Metal-Induced Mitochondrial Dysfunction

Subjects: Neurosciences
Contributor: Shaojun Li

Metals are actively involved in multiple catalytic physiological activities. However, metal overload may result in neurotoxicity as it increases formation of reactive oxygen species (ROS) and elevates oxidative stress in the nervous system. Mitochondria are a key target of metal-induced toxicity, given their role in energy production. As the brain consumes a large amount of energy, mitochondrial dysfunction and the subsequent decrease in levels of ATP may significantly disrupt brain function, resulting in neuronal cell death and ensuing neurological disorders.

Keywords: mitochondrial dysfunction ; neurological disorders ; metals ; neurotoxicity

1. Introduction

Mitochondria play a key role in many cellular physiological and pathological processes, including energy metabolism, calcium homeostasis, lipid biosynthesis, and apoptosis [1]. One of their main functions is to produce adenosine triphosphate (ATP) by coupling the electron transport chain (ETC) with phosphorylation. The ETC consists of four major protein–metal complexes (I–V) which primarily serve to generate a proton gradient to drive the production of ATP [2]. Superoxide anion, a byproduct of the ETC's operation, is extremely unstable and rapidly converted into hydrogen peroxide (H_2O_2) and ROS in the cytoplasm [3]. However, excessive production of ROS may cause oxidative stress, ETC dysfuction, mitochondrial structural damage [4][5], and oxidative damage to proteins, DNA, and lipids [6].

Neurons are highly polarized cells, heavily dependent on the energy generated by mitochondria, and the brain consumes about 20% of the body's resting ATP, while it accounts for only about 2% of the body's mass [7][8]. In addition, mitochondria are necessary calcium-buffering organelles in neurons as they regulate local calcium dynamics to control neurotransmitter release [9]. Mitochondrial dysfunction has been implicated in a variety of diseases, and is a causative factor in several neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), autism, and amyotrophic lateral sclerosis (ALS) [10][11][12].

Among the chemical elements that humans are exposed to, metals play an important role in both health and disease. Metals are natural components of the Earth's crust and enter the biosphere through a variety of human activities [13]. They are generally classified into two groups: essential and non-essential metals. The main routes of human exposure include ingestion, inhalation, and dermal contact [14]. The brain is able to regulate these metals effectively under physiological conditions. However, excessive exposure to metals, such as arsenic (As), aluminum (Al), cadmium (Cd), lead (Pb), copper (Cu), and manganese (Mn) may lead to their accumulation, and ensuing neurodegeneration [15]. Mitochondrial impairment and metal dyshomeostasis have been linked to some neurodegenerative disorders including AD, PD, HD, and ALS [12]. Metals can cause neurodegeneration by disrupting mitochondrial function, and thereby deplete ATP, induce ROS production, and ultimately lead to cell death through apoptotic and/or necrotic mechanisms [16]. There has been a growing interest in understanding the metabolism of neurotoxic metals and their role in the etiology of various neurodegenerative diseases, and a great deal of research has been done for this purpose. However, the effects of various metals on different neurodegenerative diseases are not identical, and their specific mechanisms of damage have yet to be fully clarified.

2. Molecular Mechanisms of Metal-Induced Mitochondrial Dysfunction

2.1. Arsenic (As)

As, a widely distributed toxic metalloid, is a risk for about 200 million people in more than 24 countries around the world [17][18]. It can be absorbed through skin, digestive tract, and inhalation. After absorption, As can be distributed to various organs, including kidney, lung, liver, and spleen in the animal and human bodies [19][20]. More seriously, As can enter the central nervous system (CNS) through the BBB and accumulate in different brain regions [21][22][23]. In vivo studies showed that excessive exposure to As induced neuronal apoptosis, which interrupted the neurodevelopment and cognitive functions of rats [24][25][26]. Epidemiological studies in rural-dwelling adults and elders also show that As (3–15 μg/L) levels

in water negatively correlated with the scores of cognitive performance and memory, indicating that As is a neurotoxic metalloid [27], which also acts as a risk factor for AD [28][29][30][31]. However, the mechanisms of As-induced neurotoxicity remain unclear.

To date, As-induced neurotoxicity has been related to Aβ overproduction [32][33], inflammatory responses [34][35], thiamine deficiency [36], oxidative stress, disruption of neurotransmitters [24][34], cytoskeletal gene expression, mitochondrial dysfunction, and disruption of acetyl cholinesterase activity [27][29][37]. Among them, mitochondrial dysfunction has been demonstrated to play a key role in As-induced neurotoxicity. Several in vitro studies have shown that As may induce adverse effects on mitochondrial functions. For example, Haga et al. [38] suggested that aggregated mitochondria were found in A172 cells after 50 μM arsenic trioxide (As_2O_3) treatment for 8 h. Subsequently, other investigators also suggested that sodium arsenite ($NaAsO_2$) or As_2O_3 treatment induced mitochondrial dysfunction via increasing intracellular Ca^{2+} levels, mitochondrial membrane potential (MMP), or calpain 1 levels in N_2A cells [39], SHSY-5Y cells [40], and primary astrocytes [41], as well as rats' primary neuronal cells [42]. Moreover, in vivo studies have also verified the critical roles of oxidative stress and mitochondrial dysfunctions in As-induced neurotoxicity [43][44].

It is well known that the mitochondrion is the main source of ROS formation, as well as a major target of ROS [45]. Oxidative stress is closely related to mitochondrial dysfunctions induced by As. Yadav et al. [46] showed that the activities of oxidative stress marker enzymes MnSOD and CAT were decreased by As in the mitochondrial fraction of different brain regions (including striatum, hippocampus, and frontal cortex) of rats via increasing ROS, and lipid peroxidation after exposure to $NaAsO_2$ for 28 days [44][46]. Similar results were found in sub-chronic As exposure studies done by other investigators which indicated that MnSOD, CAT, Gpx, GR, and GST activity were decreased in the mitochondrial fraction of rat brain [47][48]. Moreover, various studies suggested that As directly impaired the mitochondrial respiratory system via oxidative stress. Dwivedi et al. [43] indicated that As caused oxidative stress which in turn inhibited the activities of complexes I, II, and IV in the mitochondria of rat brain. These results have been corroborated by other labs [44][48]. Furthermore, excessive As exposure disrupted oxidative phosphorylation, and thus interrupted the ATP synthesis and mitochondrial respiration in the mitochondria of the brain [43][49]. Consistent with these results, sub-chronic exposure to low levels of As has been shown to decrease gene expression of the mitochondrial complexes II, IV, and V in mice brains [50] [51]. All of the above-mentioned studies suggested that the mechanisms of oxidative stress involved in As-induced mitochondrial dysfunctions play a pivotal role in As-induced neurotoxicity.

In summary, these studies suggest that the mitochondrial dysfunction in the CNS is the most important mechanism of As-induced neurotoxicity. It includes impairments of Ca^{2+} homeostasis [40][52], abnormal mitochondrial dynamics [53][54], and changes in membrane potential and permeability [37][55], which induces neuronal injuries via the mediating mitochondria-dependent pathway.

2.2. Aluminum (Al)

Al is a ubiquitously distributed metal on the earth, and it can be easily absorbed via skin contact, inhalation, and ingestion. Al sulfate has been ubiquitously used for water purifying, food processing, and the medicine and pharmaceutical industry, which ensure its presence in human bodies [56]. An increasing number of studies have shown that Al could accumulate in various mammalian organs, including bone, kidney, lung, liver, spleen, and brain [57][58][59]. Growing evidence has also suggested that Al accumulations in various brain regions may cause neurotoxic symptoms and learning impairment [59][60]. Studies in rodents indicated that chronic Al exposure led to Al accumulation in the hippocampus and caused neurobehavioral impairment [61][62][63]. Other studies also reported that Al caused neurofibrillary degeneration [60]. Altmann et al. showed that the impairment in cerebral function may be related to the concentrations of Al in the contaminated water [64]. Additionally, epidemiological studies suggested that Al has been considered as a potential risk factor in the development of neurodegenerative diseases, such as AD [59][65], PD [66][67], and ALS, etc. [68][69][70].

Several studies have proposed that mitochondrial dysfunction may play a critical role in the toxic effects of Al, including neurotoxicity [60][71]. Rao et al. [72] have shown that the ROS formation and mitochondrial respiratory activity, as well as glutathione depletion, were increased in the glial cells after being treated with Al for 24 h. Other groups have also depicted that Al exposure increased ROS formation and impaired the cytochrome c oxidase, which impaired mitochondrial functions in various neuronal cell types, including PC12 [73][74][75], SH-SY5Y neuroblastoma cells [76][77], and rat and cerebellar granule neuronal cells [78][79]. Mitochondrial dysfunction was also observed in in vivo studies [80][81]. Acute exposure to 50 μM Al maltonate via intracisternal injection caused the release of cytochrome c (cyt-c), accompanied by decreased Bcl-2, upregulated Bax, p53, and caspase-3, and DNA fragmentation in the mitochondria of rabbit brain [82]. Subsequently, Kumar et al. also reported that sub-chronic Al exposure for 12 weeks resulted in elevated ROS generation, and decreased ATP synthesis and cytochrome levels in a rat's brain, which implied disruption of mitochondrial function [83]. In addition, their other study also suggested that Al exposure decreased MnSOD and aconitase activities in different

regions of the rat brain [84]. Additionally, transmission electron microscope results showed that Al exposure caused mitochondrial swelling and vacuolization structures, and thus increased the diameter of mitochondria in the hippocampus nerve cells of mice and rats [71][83]. Finally, Al exposure upregulated the autophagy-related proteins LC3-II and Beclin-1, while downregulating p62 expression, suggesting that Al-induced learning and memory impairments may be related to mitophagy [71].

Recently, oxidative stress and mitochondrial disorders have been suggested as major targets for Al-induced neurotoxicity. For example, quercetin has shown protective effects on Al-induced mitochondrial swelling and chromatin condensation in rat hippocampus [85]. Naringin also has protective effects on memory impairment of sub-chronic Al-exposed rats via preventing the activations of mitochondrial oxidative damage in the brain [86]. Subsequently, *Centella asiatica*, which has antioxidant properties, was shown to ameliorate memory impairment and the activation of oxidative stress and decrease mitochondrial enzyme activity in the hippocampus and cerebral cortex induced by Al [87]. In addition, some other natural compounds also have been shown to have neuroprotective effects on Al-induced neurotoxicity, such as crocin, curcumin, and polyphenols [60][88][89]. These studies indicate that inhibition of oxidative stress and mitochondrial dysfunction may be a therapeutic strategy to prevent the neuronal injuries induced by Al.

