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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 revealing 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 A β aggregation, increasing dramatically cellular neurotoxicity. According to the "amyloid cascade hypothesis", accumulation of A β 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 A β 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 them 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; antacid 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 India. Furthermore, almost all rocks and soils contains at least trace amounts of iron (Sienko, 1977).

Iron is a very reactive metal. Most of them 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_2O_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 often 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 Kazakhstan.

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 absorption 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 ($A\beta$), 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). $A\beta$ 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 $A\beta$ (1–40) and $A\beta$ (1–42), being the latter the most neurotoxic (Rauk, 2009).

Several studies have shown that $A\beta$ 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 colaboradores 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, amiotrophic lateral esclerosis, neurofibrilar degeneration, dialysis encephalopathy syndrome and nigrostriatal 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 ($A\beta$) in senile plaques. It is interesting to note that, compared to other $A\beta$ -metal complexes ($A\beta$ -Fe, $A\beta$ -Zn, $A\beta$ -Cu), $A\beta$ -Al is unique in promoting a specific form of $A\beta$ 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 phosphorylation, 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 A β 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 A β 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 A β protein in in vivo model.

Several studies have focused on the role of metal ions including Al on the A β 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 A β aggregation in vitro, increasing cellular neurotoxicity (Kawahara et al., 2001; Kawahara, 2005; Ricchelli et al., 2005). Also, Al induces the spontaneous increase of A β 1-42 surface hydrophobicity compared to A β alone, which in turns, the complex A β 1-42-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 A β 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 particularly 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, A β insoluble aggregates have been demonstrated to be dissolved by metal chelators (Cherny et al., 1999). Iron itself has been related to neurotoxicity, and its accumulation, has been observed to precede AD lesions that 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 shown cognitive deficiencies 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 Cynomolgous 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 Cynomolgous 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 link 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 occurrence 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 late-onset 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 $AlCl_3$ 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 different 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 the genotoxic and cytotoxic effects of Aluminum sulphate on common carp (*Cyprinus carpio*). They exposed the fishes to 0.05, 120, and 239 mg/L $\text{Al}_2(\text{SO}_4)_3 \cdot 7\text{H}_2\text{O}$ 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 suggest, 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 AlCl_3 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 AlCl_3 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 AlCl_3 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 AlCl_3 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 (^{56}Fe) (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 (FeCl_3) and ferrous chloride (FeCl_2), 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 (Fe₂O₃) 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), FeSO₄, 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), FeSO₄ (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 inhaled 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 (KMnO_4) 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 potential 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 $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ (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. $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ 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 $\text{A}\beta$ aggregation leading to a specific form of $\text{A}\beta$ 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.

7. References

- Abalea, V., Cillard, J., Dubos, M.P., Sargent, O., Cillard, P. & Morel, I. (1999). Repair of iron-induced DNA oxidation by the flavonoid myricetin in primary rat hepatocyte cultures. *Free Radical Biology & Medicine*, Vol. 26, No. 11-12, (Jun. 1999), pp. 1457-1466, ISSN 0891-5849.
- Aschner, M., Gannon, M., Kimelberg, H.K. (1992). Manganese uptake and efflux in cultured rat astrocytes. *Journal of Neurochemistry*, Vol. 58, No. 2, (Feb. 1992), pp. 730-735, ISSN 0022-3042.
- Alexandrov, P.N., Zhao, Y., Pogue, A.I., Tarr, M.A., Kruck, T.P.A., Percy, M.E., Cui, J.G. & Lukiw, W.J. (2005). Synergistic effects of iron and aluminum on stress-related gene expression in primary neural cells. *Journal of Alzheimer's Disease*, Vol. 8, No. 2, (Nov. 2005), pp. 117-127, ISSN 1387-2877.
- Altschuler, E. (1999). Aluminum-containing antacids as a cause of idiopathic Parkinson's disease. *Medical Hypotheses*, 53, 22-23. Vol. 53, No.1, (Jul. 1999), pp. 22-23, ISSN 0306-9877.
- Anderson, D., Yardley-Jones, A., Hambly, R.J., Vives-Bauza, C., Smykatz-Kloss, V., Chua-Anusorn, W. & Webb, J. (2000). Effects of iron salts and haemosiderin from a thalassaemia patient on oxygen radical damage as measured in the comet assay. *Teratogenesis, Carcinogenesis and Mutagenesis*, Vol. 20, No. 1, (Sep. 2000), pp. 11-26, ISSN 0270-3211.
- Anderson, D., Yardley-Jones, A., Vives-Bauza, C., Chua-Anusorn, W., Cole, C. & Webb, J. (2000). Effect of iron salts, haemosiderins, and chelating agents on the lymphocytes of a thalassaemia patient without chelation therapy as measured in the comet assay. *Teratogenesis, Carcinogenesis and Mutagenesis*, Vol. 20, No. 5, (May 2000), pp. 251-264, ISSN 0270-3211.
- Ansari, T.M., Marr, I.L. & Tariq, N. (2004). Heavy metals in marine pollution perspective - a mini review. *Journal of Applied Sciences*, Vol. 4, No. 1, (Jan. 2004), pp. 1-20, ISSN 1812-5662.
- Antunes, L.M.G., Araújo, M.C.P., Dias, F.L. & Takahashi, C.S. (2005). Effects of H₂O₂, Fe²⁺, and Fe³⁺ on curcumin-induced chromosoma aberrations in CHO cells. *Genetics and Molecular Biology*, Vol. 28, No. 1, (Jan.-Mar. 2005), pp. 161-164, ISSN 1415-4757.

- ATSDR. Toxicological profile for manganese. 2000. Atlanta, GA, US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.
- Banasik, A., Lankoff, A., Piskulak, A., Adamowska, K., Lisowska, H. & Wojcik, A. (2005). Aluminium-induced micronuclei and apoptosis in human peripheral blood lymphocytes treated during different phases of the cell cycle. *Environmental Toxicology*, Vol. 20, No. 4, (Aug. 2005), pp. 402-406, ISSN 1520-4081.
- Banks, W.A., Niehoff, M.L., Drago, D. & Zatta, P. (2006). Aluminum complexing enhances amyloid beta protein penetration of blood-brain barrier. *Brain Research*, Vol. 1116, No.1, (Oct. 2006), pp. 215-221, ISSN 0006-8993.
- Barbouti, A., Doulias, P.T., Zhu, B.Z., Frei, B. & Galaris, D. (2001). Intracellular iron, but not copper, plays a critical role in hydrogen peroxide-induced DNA damage. *Free Radical Biology & Medicine*, Vol., 31, No. 4, (Aug. 2001), pp. 490-498, ISSN 0891-5849.
- Barceloux, D.G., (1999). Manganese. *Journal of toxicology. Clinical toxicology*, Vol. 37, No. 2, (1999), pp. 293-307, ISSN 0731-3810.
- Bartzokis, G., Mintz, J., Sultzer, D., Marx, P., Herzberg, J.S., Phelan, C.K. & Marder, S.R. (1994). In vivo MR evaluation of age-related increases in brain iron. *American Journal of Neuroradiology*, 15, 1129-1138; Vol. 15, No. 6, (Jun. 1994), pp. 1129-1138, ISSN 0306-9877.
- Beauchemin, D., Kisilevsky, R. (1998). A method based on ICP-MS for the analysis of Alzheimer's amyloid plaques. *Analytical Chemistry*, Vol. 70, No.5, (Mar. 1998), pp. 026-1029, ISSN 0003-2700.
- Beckman, R.A., Mildvan, A.S. & Loeb, L.A. (1985). On the fidelity of DNA replication: manganese mutagenesis in vitro. *Biochemistry*, Vol. 24, No. 21, (Oct. 1985), pp. 5810-17, ISSN 0006-2960.
- Behl, C., Davis, J.B., Lesley, R., Schubert, D. (1994). Hydrogen peroxide mediates amyloid beta protein toxicity. *Cell*, Vol. 17, No. 6, (Jun 1994), pp. 817-827, ISSN 0092-8674.
- Berg, D., Gerlach, M., Youdim, M.B., Double, K.L., Zecca, L., Riederer, P. & Becker, G. (2001). Brain iron pathways and their relevance to Parkinson's disease. *Journal of Neurochemistry*, Vol.79, No. 2, (Oct. 2001), pp. 225-236, ISSN 0022-3042.
- Berthon G (1996) Chemical speciation studies in relation to aluminium metabolism and toxicity. *Coordination Chemistry Reviews*, Vol. 149, (1996), pp. 241-280, ISSN 0010-8545.
- Berthon, G., (2002). Aluminium speciation in relation to aluminium bioavailability, metabolism and toxicity. *Coordination Chemistry Reviews*, Vol. 228, No. 2, (Jun. 2002), pp. 319-341, ISSN 0010-8545.
- Bogé, G. & Roche, H. (1996). Cytotoxicity of phenolic compounds on *Dicentrarchus labrax* erythrocytes. *Bull Environ Contam Toxicol.*, Vol. 57, No. 2, (Mar. 1996), pp. 171-178, ISSN 0007-4861
- Bondy, S. C. (2010). The neurotoxicity of environmental aluminum is still an issue. *NeuroToxicology*, Vol.31, No.5, (Sep. 2010), pp. 575-581, ISSN 0161-813X.
- Bornhorst, J., Ebert, F., Hartwig, A., Michalke, B. & Schwerdtle T. Manganese inhibits poly(ADP-ribosyl)ation in human cells: a possible mechanism behind manganese-induced toxicity? *J. Environ. Monit.*, Vol. 12, No. 11, (Nov. 2010), pp. 2062-9, ISSN 1464-0325.

