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REVIEW PAPER

Effects of the lead, cadmium, manganese heavy metals, and magnesium oxide nanoparticles on nerve cell function in Alzheimer's and Parkinson's diseases

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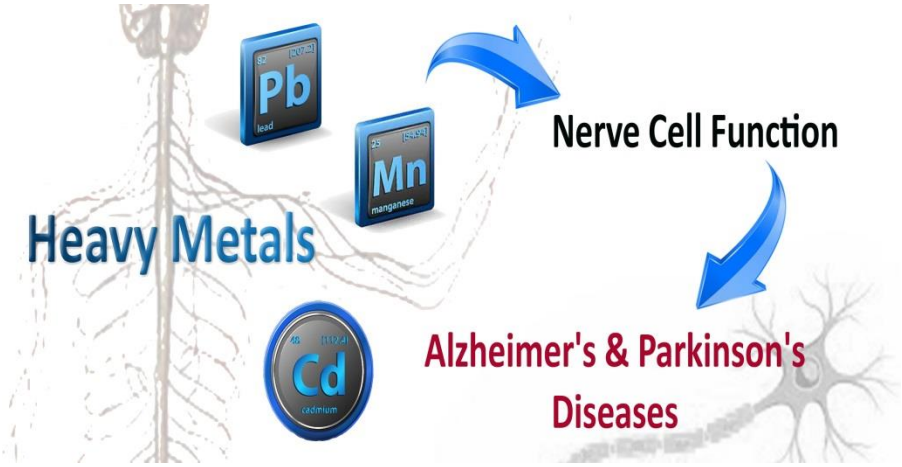
Highlights

- Alzheimer's and Parkinson's diseases are multifactorial diseases.
- The risk of developing Alzheimer's and Parkinson's increases with exposure to heavy metals.
- High and toxic levels of metals can impair mitochondrial function.
- Heavy metals could produce reactive oxygen species and activate apoptosis.

Graphical Abstract



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Abstract

Nervous disorders affect the central nervous system and cause progressive impairment of the nervous system. These disorders are usually incurable and debilitating and are characterised by a loss of nerve cell function. The most common chronic neurological disorders are Parkinson's disease (PD) and Alzheimer's disease (AD). Damage to the nerves usually progresses with age, as seen in AD and PD. Although Parkinson's and Alzheimer's diseases are multifactorial, exposure to heavy metals in neurons could increase the risk of developing these diseases. Metals are essential for maintaining cellular homeostasis and life. They have critical structural, catalytic, and regulatory functions in various types of proteins such as receptors, enzymes, and transporters. However, high and toxic concentrations of metals can stimulate the formation of reactive oxygen species (ROS) via a vicious cycle by impairing mitochondrial function, leading to a reduction in ATP and eventually cell death through an apoptotic mechanism. As life expectancy increases, individuals are certainly exposed to higher metal concentrations over a long period of time, which may lead to an increase in the incidence of neurological diseases. The aim of this study was to describe the effects of heavy metals such as manganese, lead and cadmium on the progression of the neurological diseases Parkinson's and Alzheimer's disease.

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Introduction

Neurons are key players in the central nervous system, scientists estimate that in the communication network of the brain, one neuron may have 7000 synaptic contacts with other neuron cells (1). The catabolism of nutrients and chemicals in a cell is a crucial factor for the survival and function of a healthy cell (2, 3). The brain has a lot of blood reserves than other organs and metabolizes up to 20% of the human body's energy. Dissimilar to various cells in the different tissues that have comparatively short-lived, neuron cells have a long lifespan (4). The neuronal cell must continually sustain and repair themselves. Also, neuron cells constantly regulate or regenerate their synaptic contacts by weakening or strengthening those connections, depending on the amount of stimulus they obtain from other neuronal cells (5). The adult brain might even produce novel neurons in the neurogenesis process. Reconstruction of synaptic contacts and neurogenesis is necessary for memory, learning, and probably brain repair (6). Other types of cells are important for the function of the healthy brain. Glial cells are found in abundance in the brain. Glial cells, which exist in several forms such as astrocytes, microglia, and oligodendrocytes, cover and support neurons. Damage to nerve cells can lead to a wide range of neurodegenerative diseases. One of the major factors involved in cell disorders is the effect of accumulation and toxicity of heavy metals in them (7, 8).

