urinary Hg excretion could be significantly enhanced during chelation therapy, its efficacy on the disappearance of tissue Hg deposits seems to be negligible (Lin and Lim, 1993; Rodrigues et al., 1986).

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Chelating therapy can also increase Hg excretion after MeHg exposure, which suggests its beneficial use as antidotal strategy for MeHg poisoning. Clarkson et al. (1981) studied the effects of three chelating agents (DMPS, D-penicillamine and *N*-acetyl-DL-penicillamine) and a thiolated resin in reducing the blood half-life ($T_{1/2}$) of MeHg during an outbreak of human poisoning. All four treatments significantly reduced the mean $T_{1/2}$ compared with placebo; DMPS was the most effective agent. Another study with healthy individuals showed that oral DMSA treatment produced a rise in urine Hg excretion of fish eaters; although a similar increase in renal Hg excretion was observed in non-fish eaters (Ruha et al., 2009). Existing evidence concerning the use of chelating therapy in MeHg poisoning indicates that chelators can remove MeHg from the body, but cannot reverse the damage to the CNS (Clarkson et al., 2003). This aspect is particularly important when considering the most common pattern of human MeHg exposure (low-dose/long-term exposures), which is observed in fish-eating populations. The relative short-term high-dose MeHg poisonings, such as those observed during the well known outbreaks in Minamata Bay (Harada, 1978) and Iraq (Bakir et al., 1973), do not represent the common profile of human MeHg poisoning. In fact, human exposures to MeHg in fishing communities generally occur over extended periods (months or years) due to long-term seafood intake. Thus, massive short-term MeHg exposures are not frequent and, consequently, antidotal clinical interventions (i.e. chelating therapy) are not usually necessary (and useful) in such cases. In fact, it is believed that the neurological impairments observed in humans chronically exposed to MeHg due to the ingestion of contaminated fish might not necessarily correlate with the Hg levels present in tissues. In line with this, an experimental study on the developmental exposure of mice to MeHg showed that cerebral biochemical parameters affected by MeHg exposure (i.e. lipid peroxidation, GSH levels, GPx and GR activities) remained changed in the MeHg-exposed animals even when the cerebral Hg concentration decreased to basal levels (Stringari et al., 2008). These results indicated the persistence of MeHg-induced cerebral biochemical changes even when the cerebral concentrations of the toxicant were undetectable, suggesting an enduring *toxic mark*. Such experimental observation (Stringari et al., 2008) appears to be closely related to permanent functional deficits observed at 14 years after prenatal MeHg exposure (Debes et al., 2006), where chelating therapy would probably have no beneficial effect.

There is a consensus that chelating therapy can significantly increase Hg excretion, at least in some specific cases (Bluhm et al., 1992; Clarkson et al., 1981; De Palma et al., 2008; Eyer et al., 2006). Of note, chelating therapy is greatly based on –SH-containing molecules, such as D-penicillamine, *N*-acetyl-DL-penicillamine, dimercaprol, DMPS, and DMSA. Based on the higher affinity of Hg for selenols when compared with thiols, one could ask: "why selenocompounds are not used as potential chelating agents for human Hg poisoning"? To the best of our knowledge, there is no data on the potential antidotal effects of selenocompounds against Hg toxicity in humans. However, experimental evidence indicates that organic selenocompounds not only protect against mercurials' toxicity (Farina et al., 2003a; Moretto et al., 2005; Yin et al., 2011), but also decrease Hg deposition in tissues (de Freitas et al., 2009). A comparative study on the effectiveness of thiol- and selenol-based compounds in reversing mercurial toxicity and in increasing Hg excretion is warranted.

5. Concluding remarks

Metals are constantly present in our lives, as we ingest essential metals in food and as we are exposed to them in the air dust or in contaminated water or food. Interest in the toxicity of essential trace metals has evolved from the need for government regulatory agencies such as the United States Environmental Protection Agency (EPA) to set environmental standards for these metals, as well as classic toxic metals such as Hg. The metals discussed in this review can be readily absorbed from different sources, and reach the CNS thus affecting neurons and glial cells. The mechanisms of toxicity are still not clearly understood; however their clinical features are well described and remain of great concern. Understanding these mechanisms is essential in designing novel therapeutic approaches, including antioxidants with diverse modes of action. In fact, the efficacy of antioxidants as potential therapeutic agents against Fe, Mn and Hg highlights oxidative stress as a unifying feature in their neurotoxic effect. However, the primary events triggered by these metals are mediated via distinct molecular targets. A better understanding of these mechanisms will assist in the development of multifactorial approaches to blunt or delay the progression of disease.

6. Uncited references

Blanusa et al. (2005), Crawford et al. (2011). Q5

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