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Alzheimer's Disease and Metal Contamination: Aspects on Genotoxicity

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1. Introduction

Despite the genetic and environmental factors and the aging process itself, multiple evidence from experimental models and postmortem studies in Alzheimer's disease (AD) brain tissue demonstrate that neurodegeneration is associated with morphological and biochemical features. Considerable evidence suggests a role for oxidative stress/damage (amyloid beta peptide, iron/hydrogen peroxide) or neurotoxic by-products of lipid peroxidation (4-hydroxy-2-nonenal, acrolein) and inflammation, in the pathogenesis of neuron degeneration, which, in turns, are known to cause cell death.

Recently, several reports indicate that, among factors, metal ions (Al, Zn, Cu, Fe, etc) could specifically impair protein aggregation and their oligomeric toxicity. Also, metal-induced (direct) and metal-amyloid-β (indirect) linked neuronal cell death through the formation of reactive oxygen species (ROS) being critical to the understanding of the mechanisms which metal-induced cell death, and thus its role in neurodegenerative disorders.

Some metals are essential for humans and for all forms of life. Even though metals are necessary in biological systems, they are usually required only in trace amounts; in excess, it can be toxic, if not fatal. Environmental metal exposure has been suggested to be a risk factor for AD. High-term exposure to certain metals like manganese (Mn), iron (Fe), aluminum (Al) and many others like copper (Cu), mercury (Hg), zinc (Zn), lead (Pb), arsenic (As), alone or in combination, can increase neurodegenerative process, especially to Alzheimer's disease (AD).

Aluminum is the most widely distributed metal in the environment and is extensively used in daily life that provides easy exposure to human beings. No biological function of the element has been identified, whereas some aspects of its toxicity have been described. It has been suggested that there might be a relationship between high levels of Al and increased risk of a number of pathogenic disorders, such as microcytic anemia, osteomalacia and, possibly, neurodegenerative disorders including dialysis encephalopathy, Parkinson's disease and Alzheimer's disease.

This metal is known to be extremely neurotoxic and in high levels is capable to inhibit the prenatal and post-natal development of the brain. Evidence from clinical and animal studies

demonstrated that brain Al content increases with age and that Al generates reactive oxygen species (ROS) that activates signaling pathways which leads to degeneration of neuronal cells. Together with ROS or alone, Al is biochemically attracted to the DNA reveling its genotoxic and mutagenic potential.

Furthermore, high level of Al has been found in brain lesions, such as plaques and tangles, in patients with AD. Several studies demonstrated that among others, Al appears to be the most efficient cation in promoting Aβ aggregation, increasing dramatically cellular neurotoxicity. According to the "amyloid cascade hypothesis", accumulation of Aβ in the brain is the primary event driving AD pathogenesis, increasing the evidences by which Al is involved in AD.

Iron is an essential trace element used by almost all living organisms, being often incorporated into the heme complex, which mediate redox reactions. Disturbances of brain iron homeostasis have been linked to acute neuronal injury. Moreover, iron is toxic to neural tissue, leading to neurodegenerative disorders.

Organic iron (Fe) may increase the genotoxic effects of other compounds when they are combined. Together with aluminum sulfate, at nanomolar concentrations, iron trigger the release of reactive oxygen species (ROS). In high levels, iron can be mutagenic and genotoxic. In AD, iron is an important cause of oxidative stress because of its over-accumulation in the brain and colocalizes with AD lesions, senile plaques and neurofibrillary tangles.

Recent studies also show that homeostasis of essential metals such as copper, iron, selenium and zinc may be altered in the brain of subjects with Alzheimer's disease. It is demonstrated that the plasma concentrations of manganese and total mercury were significantly higher in subjects with AD than in controls, however the concentrations of vanadium, manganese, rubidium, antimony, cesium and lead were significantly lower among subjects with AD cerebrospinal fluid.

The influence of metal ions such as Fe, Cu, and Zn in stimulating Aβ aggregation have been widely studied where they appears to vary depending on tissue pH. It should be noticed that, although there is co-localization of metal ions in the pathological markers of AD, this does not indicate a causative role for these elements in the pathogenesis of the disease. Independently of metals being a primary cause or consequence of the disease mechanism, a change in a single metal ion can cause a significant imbalance on homeostasis in elemental levels in the body (serum, CSF and brain) leading to as a sort of "domino effect". It is clear the need to understand the fundamental biochemical mechanisms linking brain biometal metabolism, environmental metal exposure, genotoxicity and AD pathophysiology. In this review, we discuss the role of metals in Alzheimer disease and its involvement in genotoxicity.

2. Source of metal exposure

Metals have been used throughout human history to make several utensils, machines, jewelry, and so on, where many of then were obtained through mining and smelting, activities that increases their distribution throughout the environment. Furthermore, the use of metals in industry, medicine, agriculture have been increased over the years, which increase the exposure, not only for those workers involved directly in working with metals but also consumers of the products and the general public through environmental contamination (Ferrer, 2003; Ansari *et al*., 2004).

Metals are among the oldest toxic agents known by humans. Its history starts prior to 2000 BC when it became available as a byproduct of silver smelting. The early Greeks and Romans documented both the toxic as well as the potential healing effects of metals. Theophrastus of Erebus (370-287 BC) and Pliny the Elder (23-79 AD) described the pernicious effects of arsenic and mercury on miners and smelters (Hollenberg, 2010).

In an industrialized world, there are thousands of types of metals in use, and humans are exposed to them at work, or as a result of contamination of food, water and environment. There is abundant evidence indicating an increase of neurodegenerative disorders like AD in industrialized countries (Veldman et al., 1998; Butterworth, 2010). The chronic exposure to metals from several years together with the advance of medical tools may explain why the diagnosis of AD and so its epidemic starts around 1980.

Aluminum is the most widely distributed metal in the environment and is extensively used in a wide variety of products: cans, foils and kitchen utensils, as well as parts of airplanes, rockets and other items that require a strong, light material. It can be deposited on the surface of glass to make mirrors, and also to make synthetic rubies and sapphires for lasers. Al is found in the environment in its natural forms or as a source of human contamination resulting from mining and smelting, activities that increase their distribution throughout the environment. Al occurs naturally only in compounds, never as a pure metal. Because of its strong affinity to oxygen, it is almost never found in the elemental state; instead it is found in oxides or silicates (WHO, 1997; Nayak, 2002).

In nature, this trace element is found in its oxidized state Al^{3+} (soluble toxic form of Al), which binds to others molecules like chloride, forming Aluminum chloride ($AlCl_3$) (Smith, 1996; WHO, 1997). Aluminum chloride ($AlCl_3$) is an important coagulant used in water treatment and purification (WHO, 1997; Zhang e Zhou, 2005) being another source for exposure. Two of the most common compounds are potassium aluminum sulfate ($KAl(SO_4)_2 \cdot 12H_2O$), and aluminum oxide (Al_2O_3).