- Botchway, S.W., Stevens, D.L., Hill, M.A., Jenner, T.J. & O'Neill, P. (1997). Induction and rejoining of DNA double-strand breaks in Chinese hamster V79-4 cells irradiated with characteristic aluminum K and copper L ultrasoft X rays. *Radiation Research*, Vol. 148, No. 4, (Oct. 1997), pp. 317-324, ISSN 0033-7587.
- Brega, S.M., Vassilieff, I., Almeida, A., Mercadante, A., Bissacot, D., Cury, P.R. & Freire-Maia, D.V. (1998). Clinical, cytogenetic and toxicological studies in rural workers exposed to pesticides in Botucatu, São Paulo, Brazil. *Reports in Public Health*, Vol. 14, Suppl. 3, (1998), pp. 109-115, ISSN 0102-311X.
- Busser, J., Geldmacher, D.S., Herrup, K. (1998). Ectopic cell cycle proteins predict the sites of neuronal cell death in Alzheimer's disease brain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, Vol. 18, No 8, (Apr. 1998), pp. 2801-2807, ISSN 0270-6474.
- Bush, A.I. (2003). The metallobiology of Alzheimer's disease. *Trends Neuroscience*, Vol. 26, No. 4, (Apr. 2003), pp. 207-214, ISSN 0166-2236.
- Butterworth, R. F. (2010). Metal Toxicity, Liver Disease and Neurodegeneration. *Neurotoxicity Research*, Vol. 18 , No. 1, (Apr. 2010), pp. 100-105, ISSN 1029-8428.
- Campbell, A., Bondy, S.C. (2000). Aluminum induced oxidative events and its relation to inflammation: a role for the metal in Alzheimer's disease. *Cellular and Molecular Biology*, Vol. 46, No. 4, (Jun. 2000), pp. 721-730, ISSN 1098-5549.
- Chen, J., Cohen, M.L., Lerner, A.J., Yang, Y. & Herrup, K. (2010). DNA damage and cell cycle events implicate cerebellar dentate nucleus neurons as targets of Alzheimer's disease. *Molecular Neurodegeneration*, Vol. 5, No. 60, (Dec. 2010), pp.1-11, ISSN 1750-1326.
- Cherny, R. A., Legg, J. T., McLean, C. A., Farlie, D.P., Huang, X., Atwood, C.S., Beyreuther, K., Tanzi, R.E., Masters, C.L. & Bush, A.L. (1999). Aqueous dissolution of Alzheimer's disease A β amyloid deposits by biometal depletion. *Journal of Biological Chemistry*, Vol. 274 , No. 33 , (Aug. 1999), pp. 23223-23228, ISSN 1083-351X.
- Connor, J. R., Benkovic, S. A. (1992). Iron regulation in the brain: histochemical, biochemical, and molecular considerations. *Annals of Neurology*, Vol. 32 , No. Suppl (1992), pp. S51-S61, ISSN 0364-5134.
- Corain, B., Bombi, G.G., Tapparo, A., Perazzolo, M., Zatta, P. (1996). Aluminium toxicity and metal speciation: established data and open questions. *Coordination Chemistry Reviews*, Vol. 149, (May 1996), pp.11-22, ISSN 0010-8545.
- Cox, P.A., (1995). *The elements on earth: inorganic chemistry in the environment*. Oxford University Press, ISBN 0198562411, Oxford, New York.
- Crapper, D.R., Krishnan, S.S., Quittkat, S. (1976). Aluminium, neurofibrillary degeneration and Alzheimer's disease. *Brain: a Journal of Neurology*, Vol. 99, No.1, (Mar. 1976), pp. 67-80, ISSN 0006-8950.
- De Meo, M., Laget, M., Castegnaro, M. & Dumenil, G. (1991). Genotoxic activity of potassium permanganate in acidic solutions. *Mutation Research*, Vol. 260, No. 3, (Jul. 1991), pp. 295-306, ISSN 0027-5107.
- Demougeot, C., Methy, D., Prigent-Tessier, A., Garnier, P., Bertrand, N., Guillard, J.C., Beley, A. & Marie C. (2003). Effects of a direct injection of liposoluble iron into rat striatum. Importance of the rate of iron delivery to cells. *Free Radical Research*, Vol. 37, No.1, (Jan. 2003), pp. 59-67, ISSN 1071-5762.

- Dennis, J., Selkoe, M.D. (2000). The Origins of Alzheimer Disease. *Journal of American Medical Association*. Vol. 283, No.12 (2000), pp.1615-1617, ISSN 1538-3598.
- Deskin R., Bursian S.J. & Edens F.W. (1980). Neurochemical alterations induced by manganese chloride in neonatal rats. *Neurotoxicology*, Vol. 2, No. 1, (Jan. 1980), pp. 65-73, ISSN 0161-813X.
- Donaldson, J., McGregor, D., LaBella, F. (1982). Manganese neurotoxicity: A model of free radical mediated neurodegeneration? *Canadian Journal of Physiology and Pharmacology*, Vol. 60, No. 11, (1982), pp. 1398-1405, ISSN 0008-4212.
- Dong, J., Atwood, C.S., Anderson, V.E., Siedlak, S.L., Smith, M.A., Perry, G. & Carrey, P.R. (2003). Metal binding and oxidation of amyloid-beta within isolated senile plaque cores: Raman microscopic evidence. *Biochemistry*, Vol. 42, No. 10, (Mar 2003), pp. 2768-2773, ISSN 0264-6021.
- Double K.L., Gerlach M., Youdim M.B., Riederer P. (2000). Impaired iron homeostasis in Parkinson's disease. *Journal of Neural Transmission Supplementum*, 60, 37-58. Vol. 60, No.1, (2000), pp. 37-58, ISSN 0303-6995.
- Dovgaliuk, A.I., Kaliniak, T.B. & Blium, I.B. (2001b). Cytogenetic effects of toxic metal salts on apical meristem cells of *Allium cepa* L. seed roots. *TSitologiia i Genetika*, Vol. 35, No. 2, (Mar./Apr. 2001), pp. 3-10, ISSN 0564-3783.
- Dovgaliuk, A.I., Kaliniak, T.B., Blium, I.B. (2001a). Assessment of phytoand cytotoxic effects of heavy metals and aluminum compounds using onion apical root meristem. *TSitologiia i Genetika*, Vol. 35, No. 1, (Jan./Feb. 2001), pp. 3-9, ISSN 0564-3783.
- Drago, D., Bettella, M., Bolognin, S., Cendron, L., Scancar, J., Milacic, R., Richelli, R., Casini, A., Messori, L., Tagnon, G. & Zatta, P. (2008). Potential pathogenic role of beta-amyloid(1-42)-aluminum complex in Alzheimer's disease. *The International Journal of Biochemistry & Cell Biology*, Vol. 40, No. 4, (Oct. 2008), pp. 731-746, ISSN 1357-2725.
- Dunkel, V.C., San, R.H., Seifried, H.E. & Whittaker, P. (1999). Genotoxicity of iron compounds in *Salmonella typhimurium* and L5178Y mouse lymphoma cells. *Environmental and Molecular Mutagenesis*, Vol. 33, No. 1 (Feb. 1999), pp. 28-41, ISSN 0893-6692.
- Durante, M., Gialanella, G., Grossi, G., Pugliese, M., Scampoli, P., Kawata, T., Yasuda, N. & Furusawa, Y. (2002). Influence of the shielding on the induction of chromosomal aberrations in human lymphocytes exposed to high-energy iron ions. *Radiation Research*, Vol. 43, Suppl. S, (Dec. 2002), pp. 107-111, ISSN 0449-3060.
- Dutta, D., Devi, S.S., Krishnamurthi, K. & Chakrabarti, T. (2006). Anticlastogenic effect of redistilled cow's urine distillate in human peripheral lymphocytes challenged with manganese dioxide and hexavalent chromium. *Biomedical and Environmental Sciences*, Vol. 19, No. 6, (Dec. 2006), pp. 487-494, ISSN 0895-3988.
- Eidelberg, D., Sotrel, A., Joachim, C., Selkoe, D., Forman, A., Pendlebury, W.W. & Perl, D.P. (1987). Adult onset Hallervorden-Spatz disease with neurofibrillary pathology. *Brain*, Vol. 110, No. 4, (Aug. 1987), pp. 993-1013, ISSN 1460-2156.
- Elmore, A.R. (2003). Final report on the safety assessment of aluminum silicate, calcium silicate, magnesium aluminum silicate, magnesium silicate, magnesium trisilicate, sodium magnesium silicate, zirconium silicate, attapulgite, bentonite, Fuller's earth, hectorite, kaolin, lithium magnesium silicate, lithium magnesium sodium silicate,