Environmental pollution and human contact with dust storms and wastewater containing heavy metals including cadmium, mercury, and lead have become a crucial ecological and health problem worldwide. In general, metals can be classified into non-essential and essential metals. Essential types include copper, chromium, cobalt, lithium, iron, nickel, magnesium, selenium, zinc, and manganese (9, 10). These trace metallic elements typically act as cofactors of enzymes to control the activity of the cell. Therefore, the mentioned metals contributed too many physiological procedures including electron transfer, protein modification, oxygen transfer, redox reactions, neurotransmitter synthesis, cell adhesion, immune responses, and metabolism of carbohydrates and protein. Sometimes these metals or related ions of these metals may even interfere with metabolic processes in both eukaryotic and prokaryotic cells (11). Damage of metal accumulation can lead to permanent damage, such as severe neurological diseases. Clinical and epidemiological projects have indicated a strong association between exposure to heavy metals and many neurological disorders such as amyotrophic lateral sclerosis, Alzheimer's disease (AD), Guillain-Barré disease, autism spectrum disorders, Huntington's disease, Gulf War syndrome, multiple sclerosis, Wilson's disease, and Parkinson's disease (PD) (12, 13).

Accumulation of metals in the brain demonstrates their main role in the neuronal system. The lack of the mentioned metals has been correlated with several neurological disorders. For example, deficiency of iron is associated with Restless Legs Syndrome, dyspnea, stroke in children, pseudo-brain tumors, and cranial nerve palsy (14). Although metals are important to animals and plants, they are usually needed in small quantities. Excess metal levels accumulate in various organs, including the brain. High levels of metals may cause harmful intracellular events, including oxidative stress, mitochondrial dysfunction, DNA fragmentation, incorrect protein folding, endoplasmic reticulum stress, autophagic disorder, and apoptotic activation (15). These impacts might change the neurotransmission process and result in nerve damage that could manifest as movement disorders, problems of cognitive, and memory impairments and learning. Neurons do not normally reproduce or replace themselves, so they cannot be exchanged by the body after they are died or even damaged. Neurodegenerative disorders are debilitating and incurable circumstances that result in progressive destruction or death of nerve cells (9, 15). Here we first explain the mechanism of development of two major neurodegenerative diseases, Parkinson's and Alzheimer's, and then describe the effects of heavy metals such as cadmium, lead, and manganese on these neurodegenerative diseases.

Alzheimer's disease

The brain usually shrinks somewhat with age, but amazingly, it does not lose a large number of nerve cells. The damage, in Alzheimer's disease, is extensive because several neuronal cells do not work, lose contact with other neuronal cells, and then die. Alzheimer's disease disturbs vital procedures for neurons including

metabolism, communication, and repair. Initially, Alzheimer's disorder usually destroys neuronal cells and their contacts in the brain parts that are contributed to the memory process, such as the hippocampus and entorhinal cortex. It later impacts the regions in the cerebral cortex that are accountable for social behavior, language, and argument. Finally, several other regions of the brain are defective. Over time, an Alzheimer's patient gradually loses the capability to function and live independently and eventually this disease results in death (16).