Although aluminum is a widespread element, almost all metallic aluminium is produced from the ore bauxite ($AlO_x(OH)_{3-2x}$). Bauxite is a complicated mixture of compounds consisting of 55% of aluminum, oxygen, and other elements (WHO, 1997; Nayak, 2002). Large reserves of bauxite are found in Australia, Brazil, Guinea, Jamaica, Russia, and the United States.

No biological function of the element has been identified, whereas some aspects of its toxicity have been described (Berthon, 1996; Corain *et al*., 1996; Suwalsky *et al*., 2001). The exposure to this toxic metal occurs through air, food, water and it is also present in medical, cosmetic and environmental products (Berthon, 2002).

Daily consumed of Al by food and beverages is 2.5 to 13 mg, where drinking water can contributes to 0.2 to 0.4 mg of Al daily. Drugs can contribute with increase levels of Al; antiacid drugs (2 tablets) can contribute up to 500 mg of Al (WHO, 1997). As the world becomes more industrialize, the chronic exposure to Al increases, increasing the risk for the development of neurodegenerative disorders like AD and PD.

The period in human history beginning in about 1200 B.C. is called the Iron Age. Iron is a transition metal and normally does not occur as a free element (Meteoric origen) (O´Neil, 1994). The most common ores of iron are hematite, or ferric oxide (Fe_2O_3); limonite, or ferric oxide (Fe_2O_3); magnetite, or iron oxide (Fe_3O_4); and siderite, or iron carbonate ($FeCO_3$). An increasingly important source of iron is taconite. Taconite is a mixture of hematite and silica (sand). The largest iron resources in the world are in China, Russia, Brazil, Canada,

Australia, and Índia. Furthermore, almost all rocks and soils contains at least trace amounts of iron (Sienko, 1977).

Iron is a very reactive metal. Most of then are found as Fe^{2+} which are oxidize to Fe^{3+}. Combines with oxygen in moist air and the product of this reaction is iron oxide ($Fe_2 O_3$) (Cox, 1995). Iron also reacts with very hot water and steam to produce hydrogen gas. It also dissolves in most acids and reacts with many other elements. All of this reaction can be a source for contamination.

Iron is a silvery-white or grayish metal. It is ductile and malleable, very high tensile strength and workable. In general, iron products can be found in automotive, construction, containers, machinery and industrial equipment, railroad tracks, oil and gas industries, electrical tools, appliances and utensils (Ilo, 1997). Furthermore, the fastest growing use of iron compounds is in water treatment systems.

Populations are exposed to iron mainly through foods and beverages. It is available in a number of foods, including meat, milk, eggs, nuts, coffee, tea, fish, grain, soil and raisins. Iron can also be found in fresh water, where recommended levels can not exceed 0.3 mg of iron in 1 liter of water (WHO, 1996). The United State Recommended Daily Allowance (USRDA) for iron is 18 milligrams, being the amount of iron that a person needs to stay healthy. Also, daily recommended doses of Fe varies among age; for children up to 3 months, 1.7 mg/kg/daily are recommended, whereas for adults this is 10 times more (18 mg/kg/daily)(WHO, 1996).

An iron deficiency can cause serious health problems in humans. Also, several alterations have been related to high iron intake where iron is toxic to neural tissue, leading to neurodegenerative disorders like AD (Montgomery, 1995; Campbell & Bondy, 2000; Stankiewicz & Brass, 2009).

Manganese is a transition metal and it took several years to discover the difference between manganese and iron, mainly because it oftens occurs together in the Earth's crust and its similarity properties.

Manganese is a moderately active metal and never occurs as a pure element in nature. It always combines with oxygen in the air to form manganese dioxide (MnO_2) or other elements. It also combines with fluorine and chloride to make manganese difluoride (MnF_2) and manganese dichloride ($MnCl_2$) (WHO, 1999). The most common ores of manganese are pyrolusite (MnO_2), manganite, psilomelane, and rhodochrosite. Manganese is also found mixed with iron ores. The largest producers of manganese ore in the world are China, South Africa, the Ukraine, Brazil, Australia, Gabon, and Kazakstan.

Early artists were familiar with pyrolusite and they used the mineral to give glass a beautiful purple color, and/or to remove color from a glass. By the middle 1700s, chemists proved that pyrolusite contained manganese dioxide. Until now, coloring agents (textiles, paints, inks, glass, and ceramics) still contains manganous chloride.

The most common alloy of manganese is ferromanganese, containing about 48 percent manganese combined with iron and carbon, being the source for making a very large variety steel products, including tools, heavy-duty machinery, railroad tracks, bank vaults, construction components, and automotive parts. Also, manganous chloride ($MnCl_2$), is an additive in animal food for cows, horses, goats, and other domestic animals. In agriculture, manganous chloride are present in fertilizers (Barceloux, 1999).

Manganese is one of the chemical elements that has both positive and negative effects on living organisms because manganese is used by many enzymes in an organism. A very small amount of the element is needed to maintain good health. The absortion of Mn is only

3 to 5%, being food the primary source of this metal. Mn is found in green vegetables, nut, raisins, and also in teas, its main source for human consumption. Low concentrations are found in Milk, meat, fish, eggs and fruits (Barceloux, 1999). Taking all together, soil, fertilizer and food, one can say that humans are exposed to Mn and that excess of manganese can create health problems. Also, a variety of drugs and supplements have Mn in its composition (WHO, 1999).
Human exposure can be also by inhalation. Workers may inhale manganese dust in the air in a factory or mine. Also, human can be exposed by the ingestion of contaminated water with fertilizers and pesticides (WHO, 1999). Exposures to high levels of manganese by ingestion or inhalation can damage the central nervous system. Daily-recommended doses of Mn for children are 0.3 mg/Kg/daily, being 3 times more for adults (10 mg/Kg/daily) (WHO, 1999).

3. Metal neurotoxicity

Abnormal production or clearance of a small peptide, the amyloid β-peptide (Aβ), which is the major constituent of the senile plaques, is a widely accepted causative agent in degenerative disorders like AD (Hardy & Selkoe, 2002; LaFerla et al., 2007; Qiu & Folstein, 2006; Rauk, 2009; Sayre et al., 1997; Selkoe, 2000). Aβ is a 39- to 43-residue peptide cleaved from the C-terminal region of a much larger protein, the amyloid precursor protein (APP), where the most abundant fragments are Aβ (1–40) and Aβ (1–42), being the latter the most neurotoxic (Rauk, 2009).
Several studies have shown that Aβ exerts its toxicity by generating reactive oxidative stress (ROS) molecules, leading to peroxidation of membrane lipids and lipoproteins, induction of H_2O_2 and hydroxynonenal (HNE) in neurons, damages DNA and transport enzymes inactivation (Behl et al., 1994; Kontush et al., 2001; Mark et al., 1997; Mark et al., 1997; Varadarajan et al., 2000; Xu et al., 2001). In addition to a high metabolically levels of ROS, there are other sources that are thought to play an important role in the AD progression. Among them, mitochondrial and metal abnormalities are the major sources of oxidative stress (Su et al., 2008).
Increasing evidences suggest that altered metal homeostasis may contribute to neuronal loss in neurodegenerative diseases (Gerlach et al., 2006; Sayre et al., 2005; Wright, 2008). Given a likely role for metal-associated oxidative stress, herein it is discuss the involvement of metals, such as Al(III), Fe(III) and Mg(II) in neurotoxicity.