- montmorillonite, pyrophyllite and zeolite. *International Journal of Toxicology*, Vol. 22, Suppl. 1, (2003), pp. 37-102, ISSN 1091-5818.
- Erbe, M.C., Ramsdorf, W.A., Vicari, T. & Cestari, M.M. (2011). Toxicity evaluation of water samples collected near a hospital waste landfill through bioassays of genotoxicity piscine micronucleus test and comet assay in fish *Astyanax* and ecotoxicity *Vibrio fischeri* and *Daphnia magna*. *Ecotoxicology*, Vol. 20, No. 2, (Mar. 2011), pp. 320-328, ISSN 0963-9292.
- Eriksson, H., Lenngren, S. & Heilbronn, E. (1987). Effect of long-term administration of manganese on biogenic amine levels in discrete striatal regions of rat brain. *Archives of Toxicology*, Vol. 59, No. 6, (Apr. 1987), pp. 426-431, ISSN 0340-5761.
- Evans, H.H., Horng, M.F., Ricanati, M., Diaz-Insua, M., Jordan, R. & Schwartz, J.L. (2001). Diverse delayed effects in human lymphoblastoid cells surviving exposure to high-LET (56)Fe particles or low-LET (137)Cs gamma radiation. *Radiation Research*, Vol. 156, No. 3, (Sep. 2001), pp. 259-271, ISSN 0449-3060.
- Evans, H.H., Horng, M.F., Ricanati, M., Diaz-Insua, M., Jordan, R. & Schwartz, J.L. (2003). Induction of genomic instability in TK6 human lymphoblasts exposed to 137Cs gamma radiation: comparison to the induction by exposure to accelerated 56Fe particles. *Radiation Research*, Vol. 159, No. 6, (Jun. 2003), pp. 737-747, ISSN 0449-3060.
- Ferrer, A. (2003). Metal poisoning. *Anales del Sistema Sanitario de Navarra*, Vol. 26, pp. 141-153, ISSN 1137-6627.
- Florence, T.M., Stauber, J.L. (1989). Manganese catalysis of dopamine oxidation. *The Science of the Total Environment*, Vol. 78, No. 1, (Jan. 1989), pp. 233-240, ISSN 0048-9697.
- Franke, S.I.R., Prá, D., Giulian, R., Dias, J.F., Yoneama, M.L., Silva, J., Erdtmann, B. & Henriques, J.A.P. (2006). Influence of orange juice in the levels and in the genotoxicity of iron and copper. *Food and Chemical Toxicology*, Vol. 44, No. 3, (Mar. 2006), pp. 425-435, ISSN 0278-6915.
- García-Medina, S., Razo-Estrada, C., Galar-Martinez, M., Cortéz-Barberena, E., Gómez-Oliván, L.M., Alvarez-González, I. & Madrigal-Bujaidar, E. (2011). Genotoxic and cytotoxic effects induced by aluminum in the lymphocytes of the common carp (*Cyprinus carpio*). *Comp. Biochem. Physiol. C. Toxicol. Pharmacol.* Vol. 153, No. 1, (Jan 2011), pp. 113-118, ISSN 1532-0456.
- Garruto, R.M., Shankar, S.K., Yanagihara, R., Salazar, A.M., Amyx, H.L., Gajdusek, D.C. (1989). Low- calcium, high-aluminum diet-induced motor neuron pathology in cynomolgus monkeys. *Acta Neuropathologica (Berl)*, Vol. 78, No. 2, (1989), pp. 210-219, ISSN: 0001-6322.
- Garry, S., Nesslany, F., Aliouat, E., Haguenoer, J.M. & Marzin, D. (2003). Hematite (Fe(2)O(3)) enhances benzo[a]pyrene genotoxicity in endo-tracheally treated rat, as determined by Comet Assay. *Mutation Research*, Vol. 538, No. 1-2, (Jul. 2003), pp.19-29, ISSN 13835742.
- George, K.A., Hada, M., Jackson, L.J., Elliott, T., Kawata, T., Pluth, J.M. & Cucinotta, F.A. (2009). Dose response of gamma rays and iron nuclei for induction of chromosomal aberrations in normal and repair-deficient cell lines. *Radiation Research*, Vol. 171, No. 6, (Jun. 2009), pp. 752-63, ISSN 0033-7587.