2.3. Copper (Cu)

Cu is an essential trace metal for human health. Cu takes part in many cellular enzymatic activities, including energy production, redox balance, and neurotransmitter biosynthesis [90]. An adequate amount of copper is critical for the maintenance of redox balance in the mitochondria [91]. The mitochondria are both a regulatory hub for Cu homeostasis and a target of Cu toxicity [92]. For example, Cu is required for metallation of the catalytic core of cytochrome c oxidase, a mitochondrial metalloenzyme in the respiratory complex chain [93]. However, overload of mitochondrial Cu is detrimental to the function of respiratory complexes, leading to elevation of ROS and mitochondria dysfunction. Wilson's disease is a genetic disorder caused by excessive mitochondrial copper in the liver [91].

Brain mitochondria are particularly sensitive to the detrimental effects of Cu [94]. Compared to the mitochondria in the liver, kidney, and heart, brain mitochondria are susceptible to elevated levels of Cu, which attacks free thiols in large molecules that are indispensable for maintaining neuronal cell function [94]. The membrane potential, efficiency in ATP production, and structural integrity of brain mitochondria were prone to damage caused by excessive Cu [94]. Chronic Cu exposure led to spatial memory impairment that was associated with mitochondrial damage in the hippocampus [95]. Specifically, beta-amyloid-induced memory deficit in rats is exacerbated by Cu exposure. Meanwhile, analysis of isolated mitochondria from rat hippocampus following Cu exposure demonstrated a significant decline in mitochondria health, including increased lipid peroxidation and glutathione oxidation [95]. Mishandling of Cu in the mitochondria has been linked to age-related neurodegenerative disorders [96][97][98]. In a mice model of AD, a proteomics study showed that low levels of Cu exposure (0.13 ppm, 2 months) induced deficits in mitochondrial dynamics, leading to increased H_2O_2 production and reduced cytochrome oxidase activity [96]. Common biochemical characteristics of PD include accumulation of iron and diminished Cu content in degenerated brain regions. The disruption of Cu metabolism was believed to be involved in the pathological process in loss of catecholamine neurons [97]. Additionally, in a 6-hydroxydopamine (6-OHDA)-induced-PD model, Cu exposure increased oxidation of 6-OHDA, resulting in an increase in the rate of p-quinone formation and H_2O_2 accumulation. In the same model, the 6-OHDA-induced lipid peroxidation and protein oxidation were potentiated by Cu exposure [98].

Mitochondrial dysfunction following chronic Cu exposure involves oxidative stress, collapse in mitochondrial membrane potential, depletion of GSH, comprised function of respiratory complexes, reduction in APT production, and structural damage to the mitochondria [94][95]. Experimental evidence showed that free protein thiols in the mitochondria are potential toxic targets of Cu [94]. GSH supplementation attenuated Cu-induced lipid peroxidation but failed to protect oxidized thiols [98]. In addition, the induction of the mitochondrial permeability transition (MPT) was associated with Cu-induced astrocytic injury [99]. Furthermore, mitochondrial health in the hippocampus is a potential in vivo target of Cu. A recent study showed that mitochondrial biogenesis and respiratory function were impaired in the hippocampus of mice chronically exposed to $CuCl_2$ [96].

2.4. Cadmium (Cd)

Cd is a heavy metal that has no nutritional roles for humans. Cd-induced cellular damage is largely mediated by disruption of mitochondrial activity [100]. Elevation of ROS in the mitochondria and induction of mitochondria-derived apoptosis signaling are involved in Cd-induced neurotoxicity [101][102]. Mitochondrial protection afforded by antioxidants can attenuate Cd-induced neuronal damage [103].

An elevation in protein and lipid peroxidation, decrease in antioxidant capacity, and structural damage to the mitochondria were shown in the brains of rats chronically exposed to Cd [104]. The structural stability of mitochondria-associated ER membranes (MAMs) is critical for the proper function of the mitochondria. Recent studies show that MAMs are not only the physical bridge to facilitate communication between the ER and mitochondria, but they are also indispensable for cellular homeostasis processes such as autophagy, lipid metabolism, and Ca^{2+} transport [105]. Cd exposure induced increased production of ROS in the mitochondria, leading to impairment of MAMs [106]. The shapes of mitochondria are subjected to transformations in response to cellular stress, which is driven by two closely related processes: mitochondrial fusion and fission. Mitochondrial fusion and fission are required for proper intracellular distribution and quality control of the organelle [107]. Mitofusin 2 (Mfn2) is a mitochondrial outer membrane-localized GTPase that is essential for mitochondrial fusion. Cd-induced neuronal necroptosis was associated with ROS-induced S-glutathionylation of Mfn2 [106]. Increased ROS levels are detrimental to the activity of key enzymes involved in lipid metabolism. Cd exposure altered the lipid profile in a rat brain, resulting in an increased level of cholesterol (CHL) in the mitochondria [108]. Furthermore, Cd exposure promotes lipid peroxidation (LPO), which is mediated by the increased level of oxygen free radicals [109]. The mitochondria are both a storage site for cellular calcium ions and regulators for calcium ion homeostasis. Cd can competitively bind receptors and ion channels that regulate calcium ion influx, modulating calcium-dependent cellular activity [110]. The Ca^{2+}/calmodulin-dependent protein kinase II (CaMK-II) regulates cytoskeletal dynamics and apoptotic cell death. Recent advances show that CaMK-II mediates the effects of Cd exposure on actin depolymerization microtubules and cadherin junctions, which are the underlying mechanisms of Cd-induced cytoskeletal disruption and alterations in cellular morphology [110]. Nutritional trace metals, such as Zn and Se, can mitigate Cd-induced mitochondrial toxicity. For example, in a cellular toxicity model of PC12 cells, Cd exposure led to depletion of cellular GSH and oxidative damage to the mitochondria, which can be attenuated by Zn supplementation [111]. Additionally, Se supplementation suppressed Cd-induced oxidative stress and the mitochondrial apoptosis pathway [101].

2.5. Mercury (Hg)

Mercury is a naturally occurring element that is found in various inorganic and organic forms [112][113]. Both organic and inorganic mercury are neurotoxic. Methylmercury (MeHg) is of special concern as it is an ubiquitous environmental contaminant and its consumption in fish can lead to a devastating neurological disorder, referred to as Minamata disease [114]. Numerous studies have shown that mercury causes brain mitochondrial dysfunction, playing a key role in Hg-induced brain damage and neurological disorders.

As early as 1974, Chang and Hartmann found that mercury was present both in neurons and in glia after MeHg or mercuric bichloride ($HgCl_2$) administrated to rats orally or subcutaneously [115]. Notably, mitochondria accumulate mercury, mostly because of their abundance of thiol (–SH) groups. Although mercury initiates multiple additive or synergistic disruptive effects, a key mechanism of disruption of mitochondrial function is associated with the production of ROS. $HgCl_2$ and/or MeHg exposure enhance ROS formation in the CNS, evidenced by both in vivo [116] and in vitro models, including primary rat cortical neuron [117], rat cortical astrocyte [118][119], cerebellar granule neurons and astrocytes [120], and microglia [121], as well as in mixed primary neuron–astrocyte culture [122]. ROS overgeneration leads to consequent oxidative stress [123] and mitochondria-mediated apoptosis. For example, MeHg exposure results in cytochrome c release, caspase-3 and caspase-9 activation, and apoptosis-induced factors (AIF) increase in primary rat cortical neuron [117]. Mitochondria-mediated apoptosis in brain cells is secondary to alteration of mitochondrial membrane potential (MMP) and transition of mitochondrial permeability [124], which have been observed in neuron/astrocyte mixed-culture [122] and astrocyte mono-culture [125][126] after mercury exposure. In addition, the mitochondrial dysfunction evoked by mercury was correlated with damage in mitochondrial bioenergetics. Mercury has been found to act as an inhibitor of the enzymatic activities of mitochondrial respiratory complexes, impairing ATP synthesis in rat hippocampal mitochondria [127]. MeHg exposure reduced GSH levels in astrocytes, increasing the vulnerability to oxidative stress [128]. Apart from a series of biochemical impairments in mitochondria induced by mercury exposure, pathological changes in mitochondrial morphology have also been demonstrated. Li et al. [129] found that a low dose of mercury, lead, and cadmium caused dose-dependent mitochondrial depletion, as well as ridge and matrix dissolution in the hippocampal neurons of rats. Additionally, an in vivo study observed that MeHg induced mitochondrial swelling in the hippocampus of MeHg-exposed F1 generation rats, and enlarged and fused mitochondria in mice cerebral cortex [127].

Dreiem and Seegal [130] found that antioxidant Trolox significantly reduced MeHg-induced ROS, while failing to restore mitochondrial function in rat striatal synaptosomes. The authors revealed that MeHg increased mitochondrial calcium levels, which are fundamental to mitochondrial function. If mitochondria take up too much Ca^{2+}, it delays the rise in cytoplasmic Ca^{2+} [131] and the opening of the MPT pore, which may promote the release of cytochrome c and other pro-apoptotic factors, culminating in apoptosis [132]. The modulatory effect of cellular calcium homeostasis by MeHg in mouse spinal motor neurons was also found [133]. In addition, proteomic analysis revealed that many mitochondrial proteins were

deregulated by mercury exposure in primary mouse cerebellar granule neuron and astrocytes [120][134], as well as in rat hippocampus [135], thus impairing mitochondrial function associated with cellular metabolism and energy production.

2.6. Lead (Pb)

Pb is an environmentally abundant metal pollutant with human exposure mainly through air inhalation and food and water intake. Pb is a strong toxicant for the developmental CNS [136][137]. Pb intoxication in children, even at low doses, is found to impair learning and memory and affect cognitive functions and intellectual development [138][139]. The brain is the primary target of Pb toxicity. Mitochondria play a key role in Pb-induced impairment of nervous system function.