The main features of Alzheimer's brain include neurofibrillary tangles, amyloid plaques, and chronic inflammation. The protein of beta-amyloid involved in Alzheimer's is present in some molecular forms and accumulates among neurons. This protein is made up of the breakdown of a greater molecule named amyloid precursor protein (APP). One of them, beta-amyloid 42, may be toxic. In the brain tissue of a person with Alzheimer's, atypical concentrations of this natural molecule join together to create plaques that accumulate among neuronal cells, disrupting the function of cells (17, 18). Neurofibrillary tangles are an anomalous accumulation of tau protein that accumulates in neuronal cells. Normal neurons are partially maintained by microtubule structures that help transport molecules and nutrients from the cell body to dendrites and axons. In normal neuronal cells, the tau usually attaches to microtubules and stabilizes them. In Alzheimer's disorder, irregular chemical alterations result in the detachment of the tau molecules from microtubules and bind together, making strands that ultimately join together and bond inside neuronal cells (19, 20). These nodes inhibit neuronal transmission, which damages the synaptic connection among neuronal cells. Evidence proposes that Alzheimer's-associated alterations in the brain might be due to a complicated interaction between atypical tau and beta-amyloid peptides and many other factors. Abnormal tau molecules accumulate in certain areas of the brain that are involved in memory. Amyloid-beta also becomes plaques between neurons. When beta-amyloid levels reach a peak, there is a quick spread of tau proteins all over the brain (21, 22).

Researches show that chronic inflammation might be produced by the accumulation of glial cells, which usually form to support the brain. Microglia as a glial cell swallows and removes wastes and toxic reagents in the normal brain. In Alzheimer's disease, microglia cells cannot remove waste products and protein complexes, such as amyloid-beta plaques. Scientists are researching to figure out why microglia cells do not play this crucial role in Alzheimer's (23, 24). One of the genes involved in inflammation is the TREM2 gene. Typically, TREM2 signals microglia to remove the plaques of beta-amyloid from the brain tissue and help the brain against inflammation (25). In people whose brains do not have normal function, plaques form among neuronal cells? Astrocytes are also a glial cell type; receive signals to remove plaque and other cell residues. These astrocytes and microglia accumulate around neuronal cells but cannot perform the function of clearing waste products. Moreover, they could release chemical reagents that result in chronic inflammation and more impair the neuronal cells they are assumed to support (26, 27).

Parkinson's disease

Parkinson's is a progressive disease that influences the neurons in the brain that are responsible for body movements. After the death of dopaminergic nerve cells, signs including tremors, slowness, problems of balance, and muscle stiffness happen. The frequency of Parkinson's disease is 1-2% at age 60 and 3-8% at age 85-89. PD is more common in men than women in a 1.5/1 ratio (28, 29). Nerve messages are transmitted from the dendrites to the axon terminal, where the vesicles of dopamine (a type of neurotransmitter) are released at the synapse area. Dopamine passes through the synapse and is located in specific receptors on the postsynaptic cell and induces the cells to transmit the neuronal signal. After sending the message, again dopamine is released to synapses via receptors, where the additional dopamine molecules are recycled in the releasing neurons. The remained dopamine breaks down by MAO-B and COMT and the synapse region is clear and prepared for the next signal (30, 31). Parkinson's disease as a progressive and degenerative impairment could affect neurons in deep regions of the brain named the substantia nigra and basal ganglia. In the substantia nigra, neurons produce the dopamine neurotransmitter and are responsible for transmitting signals that program and regulate

the movement of the body. Due to unknown factors, dopamine-producing neurons in substantia nigra start to die in certain people (32). With 80% loss of dopamine, symptoms of PD including tremors, stiffness, slowness of movement, and balance problems happen. The cerebellum and basal ganglia are responsible for guaranteeing that the movement is performed smoothly. These pulses are transmitted from one neuron to another and move rapidly from the brain to the spinal cord and eventually to the muscles. With insufficient stimulation of dopamine receptors in the striatum corpus, sections of the basal ganglia become overstimulated. This ultimately has an inhibition role on the thalamus, and then reduces the output of the thalamus and leads to tremors. Also, a high amount of glutamate, a neurotransmitter, rises in Parkinson's disease, when the body is trying to compensate for the deficiency of dopamine (33, 34).