- Gerber, G.B., Leonard, A. & Hantson, P. (2002). Carcinogenicity, mutagenicity and teratogenicity of manganese compounds. *Critical Reviews in Oncology/Hematology*, Vol. 42, No. 1, (Apr. 2002), pp. 25-34 ISSN 1040-8428.
- Gerlach, M., Double, K.L., Youdim, M.B., Riederer, P. (2006). Potential sources of increased iron in the substantia nigra of parkinsonian patients. *The Journal of Neural Transmission Supplementa*, Vol. 70, No. 1, (2006), pp. 133-142, ISSN: 0303-6995.
- Ghetti, B., Musicco, M., Morton, J., Bugiani, O. (1985). Nerve cell loss in the progressive encephalopathy induced by aluminum powder: A morphologic and semiquantitative study of the Purkinje cells. *Neuropathology and Applied Neurobiology*, Vol. 11, No. 1, (Jan. - Feb. 1985), pp. 31-53, ISSN: 0305-1846.
- Glei, M., Latunde-Dada, G.O., Klinder, A., Becker, T.W., Hermann, U., Voigt, K. & Pool-Zobel, B.I. (2002). Iron-overload induces oxidative DNA damage in the human colon carcinoma cell line HT29 clone 19A. *Mutation Research*, Vol. 519, No. 1-2, (Aug. 2002), pp. 151-161, ISSN 0027-5107.
- Good, P.F., Olanow, C.W., Perl, D.P. (1992). Neuromelanin- containing neurons of the substantia nigra accumulate iron and aluminum in Parkinson's disease: a LAMMA study. *Brain Research*, Vol. 593, No. 2, (Oct. 1992), pp. 343-346, ISSN 0006-8993.
- Griffiths, P.D., Dobson, B.R., Jones, G.R. & Clarke, D.T. (1999). Iron in the basal ganglia in Parkinson's disease. An in vitro study using extended X-ray absorption fine structure and cryo-electron microscopy. *Brain*, Vol. 122, No. 4, (Nov. 1999), pp. 667-673, ISSN 1460-2156.
- Guilarte T. R. (2010.) "APLP1, Alzheimer's-like pathology and neurodegeneration in the frontal cortex of manganese-exposed non-human primates". *NeuroToxicology*, Vol.31, No.5, (Sep. 2010), pp. 572-574, ISSN:0161-813X.
- Gupta, V.B., Anitha, S., Hegde, M.L., Zecca, L., Garruto, R.M., Ravid, R., Shankar, S.K., Stein, R., Shanmugavelu, P., Jagannatha Rao, K.S. (2005). Aluminium in Alzheimer's disease: are we still at a crossroad? *Cellular and Molecular Life Sciences*, Vol. 62, No.2, (Jan. 2005), pp. 143-158, ISSN 1420-682X.
- Guy, S.P., Jones, D., Mann, D.A.M, Itzhaki, R.F. (1991). Human neuroblastoma cells treated with aluminium express an epitope associated with Alzheimer's disease neurofibrillary tangles. *Neuroscience Letters*, Vol. 121, No. 1-2, (Jan. 1991), pp. 166-168, ISSN 0304-3940.
- Hardy, J., Selkoe, D.J. (2002). The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science*, Vol. 297, No. 5580 (Jul. 2002), pp. 353-356, ISSN: 1095-9203.
- Hasan, M.R., Morishima, D., Tomita, K., Katsuki, M. & Kotani, S. (2005). Identification of a 250 kDa putative microtubule-associated protein as bovine ferritin. Evidence for a ferritin-microtubule interaction. *The FEBS Journal*, Vol. 272, No. 3, (Dec. 2005), pp. 822-831, ISSN 0014-2956.
- Hegde, M. L., Hegde, P. M., Holthauzen, L.M.F., Hazra, T. K., Rao, K. S.J., Mitra, S. (2010). Specific inhibition of NEIL-initiated repair of oxidized base damage in human genome by copper and iron: potential etiological linkage to neurodegenerative diseases. *The Journal of Biological Chemistry*, Vol. 285, No. 37, (Jul. 2010), pp. 28812-28825, ISSN 0021-9258.
- Heidelberg, C., Freeman, A.E., Pienta, R.J., Sivak, A., Bertram, J.S., Casto, B.C., Dunkel, V.C., Francis, M.W., Kakunaga, T., Little, J.B. & Schechtman, L.M. (1983). Cell

- transformation by chemical agents – a review and analysis of the literature. A report of the US Environmental Protection Agency Gene-Tox Program. *Mutation Research*, Vol. 114, No. 3, (Apr. 1983), pp. 283–385, ISSN 0027-5107.
- Hollenberg P.F. (2010). Introduction: Mechanisms of Metal Toxicity. *Chemical Research in Toxicology*, Vol. 23, No. 15, pp. 292–293, ISSN 0893-228X.
- House, E., Collingwood, J., Khan, A., Korchazkina, O., Berthon, G., Exley, C. (2004). Aluminium, iron, zinc and copper influence the *in vitro* formation of amyloid fibrils of Abeta42 in a manner which may have consequences for metal chelation therapy in Alzheimer's disease. *Journal Alzheimer's Disease*, 6: 291-301 Vol. 6, No. 3, (Jun. 2004), pp. 291-301, ISSN 1387-2877.
- Hurley, L.S., Keen, C.L. (1987). Manganese. In: *Trace elements in human and animal nutrition*, W. Mertz, (Ed.), Vol. 1. pp. 185–223, Academic Press, New York, NY.
- International Labour Organization (ILO), (1997). *Encyclopaedia of occupational health and safety. Metals: chemical properties and toxicity*. 4th ed. Geneva, 6368 pp, ISBN 978-92-2-109816-4.
- Iwami, O., Watanabe, T., Moon, C.S., Nakatsuka, H. & Ikeda, M. (1994). Motor neuron disease on the Kii Peninsula of Japan: excess manganese intake from food coupled with low magnesium in drinking water as a risk factor. *The Science of the Total Environment*, 149(1-2), 121-35. Vol.149, No.1-2, (Jun. 1994), pp. 121-135, ISSN 0048-9697.
- Kawahara, M., Muramoto, K., Kobayashi, K., Mori, H. & Kuroda Y., (1994). Aluminum promotes the aggregation of Alzheimer's amyloid beta- protein *in vitro*. *Biochemical and Biophysical Research Communication*, Vol. 198, No. 2, (Jan. 1994), pp. 531-535, ISSN 0006-291X.
- Kawahara, M., Kato, M., Kuroda, Y. (2001). Effects of aluminium on the neurotoxicity of primary cultured neurons and on the aggregation of beta-amyloid protein. *Brain Research Bulletin*, Vol. 55, No. 2, (May 2001), pp. 211-217, ISSN 0361-9230.
- Kell, D. B., Towards a unifying, systems biology understanding of large-scale cellular death and destruction caused by poorly liganded iron: Parkinson's, Huntington's, Alzheimer's, prions, bactericides, chemical toxicology and others as examples. *Archives of Toxicology*, Vol. 84, No. 11, (Nov. 2010), pp. 825-889, ISSN 1432-0738.
- Kontush, A., Berndt, C., Weber, W., Akopyan, V., Arlt, S., Schippling, S. & Beisiegel, U. (2001). Amyloid-beta is an antioxidant for lipoproteins in cerebrospinal fluid and plasma. *Free Radical Biology & Medicine*, Vol. 30, No.1, (Dec. 2001), pp. 119-128, ISSN 0891-5849.
- Kostoryz, E.L. & Yourtee, D.M. (2001). Oxidative mutagenesis of doxorubicin-Fe(III) complex. *Mutation Research*, Vol. 490, No. 2, (Feb. 2001), pp. 131-139, ISSN 0027-5107.
- Kruman, I.I., Wersto, R.P., Cardozo-Pelaez, F., Smilenov, L., Chan, S.L., Chrest, F.J., Emokpae, R., Gorospe, M., Mattson, M.P. (2004). Cell cycle activation linked to neuronal cell death initiated by DNA damage. *Neuron*, Vol. 41, No 4, (Feb. 2004), pp. 549-561, ISSN 1097-4199.
- Kumar, V., Gill, K.D. (2009). Aluminium neurotoxicity: neurobehavioural and oxidative aspects. *Archives of Toxicology*, Vol. 83, No. 11, (Nov. 2009), pp. 730-735. ISSN 0340-5761.