An in vivo study found that the activity or levels of several mitochondrial enzymes were inhibited by Pb exposure. For example, lead acetate (PbAc) exposure in drinking water decreased aldehyde dehydrogenase (ALDH2) expression in brain nucleus accumbens [140], and PbAc exposure from postnatal day 1 (PND1) through PND21 in drinking water of the mother significantly decreased offspring activity of mitochondrial monoamine oxidase (MAO) in all brain regions, including cerebral cortex, hippocampus, and cerebellum, in a dose- and age-dependent manner [141], attributed to the high affinity of Pb for the -SH groups in enzymes, consequently damaging mitochondrial activity and function. In addition, pre- and neonatal exposure to a low dose of Pb (Pb concentration in whole blood < 10 μg/dL) induced synaptic ultrastructural abnormalities in mitochondria including elongated, swollen, and shrunken changes in mitochondria [142], indicating the mitochondrial morphological disruption induced by Pb. Mitochondria-mediated apoptosis has also been shown in Pb-induced neuronal death. PbAc intoxication caused cognitive dysfunction and anxiety-like behavior, along with altered Bax/Bcl-1 expression and increased cytochrome c release from mitochondria in rat brain [143]. In addition, $(CH_3COO)_2Pb$ exposure induced apoptosis via the mitochondrial pathway in embryonic neurocytes isolated from chicken [144]. Similarly, the combined treatment (As+Cd+Pb) in individual lethal concentration (LC)-5 induced a toxic effect on C6-glioma cells derived from rat glioma, via mitochondria-mediated apoptosis, including caspase-9 activation and Bax/Bcl-2 changes [145]. Notably, Zhu et al. found that MPT pore opening plays an important role in Pb-induced neurotoxicity. In SH-SY5Y cells, PbAc exposure significantly impaired mitochondrial function, evidenced by ATP decrease, MMP collapse, ROS production, mitochondrial apoptosis, and morphology changes (swelling and rupture). PbAc treatment significantly increased the protein level of Cyp D, a component of MPT, and induced MPT pore opening in both PC12 and SH-SY5Y cells. Inhibitor of Cyp D significantly reversed mitochondrial damages and cell death induced by Pb [146].

2.7. Zinc (Zn)

Zinc is an essential trace element that is required for the function of numerous enzymes and DNA-binding transcription factors. Excess zinc influx has been manifested to play a role in neuronal damage and death associated with traumatic brain injury, stroke, seizures, and neurodegenerative diseases [147][148]. Mitochondria have been identified as targets of the neurotoxic effects of zinc by reducing ATP production and increasing ROS.

Zinc exposure reduced the cellular nicotinamideademine dinucleotide (NAD+) in cultured mouse cortical neurons, followed with a progressive loss of ATP levels and subsequent cell death [149][150][151], indicating the potential inhibition of mitochondrial respiration enzyme. Indeed, several mitochondrial enzymes, including α-ketoglutarate dehydrogenase, NAD+-dependent isocitrate dehydrogenase, succinate dehydrogenase, and cytochrome c oxidase, have been demonstrated to be inhibited by zinc exposure in liver mitochondria [152][153]. Notably, by using bovine heart mitochondria, complex III, specifically the bc 1 complex, was identified as the site of Zn^{2+} binding and inhibition [154][155]. ROS generation has been found to be critical in zinc-induced neurotoxicity, demonstrated in diverse brain cell models [156][157]. As mitochondria are an important source of cellular ROS production, the influx of Zn^{2+} through Ca^{2+}-permeable AMPA/kainate channels also triggers rapid mitochondrial depolarization, leading to prolonged production of mitochondrial superoxide in cortical neurons [158].

In addition, several other mechanisms have been involved in the zinc-induced mitochondrial dysfunction. For example, extracellular zinc application stimulates the Ras/MEK/ERK pathway, which leads to zinc-induced mitochondrial dysfunction and consequent cell death in rat neurons [159]. An immediate early transcription factor, egr-1, was found to act downstream of ERK 1/2 to induce neuronal death after zinc exposure [160]. Furthermore, elevated intra-neuronal zinc impairs mitochondrial trafficking without altering morphology, which was restored by PI3k inhibitors, suggesting the role of PI3k activation in zinc-inhibited mitochondrial movement in neurons [159]. Apart from the adverse effects on neurons and glia, zinc overload also critically induced ROS formation in mitochondria and degradation of mitochondrial network in cerebral microvessels, which were mediated through Drp-1-dependent mitochondrial fission pathway, thus contributing to increased permeability of the BBB after cerebral ischemia.

Not only zinc overload, but also zinc defficiency, may impair neurological functions [161] and cause neuronal apoptosis via an intrinsic (mitochondrial) pathway in human neuroblastoma IMR-32 cells and primary rat cortical neurons [162]. Researchers have identified that the transposition of phosphorylated p53 into the mitochondria mediated zinc deficiency-induced mitochondrial alterations and apoptosis in neuronal precursor cell (NT-2 cell line) [163].

2.8. Iron (Fe)

Iron is a crucial trace metal for life and is the most abundant transition metal in the brain. It acts as a catalytic center for multiple enzymes and supports many elementary biological processes, including DNA synthesis and repair, oxygen transport, mitochondrial respiration, and neurotransmitter metabolism. Oxidative stress, iron deposition, and mitochondrial dysfunction have been considered as hallmarks of many neurodegenerative diseases, including PD, HD, and AD [164][165], and a positive feedback loop among these three factors seems to exist in neurological disorders.

Upregulation of cellular redox-active iron is directly related to increased ROS and with changes in intracellular reduction potential [166][167]. In the presence of H_2O_2, which is mainly produced by mitochondrial ETC, Fe^{2+} generates hydroxyl radicals (OH) via the Fenton reaction. The hydroxyl radical is considered to be one of the most reactive substances in biological systems because its reaction rate is limited only by its diffusion. This free radical can attack proteins, DNA, and lipid membranes, thus disrupting mitochondrial function and cellular integrity, and eventually leading to oxidative stress and cell apoptosis [168]. Iron overload promotes the production of mitochondrial ROS in SH-SY5Y cells, in an AMP-activated protein kinase (AMPK)-dependent manner [169], and caused ATP production defects, mitochondrial complex I inhibition, and mitochondrial apoptosis in primary cortical neurons [170]. In addition, mitochondria-targeted iron chelators showed protective effects against mitochondrial oxidative damage and neuronal death, both in rotenone-treated SH-SY5Y cells and the dopamine neurons from MPTP-intoxicated mice, which indirectly suggested that iron accumulation in mitochondria induced mitochondrial oxidative damages in neurons and consequent cell death [171]. Moreover, iron overload may induce Drp-1-dependent mitochondrial fragmentation by upregulating intracellular calcium. Lee et al. [172] found that in ferric ammonium citrate (FAC)-stimulated HT-22 hippocampal neuron cells, mitochondria were fragmentated by dephosphorylation of Drp1 (Ser637) and apoptotic neuronal death was increased. Notably, FAC-induced iron overload leads to intracellular calcium elevation and further activation of calcineurin, while inhibition of Ca^{2+} signals related to calcineurin prevents iron overload-induced mitochondrial fragmentation and neuronal cell death. Redox-sensitive ryanodine receptor (RyR)-mediated Ca^{2+} release also was shown to underlie the iron-induced mitochondrial fission in primary hippocampal neurons [173].

Recently, a new iron-dependent programmed cell death, namely ferroptosis, has been found to be a main driver of many neurodegenerative diseases. It is characterized by the accumulation of lipid peroxidation products and lethal ROS derived from iron metabolism and can be pharmacologically inhibited by iron chelators. Although the detailed mechanism by which iron overload promotes ferroptosis has yet to determined, it is reasonable to hypothesize that iron overload may drive the generation of hydroxyl radicals, which further react with liposomes to produce lipid peroxidation products and cause mitochondrial dysfunction, and eventually ferroptosis [174][175][176]. Although mitochondria have been shown to be vital regulators of iron homeostasis and ferroptosis in neurodegenerative diseases [177], more direct evidence targeting iron overload, mitochondrial dysfunction, and ferroptosis is still required. The mitochondria are also the site for the synthesis of iron–sulfur cluster biogenesis (ISCs) and heme prosthetic groups. There is evidence that mitochondrial ISC assembly defects may cause iron overload and consequent negative effects on cellular or mitochondrial function [178][179].

Therefore, iron accumulation induced by direct excessive iron exposure or secondary to iron overload has been demonstrated to play an important role in neurological diseases, via impairing mitochondrial function and inducing oxidative stress. Targeting chelatable iron and the consequent ROS, especially in mitochondria, appear as possible therapeutic options for age-related neurodegenerative conditions [180].

2.9. Manganese (Mn)

Mn is the 12th most abundant mineral element in the earth crust, and is both nutritionally essential and toxic in excess. Mn is an essential metal for normal growth, development, and cellular homeostasis, as well as a cofactor for multiple enzymes; for example, Mn-superoxide dismutase (Mn-SOD), pyruvate carboxylase, arginase, and glutamine synthase (GS). Manganese preferentially accumulates in tissues rich in mitochondria [181][182], and it is taken up by brain mitochondria via mitochondria Ca^{2+} uniporter [183].

Mn is known to induce mitochondrial dysfunction in the nervous system [184], including the inhibition of the enzymes of the tricarboxylic acid (TCA) cycle in human neuroblastoma (SK-N-SH) and astrocytoma (U87) cells [185] and a reduction in the activities of ETC in rat primary striatal neurons [186] and in PC12 cells [187], ultimately resulting in ATP depletion [188][189][190]

and mitochondria-mediated apoptosis [191][192][193]. Notably, these mitochondrial impairments have been found to be rescued by some antioxidants [188][189][194], indicating that oxidative stress is primarily involved in the mechanism of Mn-induced mitochondrial dysfunction.

Another cause of mitochondria-mediated apoptosis induced by Mn exposure is the induction of the MPT [195]. This process causes unrestricted proton movement across the inner mitochondrial membrane, resulting in mitochondrial swelling, mitochondrial membrane potential destruction, further production of ROS, and cellular apoptosis [188][196].