Effects of lead on the pathogenesis of Alzheimer's and Parkinson's disease

The heavy metal lead is responsible for about one percent of the global disease burden. In the elderly, lead contact is correlated with an elevated susceptibility of Parkinson's disease, amyotrophic lateral sclerosis, hearing loss, glaucoma, age-related cataracts, and other chronic statuses. The US Centers for Disease Control and Prevention (CDC) consider a reference amount of 5 mg/dl of blood lead for pregnant women and children (35). Nonetheless, safe levels of blood lead have not yet been recognized. Contrary to US legal attempts to diminish lead exposure, lead is still used in a variety of industrial usages, such as car batteries. Common sources of lead exposure vary depending on age and geographical location. The main routes of exposure are ingestion or inhalation. In the elderly, the endogenous source can be the main reservoir of lead exposure. The excretion of lead is comparatively slow and its accumulation is prevalent. Lead is stored in the bones during early and middle life (36). Adults who experience bone loss through osteoporosis inject lead into the bloodstream. In the elderly, 40 to 70% of blood lead could be attributed to earlier body storage. Entrance of lead to the body in earlier periods of high exposure could activate in the next decades (37).

After the entrance of lead to the body, it could absorb by tissues and cells. Inhaled particles of lead result in local impairment of the lungs. Thirty to forty percent, depending on the particle volume, could be entered into the bloodstream. Adults absorb only 10 to 15% of the lead consumed, although children and women with pregnancy conditions absorb fifty percent of the lead consumed (37). Personal factors, including diet (calcium, iron, low zinc, or phosphorus) and genetic variations (hemochromatosis and delta-aminolevulinic acid dehydratase genes) affect the absorption from the intestine. Lead, in organic form, is absorbed via the skin, and this pathway is mostly seen in the workplace. Lead could mainly enter the bloodstream via absorption into the gastrointestinal tract, lungs, or skin surfaces (9, 38). Absorbed lead circulates in the bloodstream and is transported to the brain tissue. Lead passes the barrier of the placenta and could be found in the baby's umbilical cord blood at the same amount as the mother's blood. In addition, this heavy metal could affect the blood-brain barrier (BBB). The BBB separates the water-soluble compounds in the bloodstream from the brain, and the transport process is very controlled. Lead replaces calcium by passing through the BBB and accumulating in the brain, eventually causing edema. This disrupts intracellular secondary messaging systems and changes the function of the central nervous system, which its protection is very vital (9, 39).

Cellular mechanisms associated with lead toxicity in Alzheimer's disease

Lead is a known neurotoxin that results in non-specific brain disorders. Lead causes oxidative stress (OS) by reducing thiols and via detrimental effects on the system of antioxidant defense. Ample OS leads to endoplasmic reticulum stress, mitochondrial impairment, and eventually neurons apoptosis. Lead disturbs the homeostatic amounts of necessary metals, eventually leading to neuroinflammation. Similar damage is done to supporting cells including astrocytes, oligodendrocytes, cerebrovascular endothelial cells, and microglia. Exposure to lead results in epigenetic alterations in tissues including the brain. Lead causes OS, neuroinflammation, endoplasmic reticulum stress, epigenetic alterations, apoptosis, and excitotoxicity in the brain (Figure 1). The lead primary accumulates in the hippocampus, though this heavy metal might accumulate

in some other areas of the brain (9, 40). The toxicity mechanism of lead, in ionic form, happens chiefly because of the capability of lead ions to substitute some divalent cations such as Fe2+, Mg2+, Ca2+, and monovalent cations such as sodium ion, which eventually disrupts the cell's metabolism. The toxicity mechanism of ionic lead results in substantial alterations in several biological procedures including intercellular and intracellular signaling, cell adhesion, protein folding, ion transport, neurotransmitters release, and apoptosis. Lead could replace Ca2+ even at levels of picomolar, which affect protein kinase C and nerve stimulation (41).