3.1 Aluminum and neurotoxicity

Aluminum (Al) is the third most abundant element in the earth's crust and is not an essential trace metal for mammals. However, the concentrations found in the body can be sufficient to modify the activity of several key enzymes and second messenger pathways (Bondy, 2010).
Aluminum is known to be extremely neurotoxic and in high levels is capable to inhibit the prenatal and post-natal development of the brain (Yumoto et al., 2001). Several studies correlated the risk of developing Alzheimer's disease with residing in areas where aluminum concentrations in the drinking water are 100 mg/L or greater (McLachlan et al., 1996; Rondeau et al., 2000).
The hypothesis that there is a link between aluminum and Alzheimer's disease (AD) was first brought out in the 1960s by Terry and Pena (1965) and by Klatzo and colaborators in

1965 (Terry et al., 1969). Early on 1976, high levels of aluminum have been found in brain lesions, such as plaques and tangles, in patients with AD (Crapper et al., 1976), and also in other conditions such as Parkinson's disease (PD), pre-senile dementia, amiotrofic lateral esclerosis, neurofibrilar degeneration, dialysis encephalopathy syndrome and nigroestriatal sindrome (Altschuler, 1999; Gupta et al., 2005; Nayak, 2002; Yasui et al., 1992; Zatta et al., 1991). Elevated aluminum levels have also been reported in other less common neurological disorders such as the Guamanian Parkinsonian-ALS constellation and Hallervorden-Spatz disease (Eidelberg et al., 1987; Garruto et al., 1989).

The most common neurostrutural alterations induced by high levels of aluminum in the brain is: brain ventricle dilatation and thinning of the corpus callosum (Lapresie et al., 1975), reduce neural cell density, degenerative changings like picnosis, vacuolization, chromatin condensation (Varner et al., 1998), increase neural filaments in neuron from the spinal cord and brainstem (Terry et al., 1969), axonal intumescence (Troncoso et al., 1985) and cerebellar disorder with degeneration of the Purkinje cells (Ghetti et al., 1985; Yokel, 1994).

There is some experimental evidence that Al exposure can adversely affect the dopaminergic system. Extended exposure to 100mM Al lactate increased striatal levels of the dopamine metabolite (Li et al., 2008), what, in turns, suggests that exposure to Al may cause increased turnover of dopamine. The development of an encephalopathy, characterized by cognitive deficits, in-coordination, tremor and spinocerebellar degeneration, among workers in the aluminum industry also indicates that exposure to the metal can be profoundly deleterious. Abnormal neurological symptoms have been observed in several patients receiving intramuscular injections of Al-containing vaccines.

There have been many experimental studies on animals and on isolated cells showing that aluminum has toxic effects on the nervous system. In 1991, Guy and colaborators showed that the uptake of aluminum by human neuroblastoma cells display an epitope associated with Alzheimer's diseases. Chronic exposure of animals to aluminum is associated with behavioural, neuropathological and neurochemical changes. Among them, deficits of learning and behavioural functions are most evident (Kummar et al., 2009; Ribes et al., 2010; Sethi et al., 2008). Also, when mice were injected with adjuvants containing aluminum in amounts equivalent to those given to US military service personnel, neuroinflammation and cell loss were found in spinal cord and motor cortex, together with memorial deficits (Petrik et al., 2007).

Several metals interact with β-amyloid (Aβ) in senile plaques. It is interesting to note that, compared to other Aβ-metal complexes (Aβ-Fe, Aβ-Zn, Aβ-Cu), Aβ-Al is unique in promoting a specific form of Aβ oligomerization that has marked neurotoxic effects (Drago et al., 2008).

There are a lot of ways which Al can damage neural cells: (i) interfering with glucose metabolism, leading to low amounts of Acetilcholine (Ach) precursors; (ii) interacting to ATPase Na^+/K^+ and Ca^{2+}/Mg^{2+} -depending, altering excitatory aminoacid release; (iii) inhibition the binding of Ca^{++}; (iv) incresing the production of AMPc; (v) causing changes in the cytoskeleton protein, leading to phosphorilation, proteolysis, transport and synthesis disruption; (vi) interacting directly to genomic structures, and most importantly (vii) inducing oxidative damage by lipid peroxidation (Nayak & Chatterjee, 1999).

Being involved in the production of reactive oxygen species (ROS), aluminum may cause impairments in mitochondrial bioenergetics and may lead to the generation of oxidative stress which may lead to a gradual accumulation of oxidatively modified cellular proteins, lipids and affects endogenous antioxidant enzyme activity, leading to degeneration of

neuronal cells (Kummar et al., 2009; Sethi et al., 2008; Wu et al., 2010). In this way, aluminum is a strong candidate for consideration as a subtle promoter of events typically associated with brain aging and neurodegenerative disorders.

3.2 Iron and neurotoxicity

Metal ion homeostasis is maintained through highly regulated mechanisms of uptake, storage, and secretion (Mills et al., 2010). Iron plays a role in oxygen transportation, myelin synthesis, neurotransmitter production, and electron transfers, being a crucial cofactor in normal central nervous (CNS) metabolism. Iron is also abundantly in substantia nigra and globus palladium when compared with other regions and is found to increase with age in humans (Bartzokis et al., 1994; Lee et al., 2010; Zecca et al., 2001). Normally, under healthy conditions, these metal ions are bound to ligands (e.g., transferrin), however when they are found nonbound, iron are potentially harmful mainly due to their redox activities in the synaptic cleft (Salvador et al., 2011).

Free iron catalyzes the conversion of superoxide and hydrogen peroxide into hydroxyl radicals, which promote oxidative stress by the Fenton reaction (Berg et al., 2001). Furthermore, ROS interacts with a variety of molecules, including unsaturated fatty acids, proteins and DNA leading to subsequent cell death/apoptosis, especially on CNS tissue, whereas the antioxidant defenses are rare (Demougeot et al., 2003; Stankiewicz & Brass, 2009; Willmore & Rubin, 1984). Thus, disturbances of brain iron homeostasis have been linked to acute neuronal injury leading to neurodegenerative disorders (Campbell & Bondy, 2000; Montgomery, 1995) such as Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD) diseases as well as amyotrophic lateral sclerosis (ALS) (Connor & Benkovic, 1992; Kell, 2010; Liu et al., 2006; Rouault, 2001; Youdim et al., 2005).