References

1. Smith, E.F.; Shaw, P.J.; De Vos, K.J. The role of mitochondria in amyotrophic lateral sclerosis. Neurosci. Lett. 2019, 710, 132933.
2. Cadonic, C.; Sabbir, M.G.; Albensi, B.C. Mechanisms of Mitochondrial Dysfunction in Alzheimer's Disease. Mol. Neurobiol. 2016, 53, 6078–6090.
3. Correia-Melo, C.; Passos, J.F. Mitochondria: Are they causal players in cellular senescence? Biochim. Biophys. Acta. Bioenerg. 2015, 1847, 1373–1379.
4. Richter, C. Oxidative damage to mitochondrial DNA and its relationship to ageing. Int. J. Biochem. Cell. Biol. 1995, 27, 647–653.
5. Mecocci, P.; Fano, G.; Fulle, S.; MacGarvey, U.; Shinobu, L.; Polidori, M.C.; Cherubini, A.; Vecchiet, J.; Senin, U.; Beal, M.F. Age-dependent increases in oxidative damage to DNA, lipids, and proteins in human skeletal muscle. Free Radic. Biol. Med. 1999, 26, 303–308.
6. Raha, S.; Robinson, B.H. Mitochondria, oxygen free radicals, disease and ageing. Trends Biochem. Sci. 2000, 25, 502–508.
7. Engl, E.; Attwell, D. Non-signalling energy use in the brain. J. Physiol. 2015, 593, 3419–3429.
8. Nicholls, D.G.; Budd, S.L. Mitochondria and neuronal survival. Physiol. Rev. 2000, 80, 315–360.
9. Rizzuto, R.; De Stefani, D.; Raffaello, A.; Mammucari, C. Mitochondria as sensors and regulators of calcium signalling. Nat. Rev. Mol. Cell. Biol. 2012, 13, 566–578.
10. Lezi, E.; Swerdlow, R.H. Mitochondria in neurodegeneration. Adv. Exp. Med. Biol. 2012, 942, 269–286.
11. Bjorklund, G.; Skalny, A.V.; Rahman, M.M.; Dadar, M.; Yassa, H.A.; Aaseth, J.; Chirumbolo, S.; Skalnaya, M.G.; Tinkov, A.A. Toxic metal(loid)-based pollutants and their possible role in autism spectrum disorder. Environ. Res. 2018, 166, 234–250.
12. Liddell, J.R. Targeting mitochondrial metal dyshomeostasis for the treatment of neurodegeneration. Neurodegener. Dis. Manag. 2015, 5, 345–364.
13. UN Environment Programme. UNEP Year Book 2011: Emerging Issues in Our Global Environment; UN Environment Programme: Nairobi, Kenya, 2011.
14. Prüss-Ustün, A.; Wolf, J.; Corván, C.; Bos, R.; Neira, M. Preventing Disease through Healthy Environments: A Global Assessment of the Burden of Disease from Environmental Risks; World Health Organization: Geneva, Switzerland, 2016.
15. Bowman, A.B.; Kwakye, G.F.; Herrero Hernandez, E.; Aschner, M. Role of manganese in neurodegenerative diseases. J. Trace Elem. Med. Biol. 2011, 25, 191–203.
16. Dusek, P.; Jankovic, J.; Le, W. Iron dysregulation in movement disorders. Neurobiol. Dis. 2012, 46, 1–18.
17. States, J.C.; Barchowsky, A.; Cartwright, I.L.; Reichard, J.F.; Futscher, B.W.; Lantz, R.C. Arsenic toxicology: Translating between experimental models and human pathology. Environ. Health Perspect. 2011, 119, 1356–1363.
18. Prakash, C.; Soni, M.; Kumar, V. Mitochondrial oxidative stress and dysfunction in arsenic neurotoxicity: A review. J. Appl. Toxicol. JAT 2016, 36, 179–188.
19. Kuivenhoven, M.; Mason, K. Arsenic Toxicity. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2020.
20. Osuna-Martinez, C.C.; Armienta, M.A.; Berges-Tiznado, M.E.; Paez-Osuna, F. Arsenic in waters, soils, sediments, and biota from Mexico: An environmental review. Sci. Total Environ. 2021, 752, 142062.
21. Brinkel, J.; Khan, M.H.; Kraemer, A. A systematic review of arsenic exposure and its social and mental health effects with special reference to Bangladesh. Int. J. Environ. Res. Public Health 2009, 6, 1609–1619.

22. Tsuji, J.S.; Garry, M.R.; Perez, V.; Chang, E.T. Low-level arsenic exposure and developmental neurotoxicity in children: A systematic review and risk assessment. Toxicology 2015, 337, 91–107.

23. Mochizuki, H. Arsenic Neurotoxicity in Humans. Int. J. Mol. Sci. 2019, 20, 3418.

24. Xi, S.; Guo, L.; Qi, R.; Sun, W.; Jin, Y.; Sun, G. Prenatal and early life arsenic exposure induced oxidative damage and altered activities and mRNA expressions of neurotransmitter metabolic enzymes in offspring rat brain. J. Biochem. Mol. Toxicol. 2010, 24, 368–378.

25. Pandey, R.; Rai, V.; Mishra, J.; Mandrah, K.; Kumar Roy, S.; Bandyopadhyay, S. From the Cover: Arsenic Induces Hippocampal Neuronal Apoptosis and Cognitive Impairments via an Up-Regulated BMP2/Smad-Dependent Reduced BDNF/TrkB Signaling in Rats. Toxicol. Sci. Off. J. Soc. Toxicol. 2017, 159, 137–158.

26. Chandravanshi, L.P.; Gupta, R.; Shukla, R.K. Arsenic-Induced Neurotoxicity by Dysfunctioning Cholinergic and Dopaminergic System in Brain of Developing Rats. Biol. Trace Elem. Res. 2019, 189, 118–133.

27. O'Bryant, S.E.; Edwards, M.; Menon, C.V.; Gong, G.; Barber, R. Long-term low-level arsenic exposure is associated with poorer neuropsychological functioning: A Project FRONTIER study. Int. J. Environ. Res. Public Health 2011, 8, 861–874.

28. Nino, S.A.; Morales-Martinez, A.; Chi-Ahumada, E.; Carrizales, L.; Salgado-Delgado, R.; Perez-Severiano, F.; Diaz-Cintra, S.; Jimenez-Capdeville, M.E.; Zarazua, S. Arsenic Exposure Contributes to the Bioenergetic Damage in an Alzheimer's Disease Model. ACS Chem. Neurosci. 2019, 10, 323–336.

29. Tyler, C.R.; Allan, A.M. The Effects of Arsenic Exposure on Neurological and Cognitive Dysfunction in Human and Rodent Studies: A Review. Curr. Environ. Health Rep. 2014, 1, 132–147.

30. Koseoglu, E.; Kutuk, B.; Nalbantoglu, O.U.; Koseoglu, R.; Kendirci, M. Arsenic and selenium measurements in nail and hair show important relationships to Alzheimer's disease in the elderly. J. Trace Elem. Med. Biol. Organ Soc. Miner. Trace Elem. 2020, 64, 126684.

31. Li, X.L.; Zhan, R.Q.; Zheng, W.; Jiang, H.; Zhang, D.F.; Shen, X.L. Positive association between soil arsenic concentration and mortality from alzheimer's disease in mainland China. J. Trace Elem. Med. Biol. Organ Soc. Miner. Trace Elem. 2020, 59, 126452.

32. Ashok, A.; Rai, N.K.; Tripathi, S.; Bandyopadhyay, S. Exposure to As-, Cd-, and Pb-mixture induces Abeta, amyloidogenic APP processing and cognitive impairments via oxidative stress-dependent neuroinflammation in young rats. Toxicol. Sci. 2015, 143, 64–80.

33. Zarazua, S.; Burger, S.; Delgado, J.M.; Jimenez-Capdeville, M.E.; Schliebs, R. Arsenic affects expression and processing of amyloid precursor protein (APP) in primary neuronal cells overexpressing the Swedish mutation of human APP. Off. J. Int. Soc. Dev. Neurosci. 2011, 29, 389–396.

34. Escudero-Lourdes, C. Toxicity mechanisms of arsenic that are shared with neurodegenerative diseases and cognitive impairment: Role of oxidative stress and inflammatory responses. Neurotoxicology 2016, 53, 223–235.

35. Sun, X.; He, Y.; Guo, Y.; Li, S.; Zhao, H.; Wang, Y.; Zhang, J.; Xing, M. Arsenic affects inflammatory cytokine expression in Gallus gallus brain tissues. BMC Vet. Res. 2017, 13, 157.

36. Yip, S.F.; Yeung, Y.M.; Tsui, E.Y. Severe neurotoxicity following arsenic therapy for acute promyelocytic leukemia: Potentiation by thiamine deficiency. Blood 2002, 99, 3481–3482.

37. Singh, A.P.; Goel, R.K.; Kaur, T. Mechanisms pertaining to arsenic toxicity. Toxicol. Int. 2011, 18, 87–93.

38. Haga, N.; Fujita, N.; Tsuruo, T. Involvement of mitochondrial aggregation in arsenic trioxide (As2O3)-induced apoptosis in human glioblastoma cells. Cancer Sci. 2005, 96, 825–833.

39. Lu, T.H.; Tseng, T.J.; Su, C.C.; Tang, F.C.; Yen, C.C.; Liu, Y.Y.; Yang, C.Y.; Wu, C.C.; Chen, K.L.; Hung, D.Z.; et al. Arsenic induces reactive oxygen species-caused neuronal cell apoptosis through JNK/ERK-mediated mitochondria-dependent and GRP 78/CHOP-regulated pathways. Toxicol. Lett. 2014, 224, 130–140.

40. Florea, A.M.; Splettstoesser, F.; Busselberg, D. Arsenic trioxide (As2O3) induced calcium signals and cytotoxicity in two human cell lines: SY-5Y neuroblastoma and 293 embryonic kidney (HEK). Toxicol. Appl. Pharmacol. 2007, 220, 292–301.

41. Zhao, F.; Liao, Y.; Jin, Y.; Li, G.; Lv, X.; Sun, G. Effects of arsenite on glutamate metabolism in primary cultured astrocytes. Toxicol. In Vitro Int. J. Publ. Assoc. BIBRA 2012, 26, 24–31.

42. Li, X.; Chan, L.; Zhang, H.; Zhang, H.; Niu, Q. Effects of arsenic poisoning on neuronal cell apoptosis and mRNA and protein expression of calpain 1, calpain 2, and cdk5/p25. Chin. J. Ind. Hyg. Occup. Dis. 2014, 32, 202–206.

43. Dwivedi, N.; Mehta, A.; Yadav, A.; Binukumar, B.K.; Gill, K.D.; Flora, S.J. MiADMSA reverses impaired mitochondrial energy metabolism and neuronal apoptotic cell death after arsenic exposure in rats. Toxicol. Appl. Pharmacol. 2011,

256, 241–248.