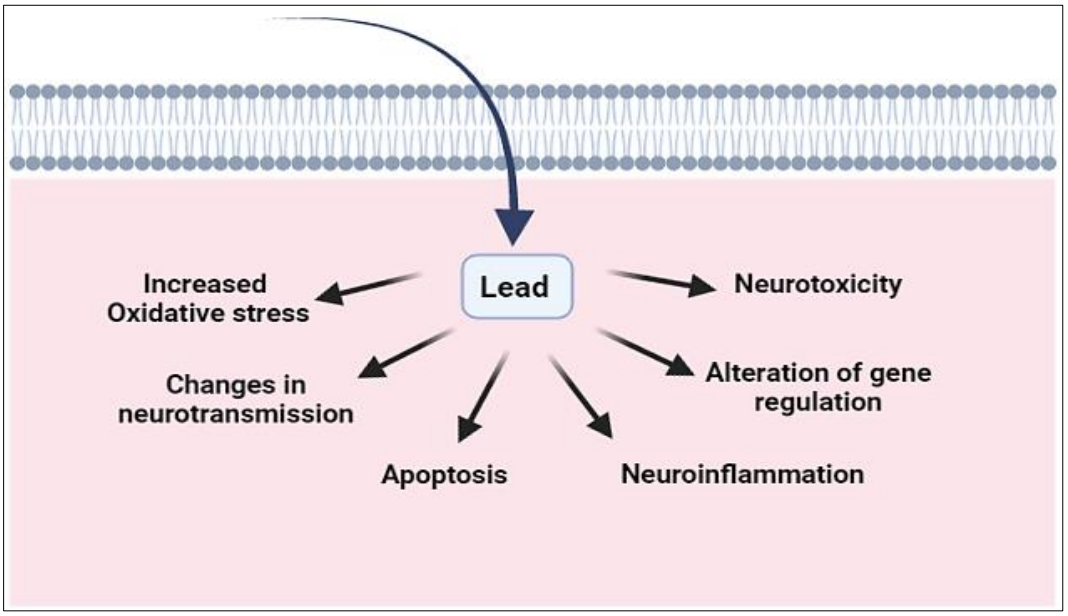

Figure 1. Mechanisms of lead pathogenicity in neurons. Lead could affect neurotoxicity, gene regulation, neuroinflammation, apoptosis, neurotransmission, and oxidative stress procedures.

Cellular mechanisms associated with lead toxicity in Parkinson's disease

Lead reduces the production of catecholamines and synaptic neurotransmitters by suppressing Ca-KCl-evoked GABA release. Chronic lead poisoning has been shown to cause oxidative stress by increasing levels of peroxidation of lipid in the liver and brain of rats. Exposure to lead decreases dopaminergic neurotransmission through dysfunction of mitochondrial, OS, and elevated glial filament in astrocytes (42). Studies have shown that lead affects cellular procedures by controlling calcium-binding protein, as well as the release and reabsorption of various neurotransmitters. It inhibits the calcium function dependence of dopamine and acetylcholine release. Studies have also shown that lead causes hyperphosphorylation of tau protein and the hippocampus accumulation of alpha-synuclein, resulting in autophagy and apoptosis activation (43). Amyloid precursor proteins (APPs) have the main action in the toxicity of lead via iron regulative pathways. According to the act that protein kinase C (PKC) is involved in the function of dopamine transport and lead easily stimulates OS through activation of PKC and leads to neurotoxicity. Lead easily crosses the blood-brain barrier and binds to sulfhydryl groups, which alter various antioxidant enzymes, increasing levels of lipid peroxidation. In the same way, lead-related toxicity initiates the lipid peroxidation process by inhibiting delta-aminolevulinic acid dehydratase (δ-ALAD) and the δ-ALA substrate accumulation, which produces free radicals (44, 45).

Effects of cadmium on the pathogenesis of Alzheimer's and Parkinson's

Cadmium (Cd) heavy metal has no basic physiological role in human body. Based on International Agency for Research on Cancer criteria, this metal is categorized as a group 1 carcinogen. Prolonged exposure to low concentrations of cadmium elevates the susceptibility to kidney damage, osteoporosis, high blood pressure, the low function of the lung and diabetes. Lately, Cd appeared as a neurotoxin, while evidence is yet limited for

humans. There is cadmium exposure for most individuals, and the amount of exposure is usually measured in blood and urine samples. Cd concentrations are usually higher in women than men because low iron elevates absorption of Cd, and Cd amounts are higher in smoker's people than in non-smokers (46, 47).