Degradation of the dopaminergic system, where catechols molecules should be produced, may play a role in the extrapyramidal symptoms in PD (Prikhojan et al, 2002; Santiago et al., 2000). *In vitro* studies have shown that iron is accumulated in microglia and astrocytes in the cerebral cortex, cerebellum, substantia nigra, and hippocampus, and it is believed that this metal would be involved in the neuroinflammation observed in AD and PD (Ong & Farooqui, 2005).

Postmortem studies in PD subjects, suggests that accumulation of iron in the substantia nigra stimulates lipid peroxidation, which can lead to cell damage (Nakano, 1993; Riederer et al., 1989). Studies conducted with PD subjects demonstrated that in mild PD, there were no significant differences in the content of total iron between the PD group and control, whereas there was an increase in total iron and iron (III) in substantia nigra of severely affected patients (Riederer et al., 1989). Indeed, lateral substantia nigra pars compacta abnormalities were observed in early PD together with increased iron content.

Within the reduction on glutathione and the change of the iron (II)/iron (III) ratio in favor of iron (III), it is suggest that these changes might contribute to pathophysiological processes underlying PD (Griffiths et al., 1999; Lan & Jiang, 1997; Martin & Wiler, 2008). Interestingly, the increase in iron in the degenerating substantia nigra (SN) occurs only in the advanced stages of the disease, suggesting that these phenomena may be a secondary event, rather than a primary (Double et al., 2000). Patients with diagnosed AD and in normal elderly patients, iron concentrations have been found to be increased in the bilateral hippocampus, parietal cortex, frontal white matter, putamen, caudate nucleus, thalamus, red nucleus, substantia nigra, and dentate nucleus subregions. Particularly in the parietal cortex, at the

early stages of AD, studies have been found to positively correlate with the severity of patients' cognitive impairment (Sullivan et al., 2009; Zhu et al., 2009).
Although extensive evidence links the iron metabolism, aging, and neurodegenerative disorders, relatively little is known about the resulting forms of iron that accumulate in the brain. Numerous techniques have been developed in order to characterize, locate, and quantify iron species and iron- containing compounds in the brain, however, more studies are needed to understand the role of this transition metal in the onset and progression of neurodegenerative diseases and neurological age-related disorders.

3.3 Manganese and neurotoxicity

Manganese is an essential element for many living organisms, especially humans, where some enzymes require (e.g., manganese superoxide dismutase), and some are activated, by manganese (Hurley & Keen, 1987). Excess accumulation of these metal by ingestion or inhalation (mostly in working place) (Agency for Toxic Substances and Disease Registry [ATSDR], 2000) can damage the central nervous system (Winder et al., 2010) most likely due to impaired transport or failure of hepatic detoxification mechanisms, what have deleterious effects on cell function and integrity (Butterworth, 2010).
It is known that astrocytes have a much higher affinity and capacity for manganese uptake compared to neurons and that exposure to manganese results primarily in alterations of astrocyte morphology and function (Aschner et al., 1992). Excessive exposure to Mn can also lead to neural lesion, primarily on the dopaminergic pathway (globus pallidus and substantia nigra pars reticulata), inhibiting dopamine metabolism (Vidal et al., 2005).
Short-term repeated pulmonary exposure to manual metal arc-hard surfacing or gas metal arc-mild steel fumes resulted in selective deposition of Mn in the brain, particularly in dopaminergic brain areas. It is interesting to note that, other constituents of the fumes like Fe, Cr, Ni or Cu did not appear to translocate to the brain despite their large accumulation in the lungs and its associated lymph nodes. Molecular markers of dopaminergic neurotoxicity and injury response can be found in the brain of welding fumes, extended beyond the globus pallidus, considered the primary site of damage in manganism, to broader dopaminergic areas (Sriram et al., 2010).
Neurotoxic effect of Mn can be due to its interaction with detoxification enzymes that protects the cells, and/or its interaction with the redox system. In this way, Mn^{2+} (necessary in the brain) can be oxidize to Mn^{3+}, a toxic compound that enhances the oxidation of dopamine leading to a lots of neurotoxic products (Donaldson et al., 1982). Recent studies reveal that repeated exposure to Mn or Mn-containing welding fumes can cause mitochondrial dysfunction and alterations in the expression of proteins in dopaminergic brain areas, also, events that contribute to dopaminergic neurotoxicity (Sriram et al., 2010).
Some evidences indicate that the neurological abnormalities can be found on the striatum and on subthalamic nucleus in the CNS of the monkey receiving $MnCl_2$ by inhalation (Newland et al., 1999). Also, undesirable neurological effects were observed in children who were exposed to excess manganese (Zheng et al., 1998), what can explain the enhanced incidence of neurological symptoms in isolated populations (Florence & Stauber, 1989; Iwami et al., 1994).
Adverse health effects can be caused by inadequate intake or overexposure to manganese. Chronic exposure to high levels of Mn induces a syndrome known as "manganism", characterized by extrapyramidal dysfunction (bradykinesia, rigidity and dystonia) and

neuropsychiatric symptoms that resemble idiopathic Parkinson's disease (Santamaria & Sulsky, 2010).
Although is not completely clear the relationship between Mn and PD patogenesis, or neurodegenerative disorders, it is suggest that this metal accelerates neuronal death and increase the risk of its development (Zheng et al., 1998).

4. Metal contamination and AD developing

Metal are essential for humans and for all forms of life. Even though metals are necessary in biological systems, they are usually required only in trace amounts. As regard to the brain, metals are essential for neuronal activities. However, if not correctly regulated, redox-active can react with molecular oxygen to generate ROS thus causing brain lipid peroxidation and protein oxidation (Salvador et al., 2011; Sayre et al., 1997; Smith et al., 1996; Smith et al., 1997). Also, metal imbalance can lead to aberrant interactions between metals and AD-related proteins, being a potential source of oxidative stress, which is evolved into the ''metal hypothesis'' of AD (Iqbal et al., 2005).
Protein misfolding associated with Aβ aggregation, is significantly affected by various biological, biophysical and chemical factors including metal ions such as Al, Cu, Zn, and Fe, which have been found in high concentration in the AD brain (Beauchemin et al., 1998; Dong et al., 2003; Lovell et al., 1993; 1998; Miu et al., 2006; Suh et al., 2000;). Also, some metals are able to accelerate the dynamic of Aβ aggregation, thus increasing the neurotoxic effects on neuronal cells (Bush, 2003; House et al., 2004; Maynard et al., 2005; Miu et al., 2006; Morgan et al., 2002; Ricchelli et al., 2005). Kawahara et al. (2001) showed that aluminum induces neuronal apoptosis in vivo as well as in vitro and causes the accumulation of hyperphosphorylated tau protein and Aβ protein in in vivo model.
Several studies have focused on the role of metal ions including Al on the Aβ aggregation properties (House et al., 2004; Kawahara et al., 1994; Pratico et al., 2002; Ricchelli et al., 2005), suggesting that, among various metal ions assessed, Al seems to be the most efficient in promoting Aβ aggregation in vitro, increasing cellular neurotoxicity (Kawahara et al., 2001; Kawahara, 2005; Ricchelli et al., 2005). Also, Al induces the spontaneous increase of Aβ1-42 surface hydrophobicity compared to Aβ alone, which in turns, the complex Aβ1-42-Al reduced the capillary sequestration increasing its permeability through the blood brain barrier resulting intracerebral accumulation as demonstrated by Banks et al. (2006).
Environmental metal exposure has been suggested to be a risk factor for AD. High-term exposure to certain metals like manganese (Mn), iron (Fe), aluminum (Al) and many others, alone or in combination, can increase neurodegenerative process, especially to Alzheimer's disease (AD).
Aluminum (Al) is the most abundant neurotoxic metal on earth, widely bioavailable to humans and repeatedly shown to accumulate in AD-susceptible neuronal foci. Furthermore, several groups reported an increased amounts of Al in neurofibrillary tangles (NFT)-bearing neurons of AD brains, suggesting the association of Al with NFTs (Good et al., 1992; Lovell et al., 1993). Evidence from clinical and animal model studies demonstrated that brain Al content increases with age, suggesting an increased exposure or a decreased ability to remove Al from brain with age (Savory et al., 1999). Furthermore, high levels of Al has been found in brain lesions, such as plaques and tangles, in patients with AD and could be involved in the aggregation of Aβ peptides to form toxic fibrils (Sakae et al., 2009).