44. Srivastava, P.; Yadav, R.S.; Chandravanshi, L.P.; Shukla, R.K.; Dhuriya, Y.K.; Chauhan, L.K.S.; Dwivedi, H.N.; Pant, A.B.; Khanna, V.K. Unraveling the mechanism of neuroprotection of curcumin in arsenic induced cholinergic dysfunctions in rats. Toxicol. Appl. Pharmacol. 2014, 279, 428–440.
45. Wang, Y.; Tang, B.; Long, L.; Luo, P.; Xiang, W.; Li, X.; Wang, H.; Jiang, Q.; Tan, X.; Luo, S.; et al. Improvement of obesity-associated disorders by a small-molecule drug targeting mitochondria of adipose tissue macrophages. Nat. Commun. 2021, 12, 102.
46. Yadav, R.S.; Sankhwar, M.L.; Shukla, R.K.; Chandra, R.; Pant, A.B.; Islam, F.; Khanna, V.K. Attenuation of arsenic neurotoxicity by curcumin in rats. Toxicol. Appl. Pharmacol. 2009, 240, 367–376.
47. Ram Kumar, M.; Flora, S.J.; Reddy, G.R. Monoisoamyl 2,3-dimercaptosuccinic acid attenuates arsenic induced toxicity: Behavioral and neurochemical approach. Environ. Toxicol. Pharmacol. 2013, 36, 231–242.
48. Prakash, C.; Soni, M.; Kumar, V. Biochemical and Molecular Alterations Following Arsenic-Induced Oxidative Stress and Mitochondrial Dysfunction in Rat Brain. Biol. Trace Elem. Res. 2015, 167, 121–129.
49. Hughes, M.F. Arsenic toxicity and potential mechanisms of action. Toxicol. Lett. 2002, 133, 1–16.
50. Falkenberg, M.; Larsson, N.G.; Gustafsson, C.M. DNA replication and transcription in mammalian mitochondria. Ann. Rev. Biochem. 2007, 76, 679–699.
51. Hong, Y.; Piao, F.; Zhao, Y.; Li, S.; Wang, Y.; Liu, P. Subchronic exposure to arsenic decreased Sdha expression in the brain of mice. Neurotoxicology 2009, 30, 538–543.
52. Gibson, G.E.; Chen, H.L.; Xu, H.; Qiu, L.; Xu, Z.; Denton, T.T.; Shi, Q. Deficits in the mitochondrial enzyme alpha-ketoglutarate dehydrogenase lead to Alzheimer's disease-like calcium dysregulation. Neurobiol. Aging 2012, 33, 1121.e13–1121.e24.
53. Liu, J.; Zhao, H.; Wang, Y.; Shao, Y.; Zong, H.; Zeng, X.; Xing, M. Arsenic trioxide and/or copper sulfate induced apoptosis and autophagy associated with oxidative stress and perturbation of mitochondrial dynamics in the thymus of Gallus gallus. Chemosphere 2019, 219, 227–235.
54. Guo, M.; Wang, Y.; Zhao, H.; Mu, M.; Yang, X.; Fei, D.; Liu, Y.; Zong, H.; Xing, M. Oxidative damage under As3+ and/or Cu2+ stress leads to apoptosis and autophagy and may be cross-talking with mitochondrial disorders in bursa of Fabricius. J. Inorg. Biochem. 2020, 205, 110989.
55. Peraza, M.A.; Cromey, D.W.; Carolus, B.; Carter, D.E.; Gandolfi, A.J. Morphological and functional alterations in human proximal tubular cell line induced by low level inorganic arsenic: Evidence for targeting of mitochondria and initiated apoptosis. J. Appl. Toxicol. JAT 2006, 26, 356–367.
56. Zhang, K.; Zhou, Q. Toxic effects of Al-based coagulants on Brassica chinensis and Raphanus sativus growing in acid and neutral conditions. Environ. Toxicol. 2005, 20, 179–187.
57. Bertholf, R.L.; Herman, M.M.; Savory, J.; Carpenter, R.M.; Sturgill, B.C.; Katsetos, C.D.; Vandenberg, S.R.; Wills, M.R. A long-term intravenous model of aluminum maltol toxicity in rabbits: Tissue distribution, hepatic, renal, and neuronal cytoskeletal changes associated with systemic exposure. Toxicol. Appl. Pharmacol. 1989, 98, 58–74.
58. Sahin, G.; Varol, I.; Temizer, A.; Benli, K.; Demirdamar, R.; Duru, S. Determination of aluminum levels in the kidney, liver, and brain of mice treated with aluminum hydroxide. Biol. Trace Elem. Res. 1994, 41, 129–135.
59. Promyo, K.; Iqbal, F.; Chaidee, N.; Chetsawang, B. Aluminum chloride-induced amyloid beta accumulation and endoplasmic reticulum stress in rat brain are averted by melatonin. Food Chem. Toxicol. Int. J. Pub. Br. Ind. Biol. Res. Assoc. 2020, 146, 111829.
60. Kumar, V.; Gill, K.D. Oxidative stress and mitochondrial dysfunction in aluminium neurotoxicity and its amelioration: A review. Neurotoxicology 2014, 41, 154–166.
61. Al-Otaibi, S.S.; Arafah, M.M.; Sharma, B.; Alhomida, A.S.; Siddiqi, N.J. Synergistic Effect of Quercetin and alpha-Lipoic Acid on Aluminium Chloride Induced Neurotoxicity in Rats. J. Toxicol. 2018, 2018, 2817036.
62. Nie, J.; Lv, S.; Fu, X.; Niu, Q. Effects of Al Exposure on Mitochondrial Dynamics in Rat Hippocampus. Neurotox. Res. 2019, 36, 334–346.
63. Liu, H.; Zhang, W.; Fang, Y.; Yang, H.; Tian, L.; Li, K.; Lai, W.; Bian, L.; Lin, B.; Liu, X.; et al. Neurotoxicity of aluminum oxide nanoparticles and their mechanistic role in dopaminergic neuron injury involving p53-related pathways. J. Hazard. Mater. 2020, 392, 122312.
64. Altmann, P.; Cunningham, J.; Dhanesha, U.; Ballard, M.; Thompson, J.; Marsh, F. Disturbance of cerebral function in people exposed to drinking water contaminated with aluminium sulphate: Retrospective study of the Camelford water incident. BMJ 1999, 319, 807–811.

65. Kandimalla, R.; Vallamkondu, J.; Corgiat, E.B.; Gill, K.D. Understanding Aspects of Aluminum Exposure in Alzheimer's Disease Development. Brain Pathol. 2016, 26, 139–154.

66. Yasui, M.; Kihira, T.; Ota, K. Calcium, magnesium and aluminum concentrations in Parkinson's disease. Neurotoxicology 1992, 13, 593–600.

67. Sanchez-Iglesias, S.; Mendez-Alvarez, E.; Iglesias-Gonzalez, J.; Munoz-Patino, A.; Sanchez-Sellero, I.; Labandeira-Garcia, J.L.; Soto-Otero, R. Brain oxidative stress and selective behaviour of aluminium in specific areas of rat brain: Potential effects in a 6-OHDA-induced model of Parkinson's disease. J. Neurochem. 2009, 109, 879–888.

68. Maya, S.; Prakash, T.; Madhu, K.D.; Goli, D. Multifaceted effects of aluminium in neurodegenerative diseases: A review. Biomed. Pharmacother. 2016, 83, 746–754.

69. Maya, S.; Prakash, T.; Goli, D. Evaluation of neuroprotective effects of wedelolactone and gallic acid on aluminium-induced neurodegeneration: Relevance to sporadic amyotrophic lateral sclerosis. Eur. J. Pharmacol. 2018, 835, 41–51.

70. McLachlan, D.R.C.; Bergeron, C.; Alexandrov, P.N.; Walsh, W.J.; Pogue, A.I.; Percy, M.E.; Kruck, T.P.A.; Fang, Z.; Sharfman, N.M.; Jaber, V.; et al. Aluminum in Neurological and Neurodegenerative Disease. Mol. Neurobiol. 2019, 56, 1531–1538.

71. Huang, T.; Guo, W.; Wang, Y.; Chang, L.; Shang, N.; Chen, J.; Fan, R.; Zhang, L.; Gao, X.; Niu, Q.; et al. Involvement of Mitophagy in Aluminum Oxide Nanoparticle-Induced Impairment of Learning and Memory in Mice. Neurotox. Res. 2020, 39, 378–391.

72. Rao, K.S.; Rao, G.V. Effect of aluminium (Al) on brain mitochondrial monoamine oxidase-A (MAO-A) activity—An in vitro kinetic study. Mol. Cell. Biochem. 1994, 137, 57–60.

73. Bosetti, F.; Solaini, G.; Tendi, E.A.; Chikhale, E.G.; Chandrasekaran, K.; Rapoport, S.I. Mitochondrial cytochrome c oxidase subunit III is selectively down-regulated by aluminum exposure in PC12S cells. Neuroreport 2001, 12, 721–724.

74. Iranpak, F.; Saberzadeh, J.; Vessal, M.; Takhshid, M.A. Sodium valproate ameliorates aluminum-induced oxidative stress and apoptosis of PC12 cells. Iran. J. Basic Med. Sci. 2019, 22, 1353–1358.

75. Rahmani, S.; Saberzadeh, J.; Takhshid, M.A. The Hydroalcoholic Extract of Saffron Protects PC12 Cells against Aluminum-Induced Cell Death and Oxidative Stress in Vitro. Iran. J. Med. Sci. 2020, 45, 59–66.

76. Wang, H.; Shao, B.; Yu, H.; Xu, F.; Wang, P.; Yu, K.; Han, Y.; Song, M.; Li, Y.; Cao, Z. Neuroprotective role of hyperforin on aluminum maltolate-induced oxidative damage and apoptosis in PC12 cells and SH-SY5Y cells. Chem. Biol. Interact. 2019, 299, 15–26.

77. Tsialtas, I.; Gorgogietas, V.A.; Michalopoulou, M.; Komninou, A.; Liakou, E.; Georgantopoulos, A.; Kalousi, F.D.; Karra, A.G.; Protopapa, E.; Psarra, A.G. Neurotoxic effects of aluminum are associated with its interference with estrogen receptors signaling. Neurotoxicology 2020, 77, 114–126.

78. Wang, P.; Wu, Q.; Wu, W.; Li, H.; Guo, Y.; Yu, P.; Gao, G.; Shi, Z.; Zhao, B.; Chang, Y.Z. Mitochondrial Ferritin Deletion Exacerbates beta-Amyloid-Induced Neurotoxicity in Mice. Oxid. Med. Cell. Longev. 2017, 2017, 1020357.

79. Tuneva, J.; Chittur, S.; Boldyrev, A.A.; Birman, I.; Carpenter, D.O. Cerebellar granule cell death induced by aluminum. Neurotox. Res. 2006, 9, 297–304.

80. Rui, D.; Yongjian, Y. Aluminum chloride induced oxidative damage on cells derived from hippocampus and cortex of ICR mice. Brain Res. 2010, 1324, 96–102.

81. Stevanovic, I.D.; Jovanovic, M.D.; Colic, M.; Ninkovic, M.; Jelenkovic, A.; Mihajlovic, R. Cytochrome c oxidase activity and nitric oxide synthase in the rat brain following aluminium intracerebral application. Folia Neuropathol. 2013, 51, 140–146.