- LaFerla, F. M., Green, K. N. Oddo, S. (2007). Intracellular amyloid- β in Alzheimer's Disease. *Nature Reviews Neuroscience*, Vol. 7 No. 8 (Jul. 2007), pp. 499– 509, ISSN 1471-003X.
- Lai, J.C., Leung T.K. & Lim L. (1984). Differences in the neurotoxic effects of manganese during development and aging: Some observations on brain regional neurotransmitter and non- neurotransmitter metabolism in a developmental rat model of chronic manganese encephalopathy. *NeuroToxicology*, Vol. 5, No. 1, (spring 1984), pp. 37–47, ISSN 0161-813X.
- Lan, J., Jiang, D.H. (1997). Excessive iron accumulation in the brain: a possible potential risk of neurodegeneration in Parkinson's disease. *Journal of Neural Transmission*, Vol. 104, No. 6-7, (1997), pp. 649-660, ISSN 0300-9564.
- Lankoff, A., Banasik, A., Duma, A., Ochniak, E., Lisowska, H., Kuszewski, T., Gózd, S. & Wojcik A. (2006). A comet assay study reveals that aluminium induces DNA damage and inhibits the repair of radiation-induced lesions in human peripheral blood lymphocytes. *Toxicology Letters*, Vol. 161, No. 1, (Feb. 2006), pp. 27–36, ISSN 0378-4274.
- Lapresle, J., Duckett, S., Galle, P., Cartier, L. (1975). Clinical, anatomical and biophysical data on a case of encephalopathy with aluminum deposition. *Comptes rendus des séances de la Société de biologie et de ses filiales*, Vol. 169, No. 2, (1975), pp. 282-285, ISSN 0037-9026.
- Lee, D.W. Andersen, J.K. (2010). Iron elevations in the aging Parkinsonian brain: a consequence of impaired iron homeostasis? *Journal of Neurochemistry*, Vol. 112, No. 2, (Jan. 2010), pp. 332-339. ISSN 0022-3042.
- Léonard A. (1988). Mechanisms in metal genotoxicity: the significance of in vitro approaches. *Mutation Research*, Vol. 198, No. 2, (Apr. 1988), pp. 321–6, ISSN 1383-5742.
- Li, H., Campbell, A., Ali, S.F., Cong, P., Bondy, S.C. (2008). Chronic exposure to low levels of aluminum alters cerebral cell signaling in response to acute MPTP treatment. *Toxicology and Industrial Health*, Vol. 23, No. 2, (Jan. 2008), pp. 515-524, ISSN 0748-2377.
- Liu G., Huang W., Moir R. D., Vanderburg, C.R., Lai, B., Peng, Z., Tanzi, R.E., Rogers, J.T. & Huang, X. (2006). Metal exposure and Alzheimer's pathogenesis. *Journal of Structural Biology*, Vol. 155, No. 1, (Jul. 2006), pp. 45-51, ISSN 1047-8477.
- Lima, P.D., Leite, D.S., Vasconcellos, M.C., Cavalcanti, B.C., Santos, R.A., Costa-Lotufo, L.V., Pessoa, C., Moraes, M.O. & Burbano, R.R. (2007). Genotoxic effects of aluminum chloride in cultured human lymphocytes treated in different phases of cell cycle. *Food and Chemical Toxicology*, Vol. 45, No. 7, (Jul. 2007), pp. 1154–1159, ISSN 0278-6915.
- Lima, P.D., Vasconcellos, M.C., Bahia, M.O., Montenegro, R.C., Pessoa, C.O., Costa-Lotufo, L.V., Moraes, M.O. & Burbano, R.R. (2008). Genotoxic and cytotoxic effects of manganese chloride in cultured human lymphocytes treated in different phases of cell cycle. *Toxicology In Vitro*, Vol. 22, No. 4, (Jun. 2008), pp. 1032-1037, ISSN 0887-2333.
- Lima, P.D., Vasconcellos, M.C., Montenegro, R.A., Sombra, C.M., Bahia, M.O., Costa-Lotufo, L.V., Pessoa, C.O., Moraes, M.O. & Burbano, R.R. (2008). Genotoxic and cytotoxic effects of iron sulfate in cultured human lymphocytes treated in different phases of

- cell cycle. *Toxicology In Vitro*, Vol. 22, No. 3, (Apr. 2008) pp. 723-729, ISSN 0887-2333.
- Lovell, M.A., Ehmann, W.D., Markesbery, W.R. (1993). Laser microprobe analysis of brain aluminum in Alzheimer's disease. *Annals of Neurology*, Vol. 33, No. 1, (Jan. 1993), pp. 36-42, ISSN 0364-5134.
- Lovell, M.A., Robertson, J.D., Teesdale, W.J., Campbell, J.L. & Markesbery, W.R. (1998). Copper, iron and zinc in Alzheimer's disease senile plaques. *Journal of the Neurological Science*, Vol. 158, No. 1, (Jun. 1998), pp. 47-52, ISSN 0022-510X.
- Lu, T., Pan, Y., Kao, S.Y., Li, C., Kohane, I., Chan, J., Yankner, B.A. (2004) Gene regulation and DNA damage in the ageing human brain. *Nature*, Vol. 429, No. 6994, (Jun. 2004), pp. 883-891, ISSN 0028-0836.
- Lukiw W.J. & Pogue A.I. (2007). Induction of specific micro RNA (miRNA) species by ROS-generating metal sulfates in primary human brain cells. *Journal of Inorganic Biochemistry*, Vol. 101, No. 9, (Sep. 2007), pp. 1265-1269, ISSN 0162-0134.
- Lukiw W.J. (2007). Micro-RNA speciation in fetal, adult and Alzheimer's disease hippocampus. *Neuroreport*. Vol. 18, No. 3, (Feb. 2007), pp. 297-300, ISSN 0959-4965.
- Lukiw W.J. In: Aluminum and Alzheimer's Disease, the Science that Describes the Link. Exley C, (Ed.), pp. 147-168, Elsevier Publishers, London.
- Lukiw, W.J. (2001). Aluminum and Gene Transcription in the Mammalian Central Nervous System—Implications for Alzheimer's Disease, In: *Aluminum and Alzheimer's Disease: the Science that Describes the Link*, Exley, C., pp. 147-68, Elsevier Publishers, ISBN, 978-0-444-50811-9, London.
- Maynard, C.J., Bush, A.I., Masters, C.L., Cappai, R. & Li, Q.X. (2005). Metals and amyloid beta in Alzheimer's disease. *International Journal of Experimental Pathology*, Vol. 86, No. 3, (Jun. 2005), pp. 147-159, ISSN 1365- 2613.
- Maenosono, S., Suzuki, T. & Saita, S. (2007). Mutagenicity of water-soluble FePt nanoparticles in Ames test. *The Journal of Toxicological Sciences*, Vol. 32, No. 5, (Dec. 2007), pp. 575-579, ISSN 0388-1350.
- Mark, R.J., Lovell, M.A., Markesbery, W.R. Uchida, K., Mattson, M.P. (1997). A role for 4-hydroxynonenal, an aldehydic product of lipid peroxidation, in disruption of ion homeostasis and neuronal death induced by amyloid beta-peptide. *Journal of Neurochemistry*, Vol. 66, No. 1, (Jan. 1997), pp. 255-264. ISSN 0022-3042.
- Mark, R.J., Pang, Z., Geddes, J.W., Uchida, K. & Mattson, M.P. (1997). Amyloid beta-peptide impairs glucose transport in hippocampal and cortical neurons: involvement of membrane lipid peroxidation. *The Journal of Neuroscience*, Vol. 17, No. 3, (Feb. 1997), pp. 1046-1054, ISSN 0270-6474.
- Martin, W.R.W., Wiler, M. (2008). Midbrain iron content in early Parkinson disease. A potential biomarker of disease status. *Neurology*, Vol. 70, No. 16 pt 2, (Apr. 2008), pp. 1411-1417, ISSN 1473-6551.
- McLachlan, D.R.C., Bergeron, C., Smith, J.E., Boomer, D. & Rifat, S.L. (1996). Risk for neuropathologically confirmed Alzheimer's disease and residual aluminum in municipal drinking water employing weighted residential histories. *Neurology*, Vol. 46, No. 2, (Apr. 1996), pp. 401-405, ISSN 1473-6551.
- Mills, E., Dong, X. P., Wang, F., Xu, H. (2010). Mechanisms of brain iron transport: insight into neurodegeneration and CNS disorders. *Future Medicinal Chemistry*, Vol. 2, No. 1, (2010), pp. 51-64, ISSN 1756-8919.