Iron is an essential trace element used by almost all living organisms. However, disturbances of brain iron homeostasis have been linked to acute neuronal injury. Increased iron levels were found both in the cortex and cerebellum from the preclinical AD cases (Sullivan et al., 2009; Zhu et al., 2009). Cellular studies have shown that iron is particular accumulated in microglia and astrocytes in the cerebral cortex, cerebellum, substantia nigra, and hippocampus, and it is believed that this metal would be involved in the neuroinflammation found in AD and PD (Ong & Farooqui, 2005; Sullivan et al., 2009; Zhu et al., 2009). It is important to note that these brain iron concentrations, especially in the parietal cortex at the early stages of AD, have been found to positively correlate with the severity of patients' cognitive impairment (Zhu et al., 2009). Interestingly, Aβ insoluble aggregates have been demonstrated to be dissolved by metal chelators (Cherny et al., 1999).
Iron itself has been related neurotoxicity, and its accumulation, has been observed to before AD lesions are measurable. In AD, iron is an important cause of oxidative stress because of its over-accumulation in the brain and colocalizes with AD lesions, senile plaques and neurofibrillary tangles. Interestingly, iron has been involved in lipid and protein oxidation and also in DNA damage. Iron is able to oxidize DNA bases, and it has been suggested that the accumulation of this transition metal in some neurodegenerative disorders could act by both increasing oxidative genome damage and also preventing its repair (Hegde et al., 2010).
Manganese (Mn) is an essential element for humans, animals, and plants and is required for growth, development, and maintenance of health, although it has been recognized as a neurotoxic metal for over 150 years (Weiss, 2010). Unbalance of Mn homeostasis has show cognitive deficiencies features that include diminished attention, reduced scores on tests of working memory, lower scores on intelligence tests, impaired learning, and slowed response speed. Also, Weiss (2010) reports that signs of Mn poisoning are impaired coordination, abnormal gait, abnormal laughter, expressionless face, weakness, bradykinesia, somnolence, dysarthria, difficulty walking, clumsiness, lack of balance, muscle pains, and diminished leg power. Furthermore, exposure to high levels of inhaled manganese, as in miners working leads to motor symptoms.
Nonhuman primates can be the most appropriate animal models for studies of manganese neurotoxicity because of their similarities to humans in brain anatomy and neurobehavioral function (Schneider et al., 2009). A recent study by Schneider et al. (2009) demonstrated that trained Cynomologous monkeys for memory test followed by a regimen of intravenous manganese sulfate injections over a period of about 230 days, displayed mild deficits in spatial memory, greater deficits in nonspatial memory, and no deficits in reference memory on animals treated. By analyzing Mn concentrations, the study showed a significant inverse relationship between working memory task performance and Mn levels.
The relationship by Mn exposure and Alzheimer's disease has also been investigated by gene array analysis of frontal cortex from Cynomologous monkeys after Schneider et al. (2009) studies (Guilarte et al., 2010). Amyloid-β Precursor-like Protein 1 (APLP1), a member of the Amyloid Precursor Protein (APP) family was the most expressed out of the 61 upregulated genes. Along with this finding, immunochemistry revealed the presence of Amyloid-β plaques in the brain of subjects with only 6–8 years of age. Thus, these findings links the Mn-induced β-amyloid deposits to impaired memory function what may be extrapolated to human brain and so the features of AD pathogenesis.

5. Metal genotoxicity

Cellular stresses, including DNA damage, have been linked to cell cycle deregulation in neurons (Park et al., 1998; Kruman et al., 2004). Studies on the biological causes of neuronal death in AD have been guided by observations of cell cycle reentry in cellular populations that degenerate in human disease (Busser et al., 1998; Yang et al., 2003). In addition to ectopic cell cycling, AD is also linked to DNA damage; accumulation of DNA damage in neurons is associated with aging (Lu et al., 2004) and is exacerbated in neurodegenerative disorders including AD (Rass et al., 2007). The occurrance of DNA damage was related in astrocytes of AD hippocampus (Myung et al., 2008) and in neurons within the cerebellar dentate nucleus that show the robust DNA damage response (Chen et al., 2010).

The appearance of DNA damage during the course of lateonset neurodegenerative disease has been attributed in part to the fact that neurons exhibit high mitochondrial respiration, which is known to lead to the production of reactive oxygen-species. Over time this oxidative stress results in the accumulated damage of mitochondrial and nuclear DNA (Rass et al., 2007). These findings emphasize the value of using direct markers of neuronal distress, like DNA damage, as neuropathological markers in AD. They augment the classical histopathological picture achieved by staining for amyloid plaques and tau inclusions by providing an early neuronal vulnerability marker (Chen et al., 2010).

As a consequence of industrial production, a large quantity of toxic material is released in the ambient. Due to the elevated concentrations of metals present in different environments, metals are ubiquitous contaminants of ecosystems; therefore, they are among the most intensely studied contaminants. They do not only deteriorate the physicochemical equilibrium of the ecosystems, but they also disrupt the food web and bring about morphological, physiological and cytogenetic changes in the inhabitants (Boge & Roche, 1996). Genotoxic studies have shown that exposure to some metals causes adverse effects to different organisms, especially to humans, and these DNA damages may be implicated in the pathogenesis of some types of cancer and neurodegenerative diseases.