82. Ghribi, O.; Herman, M.M.; Forbes, M.S.; DeWitt, D.A.; Savory, J. GDNF protects against aluminum-induced apoptosis in rabbits by upregulating Bcl-2 and Bcl-XL and inhibiting mitochondrial Bax translocation. Neurobiol. Dis. 2001, 8, 764–773.

83. Kumar, V.; Bal, A.; Gill, K.D. Impairment of mitochondrial energy metabolism in different regions of rat brain following chronic exposure to aluminium. Brain Res. 2008, 1232, 94–103.

84. Kumar, V.; Bal, A.; Gill, K.D. Susceptibility of mitochondrial superoxide dismutase to aluminium induced oxidative damage. Toxicology 2009, 255, 117–123.

85. Sharma, D.R.; Wani, W.Y.; Sunkaria, A.; Kandimalla, R.J.; Sharma, R.K.; Verma, D.; Bal, A.; Gill, K.D. Quercetin attenuates neuronal death against aluminum-induced neurodegeneration in the rat hippocampus. Neuroscience 2016, 324, 163–176.

86. Prakash, A.; Shur, B.; Kumar, A. Naringin protects memory impairment and mitochondrial oxidative damage against aluminum-induced neurotoxicity in rats. Int. J. Neurosci. 2013, 123, 636–645.
87. Prakash, A.; Kumar, A. Mitoprotective effect of Centella asiatica against aluminum-induced neurotoxicity in rats: Possible relevance to its anti-oxidant and anti-apoptosis mechanism. Neurol. Sci. Off. J. Ital. Neurol. Soc. Ital. Soc. Clin. Neurophysiol. 2013, 34, 1403–1409.
88. Kumar, A.; Dogra, S.; Prakash, A. Protective effect of curcumin (Curcuma longa), against aluminium toxicity: Possible behavioral and biochemical alterations in rats. Behav. Brain Res. 2009, 205, 384–390.
89. Wang, C.; Cai, X.; Hu, W.; Li, Z.; Kong, F.; Chen, X.; Wang, D. Investigation of the neuroprotective effects of crocin via antioxidant activities in HT22 cells and in mice with Alzheimer's disease. Int. J. Mol. Med. 2019, 43, 956–966.
90. Cobine, P.A.; Pierrel, F.; Winge, D.R. Copper trafficking to the mitochondrion and assembly of copper metalloenzymes. Biochim. Biophys. Acta 2006, 1763, 759–772.
91. Zischka, H.; Einer, C. Mitochondrial copper homeostasis and its derailment in Wilson disease. Int. J. Biochem. Cell. Biol. 2018, 102, 71–75.
92. Baker, Z.N.; Cobine, P.A.; Leary, S.C. The mitochondrion: A central architect of copper homeostasis. Metallomics 2017, 9, 1501–1512.
93. Horn, D.; Barrientos, A. Mitochondrial copper metabolism and delivery to cytochrome c oxidase. IUBMB Life 2008, 60, 421–429.
94. Borchard, S.; Bork, F.; Rieder, T.; Eberhagen, C.; Popper, B.; Lichtmannegger, J.; Schmitt, S.; Adamski, J.; Klingenspor, M.; Weiss, K.H.; et al. The exceptional sensitivity of brain mitochondria to copper. Toxicol. In Vitro 2018, 51, 11–22.
95. Behzadfar, L.; Abdollahi, M.; Sabzevari, O.; Hosseini, R.; Salimi, A.; Naserzadeh, P.; Sharifzadeh, M.; Pourahmad, J. Potentiating role of copper on spatial memory deficit induced by beta amyloid and evaluation of mitochondrial function markers in the hippocampus of rats. Metallomics 2017, 9, 969–980.
96. Chen, C.; Jiang, X.; Li, Y.; Yu, H.; Li, S.; Zhang, Z.; Xu, H.; Yang, Y.; Liu, G.; Zhu, F.; et al. Low-dose oral copper treatment changes the hippocampal phosphoproteomic profile and perturbs mitochondrial function in a mouse model of Alzheimer's disease. Free Radic Biol. Med. 2019, 135, 144–156.
97. Liddell, J.R.; White, A.R. Nexus between mitochondrial function, iron, copper and glutathione in Parkinson's disease. Neurochem. Int. 2018, 117, 126–138.
98. Cruces-Sande, A.; Méndez-Álvarez, E.; Soto-Otero, R. Copper increases the ability of 6-hydroxydopamine to generate oxidative stress and the ability of ascorbate and glutathione to potentiate this effect: Potential implications in Parkinson's disease. J. Neurochem. 2017, 141, 738–749.
99. Reddy, P.V.; Rao, K.V.; Norenberg, M.D. The mitochondrial permeability transition, and oxidative and nitrosative stress in the mechanism of copper toxicity in cultured neurons and astrocytes. Lab. Investig. 2008, 88, 816–830.
100. Cannino, G.; Ferruggia, E.; Luparello, C.; Rinaldi, A.M. Cadmium and mitochondria. Mitochondrion 2009, 9, 377–384.
101. Binte Hossain, K.F.; Rahman, M.M.; Sikder, M.T.; Saito, T.; Hosokawa, T.; Kurasaki, M. Inhibitory effects of selenium on cadmium-induced cytotoxicity in PC12 cells via regulating oxidative stress and apoptosis. Food Chem. Toxicol. 2018, 114, 180–189.
102. Xu, C.; Wang, X.; Zhu, Y.; Dong, X.; Liu, C.; Zhang, H.; Liu, L.; Huang, S.; Chen, L. Rapamycin ameliorates cadmium-induced activation of MAPK pathway and neuronal apoptosis by preventing mitochondrial ROS inactivation of PP2A. Neuropharmacology 2016, 105, 270–284.
103. Gupta, R.; Shukla, R.K.; Chandravanshi, L.P.; Srivastava, P.; Dhuriya, Y.K.; Shanker, J.; Singh, M.P.; Pant, A.B.; Khanna, V.K. Protective Role of Quercetin in Cadmium-Induced Cholinergic Dysfunctions in Rat Brain by Modulating Mitochondrial Integrity and MAP Kinase Signaling. Mol. Neurobiol. 2017, 54, 4560–4583.
104. Xu, M.Y.; Wang, P.; Sun, Y.J.; Yang, L.; Wu, Y.J. Joint toxicity of chlorpyrifos and cadmium on the oxidative stress and mitochondrial damage in neuronal cells. Food Chem. Toxicol. 2017, 103, 246–252.
105. Yang, M.; Li, C.; Yang, S.; Xiao, Y.; Xiong, X.; Chen, W.; Zhao, H.; Zhang, Q.; Han, Y.; Sun, L. Mitochondria-Associated ER Membranes—The Origin Site of Autophagy. Front. Cell. Dev. Biol. 2020, 8, 595.
106. Che, L.; Yang, C.L.; Chen, Y.; Wu, Z.L.; Du, Z.B.; Wu, J.S.; Gan, C.L.; Yan, S.P.; Huang, J.; Guo, N.J.; et al. Mitochondrial redox-driven mitofusin 2 S-glutathionylation promotes neuronal necroptosis via disrupting ER-mitochondria crosstalk in cadmium-induced neurotoxicity. Chemosphere 2021, 262, 127878.
107. Xie, L.L.; Shi, F.; Tan, Z.; Li, Y.; Bode, A.M.; Cao, Y. Mitochondrial network structure homeostasis and cell death. Cancer Sci. 2018, 109, 3686–3694.

108. Modi, H.R.; Katyare, S.S. Cadmium exposure-induced alterations in the lipid/phospholipids composition of rat brain microsomes and mitochondria. Neurosci. Lett. 2009, 464, 108–112.

109. Kumar, R.; Agarwal, A.K.; Seth, P.K. Oxidative stress-mediated neurotoxicity of cadmium. Toxicol. Lett. 1996, 89, 65–69.

110. Choong, G.; Liu, Y.; Templeton, D.M. Interplay of calcium and cadmium in mediating cadmium toxicity. Chem. Biol. Interact. 2014, 211, 54–65.

111. Rahman, M.M.; Ukiana, J.; Uson-Lopez, R.; Sikder, M.T.; Saito, T.; Kurasaki, M. Cytotoxic effects of cadmium and zinc co-exposure in PC12 cells and the underlying mechanism. Chem. Biol. Interact. 2017, 269, 41–49.

112. Clarkson, T.W. The three modern faces of mercury. Environ. Health Perspect. 2002, 110, 11–23.

113. Clarkson, T.W.; Magos, L. The toxicology of mercury and its chemical compounds. Crit. Rev. Toxicol. 2006, 36, 609–662.

114. Dórea, J.G. Persistent, bioaccumulative and toxic substances in fish: Human health considerations. Sci. Total Environ. 2008, 400, 93–114.

115. Chang, L.W.; Hartmann, H.A. Electron microscopic histochemical study on the localization and distribution of mercury in the nervous system after mercury intoxication. Exp. Neurol. 1972, 35, 122–137.

116. Oliveira, L.F.; Rodrigues, L.D.; Cardillo, G.M.; Nejm, M.B.; Guimarães-Marques, M.; Reyes-Garcia, S.Z.; Zuqui, K.; Vassallo, D.V.; Fiorini, A.C.; Scorza, C.A.; et al. Deleterious effects of chronic mercury exposure on in vitro LTP, memory process, and oxidative stress. Environ. Sci. Pollut. Res. Int. 2020, 27, 7559–7569.

117. Liu, W.; Yang, T.; Xu, Z.; Xu, B.; Deng, Y. Methyl-mercury induces apoptosis through ROS-mediated endoplasmic reticulum stress and mitochondrial apoptosis pathways activation in rat cortical neurons. Free Radic. Res. 2019, 53, 26–44.

118. Chang, J.; Yang, B.; Zhou, Y.; Yin, C.; Liu, T.; Qian, H.; Xing, G.; Wang, S.; Li, F.; Zhang, Y.; et al. Acute Methylmercury Exposure and the Hypoxia-Inducible Factor-1α Signaling Pathway under Normoxic Conditions in the Rat Brain and Astrocytes in Vitro. Environ. Health Perspect. 2019, 127, 127006.

119. Yang, B.; Yin, C.; Zhou, Y.; Wang, Q.; Jiang, Y.; Bai, Y.; Qian, H.; Xing, G.; Wang, S.; Li, F.; et al. Curcumin protects against methylmercury-induced cytotoxicity in primary rat astrocytes by activating the Nrf2/ARE pathway independently of PKCδ. Toxicology 2019, 425, 152248.