In standard circumstances, only small levels of Cd could pass the blood-brain barrier in adults. The choroid plexus maintains the homeostatic internal environment of the central nervous system. The choroid plexus is the key region of accumulation of Cd in the brain. The neuronal system of the olfactory might be the straight route of Cd transfer to the brain, thus bypassing the blood-brain barrier. Mice exposed to Cd showed lower performance in hippocampal-dependent spatial learning and memory and olfactory memory. Cd enters the central neuronal system directly via the system of olfactory and causes continuous and permanent impairment by blocking the adult neurogenesis in the olfactory bulb and hippocampus (48, 49).

Impaired regulation of Alzheimer's disease pathways

In vitro cadmium treatment caused accumulation of the 3rd repeat fragment (R3) of the microtubule tau binding region. R3 is crucial in the process of nucleation of the tau filament. Cd binds to the nitrogen of the groups of imidazole of His amino acids to form Cd-tau dimers and affects the nucleation stage in tau accumulation. Cadmium treatment increases the production of Aβ and tau tangles. Cd exposure elevates cell death in cholinergic neuronal cells and leads to changes in acetylcholinesterase and the destruction of cholinergic nerve cells. The decreased memory observed in Alzheimer's disease is due to the cholinergic neurotransmission loss because of the degeneration of cholinergic neuronal cells in the basal forebrain (9, 50).

Cadmium and Parkinson's disease

Cd increases OS by activating redox-sensitive transcription factors such as kappa B nuclear factor and activating protein A (AP-1), mammalian target of rapamycin (mTOR), Erk1/2, and JNK. These cellular pathways cause progressive dopaminergic neuronal degeneration and Parkinson's signs. Cd alters the integrity of the blood-brain barrier by a pathway of caspase-3 activation-dependent that causes the permanent opening of pannexin-1. This great transmembrane-permeable channel causes excessive ATP leakage and disruption of homeostasis of the neurovascular unit, eventually leading to nerve cell death. Cadmium inhibits the release of acetylcholine because of interference with the metabolism of calcium, which results in mental retardation, dysfunction of the olfactory, neurological disorders, learning disabilities, peripheral neuropathy, and motor dysfunction (49, 51).

Effects of manganese on the pathogenesis of Alzheimer's and Parkinson's

Manganese (Mn) is considered as the 5th most plentiful metal in the environment and the 12th most abundant element on the whole earth. This element is a crucial trace metal that is essential for suitable growth and physiological procedures including blood clotting, bone growth, metabolism of carbohydrates, immune response, and function of the brain. Manganese element is a cofactor for cellular enzymes, such as pyruvate carboxylase, arginase, manganese superoxide dismutase, and glutamine synthetase. Notwithstanding the significance of Mn in the health of human, too much Mn is toxic, and exposure to the high amount of this metal might accumulate in the brain tissue, causing a permanent Parkinson's syndrome called manganism. Exposure to high amounts of Mn leads to cognitive dysfunction and involves in AD pathogenesis. Adequate adult Mn intake is 2.3 mg/day for men and 1.8 mg for women. The usual range of Mn concentration in the overall population is 4-15 micrograms per liter in blood, 0.4-0.85 micrograms per liter in serum, and 1-8 micrograms per liter in urine (52-54).

In the overall population, the diet is the main source of Mn. This matter is plentiful in vegetable foods such as nuts, leafy vegetable rice, and whole grains. Animal foods such as eggs, fish, meat, poultry, and dairy do not have this element. The daily intake of Mn is usually between 2 and 6 mg, of which 1 to 5% is usually absorbed. Because of the double role of Mn as a powerful vital and toxic nutrient, manganese levels throughout the body

