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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 – 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