5.1 Genotoxicity of aluminum

Metal-induced genotoxicity is an important pathogenic mechanism whereby toxic metals that riches the nucleus affect the normal structure and function of the genome (Alexandrov et al., 2005; Lukiw, 2001; Sarkander et al., 1983).

There are only few studies in the literature about the genotoxic activities of Al, both in vitro and in vivo. Aluminum is biochemically attracted to interact to the phosphates that form an active part of the DNA. Its mutagenic potential has been studied by micronucleus assay, sister chromatid exchange, Ames and chromosomal aberration analysis, showing a significant genotoxicity in vitro (Banasik et al., 2005; Lankoff et al., 2006). Also, in vivo studies revealed that aluminum could induce in a dose-dependent manner an increase chromosomal aberrations (Roy et al., 1991).

In vitro chromosomal aberrations induction, mostly numeric (anaphasic), was shown first by Moreno et al., (1997), in the Balb c 3T3 cell line exposed to atmospheric dust (20–80 mg/mL), a mixture of particles of potassium aluminum silicates (98%) and sodium dioxide (2%), from Mexicali, Mexico. Other studies (Dovgaliuk et al., 2001a, 2001b) also demonstrated the cytogenetic effects of toxic metal salts including aluminum (Al[NO3]3) in meristematic cells from Allium cepa and the clastogenic and aneugenic effects (disturbances in mitosis and cytokinesis) in these cells.

More recently, the genotoxic potencial of AlCl3 on Vicia faba was investigated using cytogenetic tests, demonstrating that aluminum causes significant increase in the frequencies of micronuclei and anaphase chromosome aberrations in the root cells of Vicia faba (Yi et al., 2009).

Iron and aluminum-sulfate together, at nanomolar concentrations, trigger the release of reactive oxygen species (ROS) in cultures of human brain cells, up-regulating pro-inflammatory and pro-apoptotic genes that redirect cellular fate toward cytoplasmic dysfunction, nuclear DNA fragmentation and cell death (Alexandrov et al., 2005; Lukiw, 2001; Sarkander et al., 1983).

On neural cells from Parkinson´s disease patients, Al treatment did not increase the micronucleus frequency, indicating that Al had no amplified mutagenic effect on these patients (Trippi et al., 2001). Also, chromosome breaks were observed in V79-4 Chinese hamster cells irradiated with low-energy aluminum ions (Botchway et al., 1997). Furthermore, no teratogenic effects on the mouse fetus or genotoxic effects as detected by the Ames assay was observed for aluminum-containing cosmetic formulations (Elmore, 2003).

Lukim & Pogue (2007) first described the neurotoxic effects of aluminum-sulfate and aluminum- plus iron-sulfate on miRNA expression patterns in untransformed human brain cells in primary co-cultures of neurons and glia. Low doses of aluminum have been found to disturb RNA Pol II-directed gene transcription in isolated human brain cell nuclei (Alexandrov et al., 2005; Lukiw, 2001) suggesting an involvement of soluble aluminum- and iron-sulfate in several different aspects of human brain gene expression, specially associated with transcriptional and post-transcriptional control. Synapsin mRNA has been found to be down-regulated in both AD brain and in iron- plus aluminum-sulfate treated primary cell culture (Alexandrov et al., 2005; Lukiw, 2007; Yumei et al., 1998).

On the other hand, studies have demonstrated the mutagenic potential of Al in human cells. For example, genotoxicity of the dust derived from an electrolytic Al plant was evaluated using the Ames assay, unscheduled DNA synthesis test, sister chromatid exchange and micronuclei frequencies in human lymphocytes. The results of these four experiments indicated a high genotoxicity potential of the dust organic extract (Varella et al., 2007). The mutagenic activity of waste material originating from an Al products factory was determined by the Salmonella/microsome assay, where all extracts from the factory had mutagenic activity, especially in the YG1024 yeast strain, suggesting the presence of aromatic amines (WHO, 1997).

Scalon et al (2011) assessed the genotoxic effects in fish exposed to samples from the Sinos River (Rio Grande do Sul – Brazil), and evaluated DNA damage from aluminum, lead, chromium, copper, nickel, iron and zinc contamination. They collected samples of different sites and on differente seasons in the Sinos River, and chemical analysis of the water showed presence of Al and Fe, exceeding the accepted limits in most of the water samples. The index of DNA damage assessed by the comet assay in the peripheral blood of a native fish species demonstrated no significant differences in different seasons or at the different sampling sites. Only the frequency of cells with higher level of DNA damage showed significant difference in comparison to the sampling period. However, the increase in that parameter of genotoxicity does not seem to be related to differences between sampling periods regarding the presence or concentration of the heavy metals analysed.

Garcia-Medina et al (2011) evaluated de genotoxic and cytotoxic effects of Aluminum sulphate on common carp (Cyprinus carpio). They exposed the fishes to 0.05, 120, and 239 mg/L $Al_2 (SO_4)_3 \bullet 7H_2O$ and analysed the cells with the comet assay, flow cytometry, and the TUNEL method. The analyzed cells showed significant increase in the amount of DNA, damage, DNA content increase and ploidy modifications, as well as apoptosis and disturbances of the cell cycle progression and an increase in the amount of apoptotic cells. These results suggests, in a contrary way to the study of Scalon et al (2011), that Al caused deleterious DNA and cellular effects in aquatic organisms.

Recently our research group published a study on the genotoxic, clastogenic and cytotoxic effects of AlCl3 in different phases of the cell cycle using in vitro temporary cultures of human lymphocytes (Lima et al., 2007). Moreover, the mitotic index (MI), chromosomal aberrations (CAs) and DNA damage index were analyzed by the comet assay. The study indicated that AlCl3 induces DNA damage and is cytotoxic during all phases of the cell cycle. Also, the treatment of the cells at G1 phase resulted in polyploidy and endoreduplication, consistent with AlCl3 interacting with the mitotic spindle apparatus (Lima et al., 2007). These data, along with the results of other studies reported in the literature, indicates that AlCl3 is genotoxic and should be used with caution.

More research is needed on this topic, since the use of aluminum cookware, aluminum-containing deodorants and other products are increasing in general population. Moreover, environmental metal contamination contributes with the increase levels of metal exposure (Ansari et al., 2004).

5.2 Genotoxicity of iron

Several studies have been conducted to demonstrate the potential induction of DNA aberrations by iron (Fe) and also by drugs and compounds containing this metal. However, the results are inconclusive, and its toxicity and mutagenic effect is still incompletely understood.

Organic Fe may increase the genotoxic effects of other compounds when they are combined (WHO, 1998). For example, the mutagenic activity by doxorubicin is significantly increased within this metal, as evaluated by the Ames test (Kostoryz & Yourtee, 2001). Furthermore, Jurkat cells simultaneously treated with hydrogen peroxide and desferrioxamine (Fe chelator) significantly inhibit DNA damage, indicating that intracellular Fe, which is a redoxactive metal, plays a role in the induction of DNA strand breaks induced by hydrogen peroxide (Barbouti et al., 2001).