- Miu, A.C., Benga, O. (2006). Aluminum and Alzheimer's disease: a new look. *Journal of Alzheimer's disease*, Vol. 10, No. 2-3, (Nov. 2006), pp. 179-201, ISSN 1387-2877.
- Montgomery, E.B.J. (1995). Heavy metals and the etiology of Parkinson's disease and other movement disorders. *Toxicology*, Vol. 97, No. 1-3, (Mar. 1995), pp. 3-9, ISSN 0300-483X.
- Moreno, E.A., Rojas, G.F., Frenk, F.H., De La Huerta, A.O., Belmares, R.Q. & Vargas, A.R.O. (1997). In vitro induction of abnormal anaphases by contaminating atmospheric dust from the City of Mexicali, Baja California, Mexico. *Archives of Medical Research*, Vol. 28, No. 4, (Dec. 1997), pp. 549-553, ISSN 0188-4409.
- Morgan, D.M., Dong, J., Jacob, J., Lu, K., Apkarian, R.P., Thiagarajan, P. & Lynn, D.G. (2002). Metal switch for amyloid formation: insight into the structure of the nucleus. *Journal of the American Chemical Society*, Vol. 124, No. 43, (Oct. 2002), pp. 12644-12645, ISSN 0002-7863.
- Myung, N.H., Zhu, X., Castellani, R.J., Petersen, R.B., Siedlak, S.L., Perry, G., Smith, M.A., Lee, H.G. (2008). Evidence of DNA damage in Alzheimer disease: phosphorylation of histone H2AX in astrocytes. *Age (Dordrecht, Netherlands)*, Vol. 30, No 4, (Apr. 2008), pp. 209-215, ISSN 1574-4647.
- Nachtman, J.P., Tubben R.E. & Commissaris, R.L. (1986). Behavioral effects of chronic manganese administration in rats: Locomotor activity studies. *Neurobehavioral Toxicology and Teratology*, Vol. 8, No. 6, (Nov. - Dec. 1986), pp. 711-715, ISSN 0275-1380.
- Nakano, M. (1993). A possible mechanism of iron neurotoxicity. *European Neurology*, Vol. 33, No. 1, (1993), pp. 44-51, ISSN 0014-3022.
- Nayak, P. (2002). Aluminum: Impacts and Disease. *Environmental Research*, Vol. 89, No. 2, (Jun. 2002), pp. 101-115. ISSN 0013-9351.
- Nayak, P., Chatterjee, A.K. (1999). Biochemical view of aluminum-induced neurohazards. *Journal of environmental biology*, Vol. 20, No. (1999), pp. 77-84, ISSN 0254-8704.
- Newland, M.C., Ceckler, T.L., Kordower, J.H., Weiss, B. (1989). Visualizing manganese in the primate basal ganglia with magnetic resonance imaging. *Experimental Neurology*, Vol. 106, No. 3, (Dec. 1989), pp. 251-258. ISSN 0014-4886.
- Ogawa, H.I., Shibahara, T., Iwata, H., Okada, T., Tsuruta, S., Kakimoto, K., Sakata, K., Kato, Y., Ryo, H. & Itoh, T. (1994). Genotoxic activities in vivo of cobaltous chloride and other metal chlorides as assayed in the *Drosophila* wing spot test. *Mutation Research*, Vol. 320, No. 1-2, (Jan. 1994), pp. 133-140, ISSN 0027-5107.
- Olanow, C.W., Good, P.F., Shinotoh, H., Hewitt, K.A., Vingerhoets, F., Snow, B.J., Beal, M.F., Calne, D.B. & Perl, D.P. (1996). Manganese intoxication in the rhesus monkey: a clinical, imaging, pathologic, and biochemical study. *Neurology*, Vol. 46, No. 2, (Feb. 1996), pp. 492-8 ISSN 0028-3878.
- O'Neil, P., (1994). Major elements in the earth's crust - Iron. In: *Environmental chemistry 2nd ed.*, Chapman and Hall (Eds.), pp. 151-168, ISBN 0045510865, New York,
- Ong, W. Y., Farooqui, A. A. (2005). Iron, neuroinflammation, and Alzheimer's disease. *Journal of Alzheimer's Disease*, Vol. 8, No. 2, (Nov. 2005), pp. 183-200, ISSN 1387-2877.
- Orgel A. & Orgel L.E. (1965). Induction of mutations in bacteriophage T4 with divalent manganese. *Journal of Molecular Biology*, Vol. 14, No. 2, (Dec. 1965), pp. 453-457, ISSN 0022-2836.

- Park, J.H. & Park, E. (2011). Influence of iron-overload on DNA damage and its repair in human leukocytes in vitro. *Mutat. Res.*, Vol. 718, No. 1-2, (Jan. 2011), pp. 56-61, ISSN 1383-5742.
- Park, D.S., Morris, E.J., Padmanabhan, J., Shelanski, M.L., Geller, H.M., Greene, L.A. (1998). Cyclin-dependent kinases participate in death of neurons evoked by DNA-damaging agents. *The Journal of cell biology*, Vol. 143, No. 2, (1998), pp. 457-467, ISSN 540-8140.
- Petrik, M.S., Wong, M.C., Tabata, R.C., Garry, R.F., Shaw, C.A. (2007). Aluminum adjuvant linked to Gulf War illness induces motor neuron death in mice. *NeuroMolecular Medicine*, Vol. 9, No. 1, (2007), pp. 89-100, ISSN 1559-1174.
- Prá, D., Franke, S.I., Giulian, R., Yoneama, M.L., Dias, J.F., Erdtmann, B. & Henriques, J.A. (2008). Genotoxicity and mutagenicity of iron and copper in mice. *Biometals*, Vol. 21, No. 3, (Jun. 2008), pp. 289-297, ISSN 0966-0844.
- Pratico, D., Uryu, K., Sung, S., Tang, S., Trojanowski, J.Q., Lee, V.M. (2002). Aluminum modulates brain amyloidosis through oxidative stress in APP transgenic mice. *The FASEB Journal*, Vol. 16, No. 9, (Jul. 2002), pp. 1138-1140, ISSN 0892-6638.
- Prikhojan, A., Brannan, T., Yahr, M.D. (2002). Intrastriatal iron perfusion releases dopamine: an in-vivo microdialysis study. *Journal of Neural Transmission*, Vol. 109, No. 5-6, (May 2002), pp. 645-649, ISSN 1435-1463.
- Qiu, W.O., Folstein, M. (2006). Insulin, insulin-degrading enzyme and amyloid- β peptide in Alzheimer's disease: review and hypothesis. *Neurobiology of Aging*, Vol. 27 No. 2 (Feb. 2006), pp. 190-198, ISSN 0197-4580.
- Rass, U., Ahel, I., West, S.C. (2007). Defective DNA repair and neurodegenerative disease. *Cell*, Vol. 130, No 6, (Sep. 2007), pp. 130:991-1004, ISSN 0092-8674.
- Rauk A. (2009). The chemistry of Alzheimer's disease (AD). *Chemical Society Reviews*, Vol. 38, No. 9, (Aug. 2008), pp. 2698-2715, ISSN 0306-0012.
- Ribes, D., Colomina, M.T., Vicens, P., Domingo, J.L. (2010). Impaired spatial learning and unaltered neurogenesis in a transgenic model of Alzheimer's disease after oral aluminum exposure. *Current Alzheimer Research*, Vol. 7, No. 5, (Aug. 2010), pp. 401-408, ISSN 1567-2050.
- Ricchelli F, Drago D, Filippi B, Tognon G, Zatta P. (2005). Aluminum- triggered structural modifications and aggregation of beta- amyloids. *Cellular and Molecular Life Sciences*, Vol. 62, No. 15, (Aug. 2005), pp. 1724-1733, ISSN 1420-9071.
- Riederer, P., Sofic, E., Raush, W.D. (1989). Transition metals, ferritin, glutathione, and ascorbic acid in parkinsonian brain. *Journal of Neurochemistry*, 52, 515-520. Vol. 52, No. 2, (Feb. 1989), pp. 515-520. ISSN 0022-3042.
- Rondeau, V., Commenges, D., Jacqmin-Gadda, H., Dartigues, J.F. (2001). Relation between aluminum concentrations in drinking water and Alzheimer's disease: an 8-year follow- up study. *American Journal of Epidemiology*, Vol. 154, No. 3, (Aug. 2001), pp. 159- 166, ISSN 1476-6256.
- Rossman T.G. & Molina M., 1986. The genetic toxicology of metal compounds: II. Enhancement of ultraviolet light-induced mutagenesis in Escherichia coli WP2. *Environmental Mutagenesis*, Vol. 8, No. 2, (1986), pp. 263-71, ISSN 0192-2521.
- Rossman T.G. & Molina M., Meyer L.W. (1984). The genetic toxicology of metal compounds: I. Induction of lambda prophage in E coli WP2s(lambda). *Environmental Mutagenesis*, Vol. 6, No. 1, (1984), pp. 59-69, ISSN 0192-2521.