are closely regulated by controlling intestinal intake and metal excretion through hemostatic mechanisms. To date, manganese toxicity due to high dietary manganese intake has not been described in humans. The toxicity of manganese is typically caused by high levels of exposure to air or drinking water. Mn is extensively employed in commercial products and industrial procedures. Extreme occupational exposure to Mn is usual in welding, mining, dry battery production, processing of ore, and the use of chemical organic fungicides (55, 56). Dietary manganese could absorb from the intestine and could pass through the BBB. Also, the blood-cerebrospinal fluid might be the main connection for the uptake of Mn into the brain. Manganese in the air can be absorbed into the blood systemic circulation via the system pulmonary or into the brain via the olfactory neuronal system. The nose-brain pathway bypasses the blood-brain barrier and permits direct exposure to the brain. Therefore, exposure to the Mn in the air has been the main concern for toxicity in neurons. However, the mechanisms of manganese uptake and distribution in the brain are not well understood (57, 58).

Several carriers are involved in transporting manganese into the brain, the greatest of which transport also other vital metals including zinc and iron. Three transporters of metal ions are necessary for sustaining manganese homeostasis: SLC30A10, SLC39A14, and SLC39A. Functional mutations in the SLC30A10 gene were described in cases with high levels of Mn in the blood, accumulation of manganese in the brain and liver, and parkinsonism. Mice lacking Slc30a10 accumulate too much Mn in the liver, brain, and blood (The gene structure and cell localization of human SLC30A10 are demonstrated in Figure 2). In addition, the SLC39A14 gene mutations were described in cases with a high concentration of manganese in the blood and Mn accumulation in the brain, but not in the liver. Manganese and iron are similar in atomic mass, structure and radius of electrons and have common transport mechanisms. DMT1 is the main importer of manganese. Iron exporter ferroportin could export manganese and iron from the cell. In addition to iron, ferroportin transports manganese and protects against manganese toxicity and oxidative stress in dopaminergic cells (59-61).