High levels of chromosome and chromatid aberrations were found in human lymphocytes and TK6 lymphoblast cells exposed to high-energy iron ions (56Fe) (Durante et al., 2002; Evans et al., 2001, 2003). Significant DNA damage was detected, by microgel electrophoresis, in differentiated human colon tumor cells (HT29 clone 19A) treated with ferric-nitrilotriacetate (Fe-NTA) (Glei et al., 2002). Mutagenic activity was also found in elemental and salt forms of Fe, evaluated by mutagenicity tests in Salmonella typhimurium and L5178Y mouse lymphoma cells (Dunkel et al., 1999).

Iron compounds have also been reported to be mutagenic in mammalian cells, as detected by the Syrian hamster embryo cell transformation/viral enhancement assay (Heidelberger et al., 1983), sister chromatid exchange (SCE) in hamster cells (Tucker et al., 1993) and base tautomerization in rat hepatocyte cultures (Abalea et al., 1999).

Few or no DNA damage (detected by the comet assay) occurred after treatment of human lymphocytes with ferric chloride (FeCl3) and ferrous chloride (FeCl2), all of them known to

be iron compounds (Anderson et al., 2000a, 2000b). Also, low concentrations of either Fe2+ or Fe3+ were not mutagenic in Chinese hamster ovary cells (CHO-9) treated in vitro, and the mitotic index was also unaffected when compared to negative control. In the other hand, high concentrations of ferrous sulfate, induces significant DNA damage, probably as a consequence of chemical contamination of the metal salt (Antunes et al., 2005).

Mutagenic potential of metallic agents used in dietary supplementation, including iron sulfate, was also investigated by means of the comet assay. The authors reported a genotoxic effect of this metal in mouse blood cells after 24 h of treatment, at all tested concentrations (Franke et al., 2006). Genotoxic effects of Fe were also reported by Garry et al. (2003) in rats treated with iron oxide (Fe_2O_5) for 24 h. They observed that this metal only showed mutagenic potential when the animals were simultaneously treated with benzopyrene.

Furthermore, Hasan et al. (2005) reported that ferritin, an ubiquitously distributed iron storage protein, interacts with microtubules in vitro. In a study conducted by Maenosono et al. (2007) the bacterial reverse mutation assay using S. typhimurium was weakly positive for water-soluble FePt nanoparticles capped with tetramethylammonium hydroxide. Mice subchronically exposed to 33.2 mg/Kg Fe displayed genotoxic effects in whole blood in the alkaline version of the comet assay, with a significant increase in the hepatic level of Fe (Prá et al., 2008).

High-energy iron ions (LET=151 keV/microM) could induce chromosomal aberrations (measured using the fluorescence whole-chromosome painting technique) in normal and repair-deficient human fibroblasts cell lines (George et al., 2009).

Park & Park (2011) screened the potential toxicity of various iron-overloads on human leukocytes using comet assay. Ferric-nitrilotriacetate (Fe-NTA), FeSO(4), hemoglobin and myoglobin were not cytotoxic in the range of 10-1000 microM by trypan blue exclusion assay. The exposure of leukocytes to Fe-NTA (500 and 1000 microM), $FeSO_4$ (250-1000 microM), hemoglobin (10 microM) and myoglobin (250 microM) for 30 min induced significant DNA damage. Iron-overloads generated DNA strand break were rejoined from the first 1h, but no genotoxic effect was observed at 24h.

Recently, our research group conducted an in vitro study aiming to investigate the genotoxic, clastogenic and cytotoxic effects of FeSO4 in different phases of the cell cycle, using short-term cultures of human lymphocytes. The bioactivity parameters tested were the mitotic index, chromosomal aberrations and DNA damage index as detected by the comet assay. Our results showed that Fe induces alterations and inhibition of DNA synthesis, which together explains the concomitant occurrence of mutagenicity and cytotoxicity (Lima et al., 2008).

5.3 Genotoxicity of manganese

Manganese displays an interestingly behavior with regard to its toxicity, since it is relatively non-toxic to the adult organism with an exception to the brain. Even at moderate amounts in a long period of time, when inhaleted can causes Parkinson-like symptoms. Those findings were also observed in animal studies which repeated intravenous Mn administration to monkeys (Olanow et al., 1996) produced a Parkinson-like syndrome characterized by bradykinesia, rigidity, and facial grimacing.

The association of Mn with the risk of developing neurodegenerative processes can be related to DNA damage. Relatively high doses of Mn can disrupt DNA integrity and DNA replication (Beckman et al., 1985; De Meo et al., 1991; Van de Sande et al., 1982) and causes

mutations in microorganism (Orgel & Orgel 1965; Rossman et al., 1984; Rossman & Molina, 1986) and mammalian cells although the Ames test does not appear to be particularly responsive to manganese or no suitable to detect toxicity of metal salts (Léonard, 1988).

There are few studies in the literature on the genotoxic action of Mn. Its toxic potential has been studied by in vitro tests in bacteria and by in vivo/in vitro tests in insect and mammalian cells, showing that some chemical forms of this metal have mutagenic potential. Gerber et al. (2002) demonstrated that high doses (0.05 M) of various Mn compounds could affect DNA replication and repair in bacteria. As for mammalian cells, high doses of Mn (compared to the Mn doses recommended for daily consumption) can affect fertilization and are toxic to the embryo and fetus, demonstrating the teratogenic potential of this metal.

Dutta et al. (2006) suggests the manganese dioxide as an established genotoxicant and clastogenic metal that can induce DNA strand breaks, chromosomal aberration and micronucleus in human peripheral lymphocytes. Manganese chloride ($MnCl_2$) was also subjected to the wing spot test of Drosophila melanogaster and was shown to be clearly effective in inducing spots with one or two mutant hairs (small spots) at concentrations over 12 μM (Ogawa et al., 1994).

Concentrations of manganese in the general environment and manufacture products vary widely. Brega et al. (1998) demonstrated that farm workers exposed to pesticides containing Mn, even at a low levels, revealed an increased in the mutagenic potential of those pesticides, as evidenced by an increased number of CAs. It is possible that, at low doses, Mn has genotoxic effects only with long-term exposure, and this may be the reason why Timchenko et al. (1991) did not find CAs in the nasal mucosa of mammals exposed to Mn dioxide aerosol (40–12,000 Hz, 80–100 dB). Furthermore, it is possible that chronic exposure to low doses of Mn can induces CAs over the years.

Studies on eukaryotic cell, revealed that manganese sulfate ($MnSO_4$) did not display mutagenic potential in different strains of Salmonella typhimurium, while, manganese chloride, showed mutagenicity in the TA1537 strain of S. typhimurium as well as in the T7 strain of Saccharomyces cerevisiae (doses over 0.5 mM) (WHO, 1999). In vivo studies have demonstrated that oral doses of manganese sulfate or potassium permanganate (KMnO4) induce CAs in the bone marrow of animals, whereas no CAs have been seemed after oral doses of manganese chloride, even at concentrations over 12 μM (WHO, 1999). These results show that the mutagenic potential of compounds of Mn may be different in permanganate salts and in manganese salts, depending on its chemical formulation, and thus being able to altering their biological availability, activity, and consequently, their toxicity.