- Rouault, T. A. (2001). Systemic iron metabolism: a review and implications for brain iron metabolism. *Pediatric Neurology, Journal of Neurochemistry*, Vol. 25, No. 2, (Aug. 2001), pp. 130-137, ISSN 1304-2580.
- Roy, A.K., Sharma A. & Talukder, G. (1991). Effects of aluminium salts on bone marrow chromosomes in rats in vivo. *Cytobios*, Vol. 66, No. 265 (1991), pp. 105-11, ISSN 0011-4529.
- Santiago, M., Matarredona, E.R., Granero, L., Cano, J., Machado, A. (2000). Neurotoxic relationship between dopamine and iron in the striatal dopaminergic nerve terminals. *Brain Research*, Vol. 858, No. 1, (Mar. 2000), pp. 26-32, ISSN 0006-8993.
- Sakae, Y., Shigeo, K., Akihiro, O., Akira, I. (2009). Demonstration of aluminum in amyloid fibers in the cores of senile plaques in the brains of patients with Alzheimer's disease. *Journal of Inorganic Biochemistry*, Vol. 103, No. 11, (Nov. 2009), pp. 1579-1584 ISSN 0162-0134.
- Salvador, G.A., Uranga, R.M., Giusto, N.M. (2010). Iron and Mechanisms of Neurotoxicity. *International Journal of Alzheimer's Disease*, Vol. 2011, No. 1, (Dec. 2010), pp. 1-9, ISSN 2090-0252.
- Santamaria, A.B., Sulsky, S.I. (2010). Risk assessment of an essential element: manganese. *Journal of Toxicology and Environmental Health A*, Vol. 73, No. 2, (2010), pp. 128-155, ISSN 1087-2620.
- Savory, J., Jagannatha Rao K.S., Huang, Y., Letada, P.R. & Herman, M.M. (1999). Age-related hippocampal changes in Bcl-2:Bax ratio, oxidative stress, redox-active iron and apoptosis associated with aluminium- induced neurodegeneration: increased susceptibility with aging. *NeuroToxicology*, Vol. 20, No. 5, (Oct. 2008), pp. 805-818, ISSN 0161-813X.
- Sarkander H.I., Balb, G., Schlosser, H., Stoltenburg, G. & Lux, R.M. (1983). In: *Brain Aging: Neuropathology and Neuropharmacology*, Cervos-Navarro, J. & Sarkander, H.I., pp. 259-274, Raven Press, New York
- Sayre, L. M., Zagorski, M. G., Surewicz, W. K., Krafft, G. A. & Perry, G. (1997). Mechanism of neurotoxicity associated with amyloid β deposition and the role of free radicals in the pathogenesis of Alzheimer's disease: a critical appraisal. *Chemical Research in Toxicology*, Vol. 10, No. 5 (May 1997), pp.518-526, ISSN 0893-228X.
- Sayre, L. M., Zelasko, D.A., Harris, P.L.R., Perry, G., Salomon, R.G. & Smith, M.A. (1997). 4-Hydroxynonenal-derived advanced lipid peroxidation end products are increased in Alzheimer's disease. *Journal of Neurochemistry*, Vol. 68, No. 5, (May 1997), pp. 730-735. ISSN 0022-3042.
- Sayre, L.M., Moreira, P.I., Smith, M.A., Perry, G. (2005). Metal ions and oxidative protein modification in neurological disease. *Annali dell'Istituto Superiore di Sanità*, Vol. 41, No. 2, (2005), pp. 143-164, ISSN 0021-2571.
- Scalon, M.C., Rechenmacher, C., Siebel, A.M., Kayser, M.L., Rodrigues, M.T., Maluf, S.W., Rodrigues, M.A. & Silva, L.B. (2010). Evaluation of Sinos River water genotoxicity using the comet assay in fish. *Braz. J. Biol.*, Vol. 70, No. 4 (Suppl), (2010), pp. 1217-22, ISSN 1519-6984.
- Schneider, J. S., Decamp, E., Clark, K., Bouquio, C., Syversen, T. & Guilarte, T. R. (2009). Effects of chronic manganese exposure on working memory in non-human primates. *Brain Research*, Vol. 1258, No. 3, (Dec. 2009), pp. 86-95, ISSN 0006-8993.

- Sethi, P., Jyoti, A., Singh, R., Hussain, E., Sharma, D. (2008). Aluminium-induced electrophysiological, biochemical and cognitive modifications in the hippocampus of aging rats. *NeuroToxicology*, Vol. 29, No.2, (Nov. 2008), pp. 1069-1079, ISSN 0161-813X.
- Sienko, M.J., Plane, R.A., (1977). Elementos de transição II. In: *Química 5 ed*, Sienko, M.J., Plane, R.A. (Eds.), pp. 436-454. São Paulo.
- Smith, M. A., Tabaton, M., Perry, G. (1996). Early contribution of oxidative glycation in Alzheimer disease. *Neuroscience Letters*, Vol. 217, No. 2-3, (Oct. 1996), pp. 210-211, ISSN 0304-3940.
- Smith, M. A., Harris, P. L. R., Sayre, L. M., Perry, G. (1997) Iron accumulation in Alzheimer disease is a source of redox- generated free radicals. *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 94, No. 18, (Sep. 1997), pp. 9866-9868, ISSN 0027-8424.
- Sriram, K., Lin G.X., Jefferson, A.M., Roberts, J.R., Chapman, R.S., Chen, B.T., Soukup, J.M., Ghio, A.J. & Antonini, J.M. (2010). Dopaminergic neurotoxicity following pulmonary exposure to manganese-containing welding fumes. *Archives of Toxicology*, Vol. 84, No. 7, (Jul. 2010), pp. 521-540, ISSN 0340-5761.
- Stankiewicz, J.M., Brass, S.D. (2009). Role of iron in neurotoxicity: a cause for concern in the elderly? *Current Opinion in Clinical Nutrition and Metabolic Care*, Vol. 12, No. 1, (Jan. 2009), pp. 22-29, ISSN 1363-1950.
- Su, B., Wang, X., Nunomura, A., Moreira, P.I., Lee, H.-gon, Perry, G., Smith, M.A. & Zhu., X. (2008). Oxidative Stress Signaling in Alzheimer's Disease. *Current Alzheimer Research*, Vol. 5, No. 6, (Dec. 2008), pp.525-532, ISSN 1567-2050.
- Subhash, M.N. & Padmashree, T.S. (1990). Regional distribution of dopamine β -hydroxylase and monoamine oxidase in the brains of rats exposed to manganese. *Food Chemistry and Toxicology*, Vol. 28, No. 8, (Aug. 1990), pp. 567-570, ISSN 0278-6915.
- Suh, S.W., Jensen, K.B., Jensen, M.S., Silva, D.S., Kesslak, P.J., Danscher, G. & Frederickson, C.J. (2000). Histochemically-reactive zinc in amyloid plaques, angiopathy, and degenerating neurons of Alzheimer's diseased brains. *Brain Research*, Vol. 852, No. 2, (Jan. 2000), pp. 274-278, ISSN 0006-8993.
- Sullivan, E. V., Adalsteinsson, E., Rohlfing, T., Pfefferbaum A. (2009). Relevance of iron deposition in deep gray matter brain structures to cognitive and motor performance in healthy elderly men and women: exploratory findings. *Brain Imaging and Behavior, Journal of Neurochemistry*, Vol. 3, No. 2, (Jun. 2009), pp. 167-175, ISSN 1931-7565.
- Suwalsky, M., Ungerer, B., Villena, F., Norris, B., Cardenas, H., Zatta, P., (2001). Effects of AlCl₃ on toad skin, human erythrocytes, and model cell membranes. *Brain research bulletin*, Vol. 55, No 2, (May 2001), pp. 205-210, ISSN . 0361-9230.
- Terry, R.D., Pena, C. (1965). Experimental production of neurofibrillary degeneration (2) Electron microscopic, phosphatase histochemistry and electron probe analysis. *Journal of Neuropathology and Experimental Neurology*, Vol. 24, No.1, (Apr. 1965), pp. 200-210, ISSN 0022-3069.
- Timchenko, O.I., Paran'Ko, N.M., Shantyr, E.E. & Kuz'Menko, S.D. (1991). The cytogenetic effects of separate and combined exposures to a manganese dioxide aerosol and wide-band noise. *Gigiena i Sanitariia*, No. 11, (Nov. 1991), pp. 70-72 , ISSN 0016-9900.