120. Shao, Y.; Wang, L.; Langlois, P.; Mironov, G.; Chan, H.M. Proteome changes in methylmercury-exposed mouse primary cerebellar granule neurons and astrocytes. Toxicol. In Vitro Int. J. Pub. Assoc. BIBRA 2019, 57, 96–104.

121. Ni, M.; Li, X.; Yin, Z.; Sidoryk-Węgrzynowicz, M.; Jiang, H.; Farina, M.; Rocha, J.B.; Syversen, T.; Aschner, M. Comparative study on the response of rat primary astrocytes and microglia to methylmercury toxicity. Glia 2011, 59, 810–820.

122. Zhang, J.; Zhang, X.; Wen, C.; Duan, Y.; Zhang, H. Lotus seedpod proanthocyanidins protect against neurotoxicity after methyl-mercuric chloride injury. Ecotoxicol. Environ. Saf. 2019, 183, 109560.

123. Shanker, G.; Syversen, T.; Aschner, J.L.; Aschner, M. Modulatory effect of glutathione status and antioxidants on methylmercury-induced free radical formation in primary cultures of cerebral astrocytes. Mol. Brain Res. 2005, 137, 11–22.

124. Ly, J.D.; Grubb, D.R.; Lawen, A. The mitochondrial membrane potential (deltapsi(m)) in apoptosis; an update. Apoptosis 2003, 8, 115–128.

125. Yin, Z.; Milatovic, D.; Aschner, J.L.; Syversen, T.; Rocha, J.B.; Souza, D.O.; Sidoryk, M.; Albrecht, J.; Aschner, M. Methylmercury induces oxidative injury, alterations in permeability and glutamine transport in cultured astrocytes. Brain Res. 2007, 1131, 1–10.

126. Yin, Z.; Lee, E.; Ni, M.; Jiang, H.; Milatovic, D.; Rongzhu, L.; Farina, M.; Rocha, J.B.; Aschner, M. Methylmercury-induced alterations in astrocyte functions are attenuated by ebselen. Neurotoxicology 2011, 32, 291–299.

127. Jacob, S.; Thangarajan, S. Fisetin impedes developmental methylmercury neurotoxicity via downregulating apoptotic signalling pathway and upregulating Rho GTPase signalling pathway in hippocampus of F(1) generation rats. Int. J. Dev. Neurosci. Off. J. Int. Soc. Dev. Neurosci. 2018, 69, 88–96.

128. Allen, J.W.; Shanker, G.; Tan, K.H.; Aschner, M. The Consequences of Methylmercury Exposure on Interactive Functions between Astrocytes and Neurons. Neurotoxicology 2002, 23, 755–759.

129. Li, Z.G.; Zhou, F.K.; Yin, A.M.; Gao, Y.Y.; Jiang, X.; Liu, S.S.; Zhang, Y.Y.; Bo, D.D.; Xie, J.; Jia, Q.Y.; et al. Cellular damage of low-dose combined exposure to mercury, lead and cadmium on hippocampal neurons in rats. Chin. J. Prev. Med. 2018, 52, 976–982.

130. Dreiem, A.; Seegal, R.F. Methylmercury-induced changes in mitochondrial function in striatal synaptosomes are calcium-dependent and ROS-independent. Neurotoxicol. 2007, 28, 720–726.

131. Pivovarova, N.B.; Nguyen, H.V.; Winters, C.A.; Brantner, C.A.; Smith, C.L.; Andrews, S.B. Excitotoxic calcium overload in a subpopulation of mitochondria triggers delayed death in hippocampal neurons. J. Neurosci. Off. J. Soc. Neurosci. 2004, 24, 5611–5622.

132. Calvo, M.; Villalobos, C.; Núñez, L. Calcium imaging in neuron cell death. Methods Mol. Biol. 2015, 1254, 73–85.

133. Ramanathan, G.; Atchison, W.D. Ca2+ entry pathways in mouse spinal motor neurons in culture following in vitro exposure to methylmercury. Neurotoxicology 2011, 32, 742–750.

134. Vendrell, I.; Carrascal, M.; Vilaró, M.T.; Abián, J.; Rodríguez-Farré, E.; Suñol, C. Cell viability and proteomic analysis in cultured neurons exposed to methylmercury. Hum. Exp. Toxicol. 2007, 26, 263–272.

135. Bittencourt, L.O.; Dionizio, A.; Nascimento, P.C.; Puty, B.; Leão, L.K.R.; Luz, D.A.; Silva, M.C.F.; Amado, L.L.; Leite, A.; Buzalaf, M.R.; et al. Proteomic approach underlying the hippocampal neurodegeneration caused by low doses of methylmercury after long-term exposure in adult rats. Metallomics 2019, 11, 390–403.

136. Sanders, T.; Liu, Y.; Buchner, V.; Tchounwou, P.B. Neurotoxic effects and biomarkers of lead exposure: A review. Rev. Environ. Health 2009, 24, 15–45.

137. Bakulski, K.M.; Rozek, L.S.; Dolinoy, D.C.; Paulson, H.L.; Hu, H. Alzheimer's disease and environmental exposure to lead: The epidemiologic evidence and potential role of epigenetics. Curr. Alzheimer Res. 2012, 9, 563–573.

138. Senut, M.C.; Cingolani, P.; Sen, A.; Kruger, A.; Shaik, A.; Hirsch, H.; Suhr, S.T.; Ruden, D. Epigenetics of early-life lead exposure and effects on brain development. Epigenomics 2012, 4, 665–674.

139. Dórea, J.G. Environmental exposure to low-level lead (Pb) co-occurring with other neurotoxicants in early life and neurodevelopment of children. Environ. Res. 2019, 177, 108641.

140. Mattalloni, M.S.; Deza-Ponzio, R.; Albrecht, P.A.; Fernandez-Hubeid, L.E.; Cancela, L.M.; Virgolini, M.B. Brain ethanol-metabolizing enzymes are differentially expressed in lead-exposed animals after voluntary ethanol consumption: Pharmacological approaches. Neurotoxicology 2019, 75, 174–185.

141. Devi, C.B.; Reddy, G.H.; Prasanthi, R.P.; Chetty, C.S.; Reddy, G.R. Developmental lead exposure alters mitochondrial monoamine oxidase and synaptosomal catecholamine levels in rat brain. Int. J. Dev. Neurosci. Off. J. Int. Soc. Dev. Neurosci. 2005, 23, 375–381.

142. Gąssowska, M.; Baranowska-Bosiacka, I.; Moczydłowska, J.; Frontczak-Baniewicz, M.; Gewartowska, M.; Strużyńska, L.; Gutowska, I.; Chlubek, D.; Adamczyk, A. Perinatal exposure to lead (Pb) induces ultrastructural and molecular alterations in synapses of rat offspring. Toxicology 2016, 373, 13–29.

143. Thangarajan, S.; Vedagiri, A.; Somasundaram, S.; Sakthimanogaran, R.; Murugesan, M. Neuroprotective effect of morin on lead acetate-induced apoptosis by preventing cytochrome c translocation via regulation of Bax/Bcl-2 ratio. Neurotoxicol. Teratol. 2018, 66, 35–45.

144. Zhu, Y.; Jiao, X.; An, Y.; Li, S.; Teng, X. Selenium against lead-induced apoptosis in chicken nervous tissues via mitochondrial pathway. Oncotarget 2017, 8, 108130–108145.

145. He, W.; Li, Y.; Tian, J.; Jiang, N.; Du, B.; Peng, Y. Optimized mixture of As, Cd and Pb induce mitochondria-mediated apoptosis in C6-glioma via astroglial activation, inflammation and P38-MAPK. Am. J. Cancer Res. 2015, 5, 2396–2408.

146. Ye, F.; Li, X.; Li, F.; Li, J.; Chang, W.; Yuan, J.; Chen, J. Cyclosporin A protects against Lead neurotoxicity through inhibiting mitochondrial permeability transition pore opening in nerve cells. Neurotoxicology 2016, 57, 203–213.

147. Szewczyk, B. Zinc homeostasis and neurodegenerative disorders. Front. Aging Neurosci. 2013, 5, 33.

148. Kawahara, M.; Tanaka, K.I.; Kato-Negishi, M. Zinc, Carnosine, and Neurodegenerative Diseases. Nutrients 2018, 10, 147.

149. Sheline, C.T.; Behrens, M.M.; Choi, D.W. Zinc-induced cortical neuronal death: Contribution of energy failure attributable to loss of NAD(+) and inhibition of glycolysis. J. Neurosci. Off. J. Soc. Neurosci. 2000, 20, 3139–3146.

150. Cai, A.L.; Zipfel, G.J.; Sheline, C.T. Zinc neurotoxicity is dependent on intracellular NAD levels and the sirtuin pathway. Eur. J. Neurosci. 2006, 24, 2169–2176.

151. Sheline, C.T.; Cai, A.L.; Zhu, J.; Shi, C. Serum or target deprivation-induced neuronal death causes oxidative neuronal accumulation of Zn2+ and loss of NAD+. Eur. J. Neurosci. 2010, 32, 894–904.

152. Brown, A.M.; Kristal, B.S.; Effron, M.S.; Shestopalov, A.I.; Ullucci, P.A.; Sheu, K.F.; Blass, J.P.; Cooper, A.J. Zn2+ inhibits alpha-ketoglutarate-stimulated mitochondrial respiration and the isolated alpha-ketoglutarate dehydrogenase complex. J. Biol. Chem. 2000, 275, 13441–13447.

153. Lemire, J.; Mailloux, R.; Appanna, V.D. Zinc toxicity alters mitochondrial metabolism and leads to decreased ATP production in hepatocytes. J. Appl. Toxicol. JAT 2008, 28, 175–182.

154. Lorusso, M.; Cocco, T.; Sardanelli, A.M.; Minuto, M.; Bonomi, F.; Papa, S. Interaction of Zn2+ with the bovine-heart mitochondrial bc1 complex. Eur. J. Biochem. 1991, 197, 555–561.

155. Link, T.A.; von Jagow, G. Zinc ions inhibit the QP center of bovine heart mitochondrial bc1 complex by blocking a protonatable group. J. Biol. Chem. 1995, 270, 25001–25006.

156. Manev, H.; Kharlamov, E.; Uz, T.; Mason, R.P.; Cagnoli, C.M. Characterization of zinc-induced neuronal death in primary cultures of rat cerebellar granule cells. Exp. Neurol. 1997, 146, 171–178.