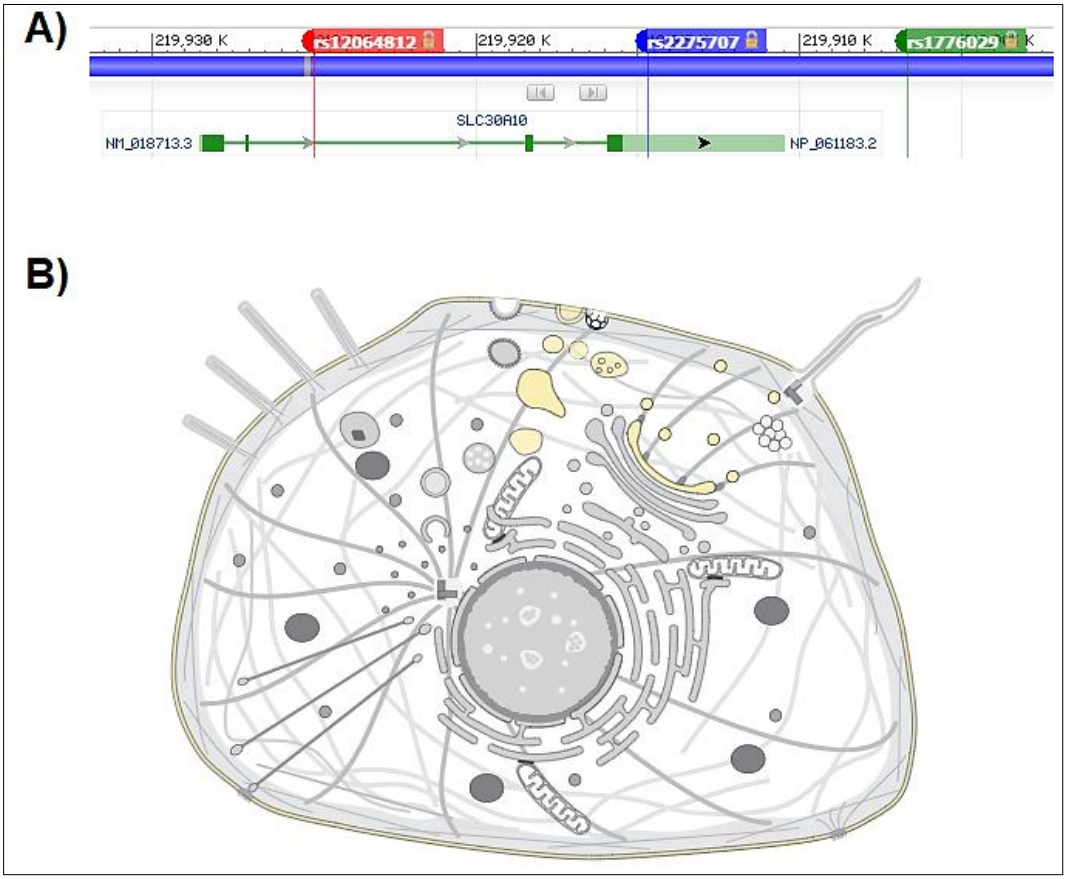

Figure 2. SLC30A10 Gene structure and cellular location. The SLC30A10 gene is contained three exons (A) with a location on cell membrane, endosome, Golgi apparatus (B). The figure was deduced from NCBI and UniProtKB databases.

Exposure to manganese causes general neurotoxicity. Underlying mechanisms include OS, dysfunction of mitochondria, and regulation of autophagy, apoptosis, and accumulation of toxic cellular metabolites. Mitochondria have an important role in neurological diseases associated with aging, including Alzheimer's. Mn accumulates in the mitochondria of the brain, although its output is too slow. MnSOD is a strong antioxidant enzyme found in mitochondria. The activity of MnSOD decreases through the process of aging. Extra Mn could disrupt the activity of MnSOD, thus elevating the production of ROSs and ultimately resulting in dysfunction of mitochondrial. Minor MnSOD deficiency caused OS and increased amounts of Aβ in the brain and Aβ plaques. High Mn decreases the expression of the two main enzymes involved in Aβ degradation, insulin-degrading enzyme and neprilysin, without changing AβPP expression. Also, Mn exposure could result in tau hyperphosphorylation, which might result in the production of neurofibrillary tangles, the main clinical structural alterations in AD. Mn has an affinity for Aβ, and Mn exposure in high concentrations might accelerate the accumulation of Aβ in the brain, thus elevating Aβ neurotoxicity and increasing the disease progression (62-64).

Cytotoxicity of magnesium oxide nanoparticles

Metal or metal oxide nanoparticles are novel materials in the nanoscopic scale (1-100 nm), which can have useful and harmful depending on their type, size, shapes, ingredients, and concentration (65, 66). For example, cytotoxicity on human nerve cells was observed for titanium dioxide (TiO2) as apoptosis and necrosis. However, magnesium oxide (MgO) nanoparticles showed less cytotoxic to human neural cells compared to TiO2 and zinc oxide (ZnO) nanoparticles (67). In contrast, the results of another study exhibited that MgO nanoparticles are not toxic to both undifferentiated and differentiated SH-SY5Y cells, a cell line derived from the SK-N-SH neuroblastoma cell line, for periods of 24, 48 and even 72 h.

Conclusion

Metals have a main role in our daily lives because they are generally contributed to many activities of enzymes. Some of these metals are necessary for small quantities. However, extreme levels in the body of human typically lead to the neurotoxicity of ALS, autism, PD, and AD are usually correlated with metals overexposure. When metals accumulate in the neuronal system, dysfunction of mitochondria, oxidative stress, and incorrect protein folding are the most usual defects correlated with the toxicity of metal. Because the neuronal system does not reproduce like other tissues, nerve damage and disorders typically progress with age, as is commonly observed in PD and AD. As life expectancy increases in the general population, there is certainly a long time for individuals to be exposed to higher levels of metals and a possible increase in the incidence of neurological disorders. Therefore, there is an increasing demand for neurotoxicity researches due to metal exposure. Future studies are required to focus more on the common influence of metal combination exposure, the identification of special carriers of each metal, and the development of specific target therapies for patients with metal intoxication.

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