- Trippi, F., Botto, N., Scarpato, R., Petrozzi, L., Bonuccelli, U., Latorraca, S., Sorbi, S. & Migliore, L. (2001). Spontaneous and induced chromosome damage in somatic cells of sporadic and familial Alzheimer's disease patients. *Mutagenesis*, Vol. 16, No. 4, (Jul. 2001), pp. 323-327, ISSN 0267-8357.
- Troncoso, J.C., Price, D.L., Griffin, J.W. & Perhad, I.M. (1982). Neurofibrillary axonal pathology in aluminum intoxication. *Annals of Neurology*, Vol. 12, No. 3, (Sep. 1982), pp. 278-283, ISSN 0364-5134.
- Tucker, J.D., Auletta, A., Cimino, M.C., Dearfield, K.L., Jacobson-Kram, D., Tice, R.R. & Carrano, A.V. (1993). Sister-chromatid exchange: second report of the Gene-Tox Program. *Mutation Research*, Vol. 297, No. 2, (Sep. 1993), pp. 101-180, ISSN 0027-5107.
- Van de Sande, J.H., McIntosh, I.P. & Jovin, T.N. (1982). Mn^{2+} and other transition metals at low concentrations at low concentration induce the right-to-left helical transformation of poly d(G-C). *The EMBO Journal*, Vol. 1, No. 7, (1982), pp. 777-782, ISSN 0261-4189.
- Varadarajan, S., Yatin, S., Aksenova, M. Butterfield, D.A. (2000). Review: Alzheimer's amyloid beta-peptide-associated free radical oxidative stress and neurotoxicity. *Journal of Structural Biology*, Vol. 130, No. 2-3, (Jun. 2000), pp. 184-208, ISSN 1095-8657.
- Varner, J.A., Jensen, K.F., Hovarth, W., Issacson, R.L., (1998). Chronic administration of aluminium fluoride or sodium fluoride to rats in drinking water: Alterations in neuronal and cerebrovascular integrity. *Brain Research*, Vol. 784, No. 16, (Feb. 1998), pp. 284-298, ISSN 0006-8993.
- Varella, S.D., Pozetti, G.L., Vilegas, W. & Varanda, E.A. (2004). Mutagenic activity in waste from an aluminum products factory in Salmonella/microsome assay. *Toxicology In Vitro*, Vol. 18, No. 8, (Dec. 2004), pp. 895-900, ISSN 0887-2333.
- Veldman, B.A., Widn, A.M., Knoers, N., Pramstra, P., Horstink, M.W., (1998). Genetic and environmental risk factors in Parkinson's disease. *Clinical neurology and neurosurgery*, Vol. 100, No. 1, (Mar. 1998), pp. 295-301, ISSN 0303-8467.
- Vidal, L., Alfonso, M., Campos, F., Faro, L.R., Cervantes, R.C. & Duran, R. (2005). Effects of manganese on extracellular levels of dopamine in rat striatum: an analysis in vivo by brain microdialysis. *Neurochemical Research*, Vol. 30, No. 9, (Sep. 2005), pp. 147-1154, ISSN 1573-6903.
- Weiss, B. (2010). Lead, Manganese, and Methylmercury as risk factors for neurobehavioral impairment in advanced age. *International Journal of Alzheimer's Disease*, Vol. 2011, No. 27, (Dec. 2010), pp. 1-11, ISSN 2090-0252.
- Wen-zhen, Z., Wei-de, Z., Wei, W., Chuan-jia, Z., Cheng-yuan, W., Jian-pin, Q., Jian-zhi, W. & Ting, L. (2009). Quantitative MR phase-corrected imaging to investigate increased brain iron deposition of patients with Alzheimer disease. *Radiology*, Vol. 253, No. 2, (Nov. 2009), pp. 497-504, ISSN 1527-1315.
- Willmore, L.J., Rubin, J.J. (1984). The effect of tocopherol and dimethyl sulfoxide on focal edema and lipid peroxidation induced by isocortical injection of ferrous chloride. *Brain Research*, Vol. 296, No. 2, (Apr. 1984), pp. 389-392, ISSN 0006-8993.
- Winder, B.S., Salmon, A.G., Marty, M.A. (2010). Inhalation of an essential metal: development of reference exposure levels for manganese. *Regulatory Toxicology and Pharmacology*, Vol. 57, No. 2-3, (Jul. - Aug. 2010), pp. 195-199, ISSN 0273-2300.

- Wright, J.A., Brown, D.R. (2008). Alpha-synuclein and its role in metal binding: relevance to Parkinson's disease. *The Journal of Neuroscience Research*, Vol. 86, No. 3, (Feb. 2008), pp. 496-503, ISSN 0360-4012.
- World Health Organization (WHO), (1996). Guidelines for drinking - water quality recommendations. 2nd ed. Geneva.
- World Health Organization (WHO). (1997). Aluminium. Environmental Health Criteria, N° 194, Geneva.
- World Health Organization (WHO). (1998). Trace elements in human nutrition and health.
- World Health Organization (WHO), (1999). Manganese and its compounds. Concise International Chemical Assessment Document 12. WHO, Geneva.
- Wu, Z., Du, Y., Xue, H., Wu, Y. & Zhou, B. (2010). Aluminum induces neurodegeneration and its toxicity arises from increased iron accumulation and reactive oxygen species (ROS) production. *Neurobiol of Aging*. Jul 29. [Epub ahead of print], ISSN 0197-4580.
- Xu J, Chen S, Ahmed SH, Chen H, Ku G, Goldberg MP, Hsu, C.Y. (2001). Amyloid-beta peptides are cytotoxic to oligodendrocytes. *The Journal of Neuroscience*, Vol. 21, No. 1, (Jan. 2001), pp. 1-6, ISSN 0270-6474.
- Yang, Y., Mufson, E.J., Herrup, K. (2003). Neuronal cell death is preceded by cell cycle events at all stages of Alzheimer's disease. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, Vol. 23, No. 7, (Apr. 2003), pp. 2557-2563, ISSN 0270-6474.
- Yasui, M., Kihira, T., Ota, K. (1992). Calcium, magnesium and aluminum concentrations in Parkinson's disease. *NeuroToxicology*, Vol. 13, No. 3, (1992), pp. 593-600, ISSN 0161-813X.
- Yi, M., Yi, H., Li, H. & Wu, L. (2010). Aluminum induces chromosome aberrations, micronuclei, and cell cycle dysfunction in root cells of *Vicia faba*. *Environmental Toxicology*, Vol. 25, No. 2, (Apr. 2010), pp. 124-9, ISSN 1520-4081.
- Yumei, W., Jinfeng, J., Xiaohong, Z. & Baoshan, Y. (1998). Genotoxicity of the dust organic extract and its fractions derived from an aluminium electrolytic plant. *Toxicology Letters*, Vol. 98, No. 3, (Sep. 1998), pp. 147-153, ISSN 0378-4274.
- Yokel, R.A. (1994). Aluminum exposure produces learning and memory deficits, a model of Alzheimer's disease. In: *Toxin-Induced Models of Neurological Disorders*, Woodruff, M.L. and Nonneman, A.J., pp. 301-318, Plenum, ISBN 03064-46146, New York.
- Youdim, M. B. H., Fridkin, M., Zheng, H. (2005). Bifunctional drug derivatives of MAO-B inhibitor rasagiline and iron chelator VK-28 as a more effective approach to treatment of brain ageing and ageing neurodegenerative. diseases. *Mechanisms of Ageing and Development*, Vol. 126, No. 2, (Feb. 2005), pp. 317-326, ISSN 0047-6374.
- Yumoto, S., Nagai, H., Matsuzaki, H., Matsumura, H., Tada, W., Nagatsma, E., Kobayashi, K. (2001). Aluminium incorporation into the brain of rat fetuses and sucklings. *Brain Research Bulletin*, Vol.55, No. 2, (May 2001), pp. 229-234, ISSN 0361-9230.
- Zatta, P.F., Nicolini, M., Corain B. (1991). Aluminum (III) toxicity and blood-brain barrier permeability. In: *Aluminum in Chemistry, Biology and Medicine*, Nicolini, M., Zatta, P.F., Corain, B., pp. 97-12, Cortina International, ISBN 3642105580, Verona.

- Zecca, L., Gallorini, M., Schunemann, V., Trautwein, A. X., Gerlach, M., Riederer, P., Vezzoni, P., Tampellini, D. (2001). Iron, neuro- melanin and ferritin content in the substantia nigra of normal subjects at different ages: consequences for iron storage and neurodegenerative processes. *Journal of Neurochemistry*, Vol. 76, No. 6, (Mar. 2001), pp. 1766-1773, ISSN 0022-3042.
- Zheng, W., Ren, S., Graziano, J.H., (1998). Manganese inhibits mitochondrial aconitase: a mechanism of manganese neurotoxicity. *Brain Research*, Vol. 799, No. 2, (Jul. 1998), pp. 334-342, ISSN 0006-8993.

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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