De Meo et al. (1991) evaluated the genotoxicity of potassium permanganate ($KMnO_4$), manganese sulfate and manganese chloride using the Ames test within TA97, TA98, TA100 and TA102 strains, with and without metabolic activation. The presence of direct-acting mutagens was detected in all Mn samples in TA102 strain without metabolic activation. Only manganese chloride induced DNA damage in human lymphocytes with a dose-dependent response, as determined by the comet assay.

Animal studies, demonstrated that acute lethality of manganese appears to vary depending on the chemical species. The central nervous system is the chief target of manganese toxicity. Oral doses produced a number of neurological effects in rats and mice, mainly involving alterations in neurotransmitter and enzyme levels in the brain (ATSDR, 2000; Deskin et al., 1980), which can be accompanied to changes in activity level (ATSDR, 2000). Chronic ingestion of manganese (1–2 mg/kg/day) changes appetite and reduces haemoglobin synthesis in different animals (Hurley & Keen, 1987).

Long-term exposure to manganese can cause transient effects on biogenic amine levels and activities of dopamine β-hydroxylase and monoamine oxidase in rat brain (Eriksson et al., 1987; Lai et al., 1984; Nachtman et al., 1986; Subhash & Padmashree, 1990). Also, high doses (1800–2250 mg/kg/day as manganese (II) sulfate) in mice induce hyperplasia, erosion and inflammation in the stomach. Also, number of chromosomal aberrations and micronuclei were observed in rat bone marrow (ATSRD, 2000).

According to WHO (1999) data, other chemical forms of Mn have mutagenic potential, both in vitro and in vivo. Thus, more studies are necessary in order to elucidate the probable mutagenicity of Mn and its chemical forms and their effects on human health.

Erbe et al. (2011) evaluated damage to the genetic material of fish (Astyanax sp. B) exposed to samples of water from a river and a lake located near a hospital waste landfill. Among other parameters, aluminum and manganese were above acceptable levels that have been established in environmental legislation. The comet assay detected significant damage to genetic material in fish that were acutely exposed in the laboratory to these water samples.

Bomhorst et al (2010) evaluated the cytotoxicity and genotoxicity potencial of $MnCl_2$, as well as its impact on the DNA damage response in human cells (HeLa S3) in culture. Whereas up to 10 μM $MnCl_2$ showed no induction of DNA strand breaks after 24 h incubation, manganese strongly inhibited H_2O_2-stimulated poly(ADP-ribosyl)ation at low, completely non-cytotoxic, for certain human exposure, relevant concentrations starting at 1 μM. These results indicate that manganese, under conditions of either overload due to high exposure or disturbed homeostasis can disturb the cellular response to DNA strand breaks, which has been shown before to result in neurological diseases.

Our research group also conducted an in vitro study on the genotoxic, clastogenic and cytotoxic potential of $MnCl_2$-$4H_2O$ (one of the most common forms of Mn) in different phases of the cell cycle, using short-term cultures of human lymphocytes. These effects were determined by the mitotic index (MI), chromosomal aberrations (CAs) and DNA damage index as detected by the comet assay. $MnCl_2$-$4H_2O$ displayed a strong cytotoxicity in all phases of the cell cycle. Genotoxicity was observed at G2 phase of the cell cycle and also in the comet assay, what may be related to the lack of time for the cellular repair system to act. The absence of CAs in the other phases of the cell cycle suggests that Mn-mediated damage may be repaired in vitro (Lima et al., 2008).

6. Conclusion

Metal are essential for humans and for all forms of life. Even though metals are necessary in biological systems, they are usually required only in trace amounts. As regard to the brain, metals are essential for neuronal activities. However, if not correctly regulated, redox-active can react with molecular oxygen to generate ROS thus causing brain tissue damage.

In this chapter, the authors compile several studies that allow to propose that environmental metal exposure are a risk factor for neurodegenerative process. A large quantity of toxic material is released in the ambient as a consequence of industrial production. High-term exposure to certain metals like manganese (Mn), iron (Fe), aluminum (Al) and many others, alone or in combination, can lead to neuronal losts and increase Alzheimer's disease (AD).

In the cellular neurotoxicity, the Al seems to be the most efficient in promoting Aβ aggregation leading to a specific form of Aβ oligomerization that has marked neurotoxic effects. Iron has been found to be accumulated in the substantia nigra and is more related with neurodegenerative disorders, such as Alzheimer's (AD) and Huntington's (HD)

diseases and its severity on cognitive impairment aspect (parietal cortex). As for Mn its toxicity has been associated with dopamine metabolism leading to neuropsychiatric symptoms that resemble idiopathic Parkinson's disease.

Our research group published studies on the genotoxic, clastogenic and cytotoxic effects of Al, MN and Fe in different phases of the cell cycle using in vitro temporary cultures of human lymphocytes. The study indicated that these metals induce DNA damage and is cytotoxic during all phases of the cell cycle. Genotoxic studies have shown that exposure to some metals cause adverse effects to humans and may be implicated in the pathogenesis of some types of neurodegenerative diseases as the AD.

Although is not completely clear the relationship between some metals and neurodegenerative disorders, this chapter suggest that Al, Mn and Fe metals can accelerates neuronal death and increase the risk of its development.

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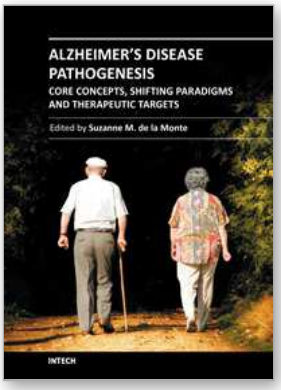

Alzheimer's Disease Pathogenesis-Core Concepts, Shifting Paradigms and Therapeutic Targets

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Alzheimer's Disease Pathogenesis: Core Concepts, Shifting Paradigms, and Therapeutic Targets, delivers the concepts embodied within its title. This exciting book presents the full array of theories about the causes of Alzheimer's, including fresh concepts that have gained ground among both professionals and the lay public. Acknowledged experts provide highly informative yet critical reviews of the factors that most likely contribute to Alzheimer's, including genetics, metabolic deficiencies, oxidative stress, and possibly environmental exposures. Evidence that Alzheimer's resembles a brain form of diabetes is discussed from different perspectives, ranging from disease mechanisms to therapeutics. This book is further energized by discussions of how neurotransmitter deficits, neuro-inflammation, and oxidative stress impair neuronal plasticity and contribute to Alzheimer's neurodegeneration. The diversity of topics presented in just the right depth will interest clinicians and researchers alike. This book inspires confidence that effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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