157. Kim, E.Y.; Koh, J.Y.; Kim, Y.H.; Sohn, S.; Joe, E.; Gwag, B.J. Zn2+ entry produces oxidative neuronal necrosis in cortical cell cultures. Eur. J. Neurosci. 1999, 11, 327–334.

158. Sensi, S.L.; Yin, H.Z.; Carriedo, S.G.; Rao, S.S.; Weiss, J.H. Preferential Zn2+ influx through Ca2+-permeable AMPA/kainate channels triggers prolonged mitochondrial superoxide production. Proc. Natl. Acad. Sci. USA 1999, 96, 2414–2419.

159. He, K.; Aizenman, E. ERK signaling leads to mitochondrial dysfunction in extracellular zinc-induced neurotoxicity. J. Neurochem. 2010, 114, 452–461.

160. Park, J.A.; Koh, J.Y. Induction of an immediate early gene egr-1 by zinc through extracellular signal-regulated kinase activation in cortical culture: Its role in zinc-induced neuronal death. J. Neurochem. 1999, 73, 450–456.

161. Prasad, A.S. Discovery of human zinc deficiency: Its impact on human health and disease. Adv. Nutr. 2013, 4, 176–190.

162. Adamo, A.M.; Zago, M.P.; Mackenzie, G.G.; Aimo, L.; Keen, C.L.; Keenan, A.; Oteiza, P.I. The role of zinc in the modulation of neuronal proliferation and apoptosis. Neurotox. Res. 2010, 17, 1–14.

163. Seth, R.; Corniola, R.S.; Gower-Winter, S.D.; Morgan, T.J., Jr.; Bishop, B.; Levenson, C.W. Zinc deficiency induces apoptosis via mitochondrial p53- and caspase-dependent pathways in human neuronal precursor cells. J. Trace Elem. Med. Biol. Organ Soc. Miner. Trace Elem. 2015, 30, 59–65.

164. Li, L.B.; Chai, R.; Zhang, S.; Xu, S.F.; Zhang, Y.H.; Li, H.L.; Fan, Y.G.; Guo, C. Iron Exposure and the Cellular Mechanisms Linked to Neuron Degeneration in Adult Mice. Cells 2019, 8, 198.

165. Jiang, H.; Wang, J.; Rogers, J.; Xie, J. Brain Iron Metabolism Dysfunction in Parkinson's Disease. Mol. Neurobiol. 2017, 54, 3078–3101.

166. Kruszewski, M. Labile iron pool: The main determinant of cellular response to oxidative stress. Mutat. Res. 2003, 531, 81–92.

167. Núñez, M.T.; Gallardo, V.; Muñoz, P.; Tapia, V.; Esparza, A.; Salazar, J.; Speisky, H. Progressive iron accumulation induces a biphasic change in the glutathione content of neuroblastoma cells. Free Radic. Biol. Med. 2004, 37, 953–960.

168. Lipinski, B. Hydroxyl radical and its scavengers in health and disease. Oxid. Med. Cell. Longev. 2011, 2011, 809696.

169. Huang, H.; Chen, J.; Lu, H.; Zhou, M.; Chai, Z.; Hu, Y. Iron-induced generation of mitochondrial ROS depends on AMPK activity. Biomet. Int. J. Met. Ions Biol. Biochem. Med. 2017, 30, 623–628.

170. Huang, X.T.; Liu, X.; Ye, C.Y.; Tao, L.X.; Zhou, H.; Zhang, H.Y. Iron-induced energy supply deficiency and mitochondrial fragmentation in neurons. J. Neurochem. 2018, 147, 816–830.

171. Mena, N.P.; García-Beltrán, O.; Lourido, F.; Urrutia, P.J.; Mena, R.; Castro-Castillo, V.; Cassels, B.K.; Núñez, M.T. The novel mitochondrial iron chelator 5-((methylamino)methyl)-8-hydroxyquinoline protects against mitochondrial-induced oxidative damage and neuronal death. Biochem. Biophys. Res. Commun. 2015, 463, 787–792.

172. Lee, D.G.; Park, J.; Lee, H.S.; Lee, S.R.; Lee, D.S. Iron overload-induced calcium signals modulate mitochondrial fragmentation in HT-22 hippocampal neuron cells. Toxicology 2016, 365, 17–24.

173. Sanmartín, C.D.; Paula-Lima, A.C.; García, A.; Barattini, P.; Hartel, S.; Núñez, M.T.; Hidalgo, C. Ryanodine receptor-mediated Ca2+ release underlies iron-induced mitochondrial fission and stimulates mitochondrial Ca2+ uptake in primary hippocampal neurons. Front. Mol. Neurosci. 2014, 7, 13.

174. Liu, T.; Liu, W.; Zhang, M.; Yu, W.; Gao, F.; Li, C.; Wang, S.B.; Feng, J.; Zhang, X.Z. Ferrous-Supply-Regeneration Nanoengineering for Cancer-Cell-Specific Ferroptosis in Combination with Imaging-Guided Photodynamic Therapy. ACS Nano 2018, 12, 12181–12192.

175. Gao, M.; Yi, J.; Zhu, J.; Minikes, A.M.; Monian, P.; Thompson, C.B.; Jiang, X. Role of Mitochondria in Ferroptosis. Mol. Cell. 2019, 73, 354–363.

176. Sumneang, N.; Siri-Angkul, N.; Kumfu, S.; Chattipakorn, S.C.; Chattipakorn, N. The effects of iron overload on mitochondrial function, mitochondrial dynamics, and ferroptosis in cardiomyocytes. Arch. Biochem. Biophys. 2020, 680, 108241.

177. Zhou, J.; Jin, Y.; Lei, Y.; Liu, T.; Wan, Z.; Meng, H.; Wang, H. Ferroptosis Is Regulated by Mitochondria in Neurodegenerative Diseases. Neuro Degener. Dis. 2020, 20, 20–34.

178. Dong, Y.; Zhang, D.; Yu, Q.; Zhao, Q.; Xiao, C.; Zhang, K.; Jia, C.; Chen, S.; Zhang, B.; Zhang, B.; et al. Loss of Ssq1 leads to mitochondrial dysfunction, activation of autophagy and cell cycle arrest due to iron overload triggered by mitochondrial iron-sulfur cluster assembly defects in Candida albicans. Int. J. Biochem. Cell Biol. 2017, 85, 44–55.

179. Maio, N.; Rouault, T.A. Iron-sulfur cluster biogenesis in mammalian cells: New insights into the molecular mechanisms of cluster delivery. Biochim. Biophys. Acta 2015, 1853, 1493–1512.

180. Isaya, G. Mitochondrial iron-sulfur cluster dysfunction in neurodegenerative disease. Front. Pharmacol. 2014, 5, 29.

181. Maynard, L.S.; Cotzias, G.C. The partition of manganese among organs and intracellular organelles of the rat. J. Biol. Chem. 1955, 214, 489–495.

182. Gavin, C.E.; Gunter, K.K.; Gunter, T.E. Manganese and calcium transport in mitochondria: Implications for manganese toxicity. Neurotoxicology 1999, 20, 445–453.

183. Gunter, T.E.; Puskin, J.S. Manganous ion as a spin label in studies of mitochondrial uptake of manganese. Biophys. J. 1972, 12, 625–635.

184. Gavin, C.E.; Gunter, K.K.; Gunter, T.E. Manganese and calcium efflux kinetics in brain mitochondria. Relevance to manganese toxicity. Biochem. J. 1990, 266, 329–334.

185. Malthankar, G.V.; White, B.K.; Bhushan, A.; Daniels, C.K.; Rodnick, K.J.; Lai, J.C. Differential lowering by manganese treatment of activities of glycolytic and tricarboxylic acid (TCA) cycle enzymes investigated in neuroblastoma and astrocytoma cells is associated with manganese-induced cell death. Neurochem. Res. 2004, 29, 709–717.

186. Malecki, E.A. Manganese toxicity is associated with mitochondrial dysfunction and DNA fragmentation in rat primary striatal neurons. Brain Res. Bull. 2001, 55, 225–228.

187. Galvani, P.; Fumagalli, P.; Santagostino, A. Vulnerability of mitochondrial complex I in PC12 cells exposed to manganese. Eur. J. Pharmacol. 1995, 293, 377–383.

188. Ahmadi, N.; Ghanbarinejad, V.; Ommati, M.M.; Jamshidzadeh, A.; Heidari, R. Taurine prevents mitochondrial membrane permeabilization and swelling upon interaction with manganese: Implication in the treatment of cirrhosis-associated central nervous system complications. J. Biochem. Mol. Toxicol. 2018, 32, e22216.

189. Sarkar, S.; Malovic, E.; Harischandra, D.S.; Ngwa, H.A.; Ghosh, A.; Hogan, C.; Rokad, D.; Zenitsky, G.; Jin, H.; Anantharam, V.; et al. Manganese exposure induces neuroinflammation by impairing mitochondrial dynamics in astrocytes. Neurotoxicology 2018, 64, 204–218.

190. Sarkar, S.; Rokad, D.; Malovic, E.; Luo, J.; Harischandra, D.S.; Jin, H.; Anantharam, V.; Huang, X.; Lewis, M.; Kanthasamy, A.; et al. Manganese activates NLRP3 inflammasome signaling and propagates exosomal release of ASC in microglial cells. Sci. Signal 2019, 12.

191. Gonzalez, L.E.; Juknat, A.A.; Venosa, A.J.; Verrengia, N.; Kotler, M.L. Manganese activates the mitochondrial apoptotic pathway in rat astrocytes by modulating the expression of proteins of the Bcl-2 family. Neurochem. Int. 2008, 53, 408–415.

192. Tamm, C.; Sabri, F.; Ceccatelli, S. Mitochondrial-mediated apoptosis in neural stem cells exposed to manganese. Toxicol. Sci. 2008, 101, 310–320.

193. Yin, Z.; Aschner, J.L.; dos Santos, A.P.; Aschner, M. Mitochondrial-dependent manganese neurotoxicity in rat primary astrocyte cultures. Brain Res. 2008, 1203, 1–11.

194. Gorojod, R.M.; Alaimo, A.; Porte Alcon, S.; Martinez, J.H.; Cortina, M.E.; Vazquez, E.S.; Kotler, M.L. Heme Oxygenase-1 protects astroglia against manganese-induced oxidative injury by regulating mitochondrial quality control. Toxicol. Lett. 2018, 295, 357–368.

195. Rao, K.V.; Norenberg, M.D. Manganese induces the mitochondrial permeability transition in cultured astrocytes. J. Biol. Chem. 2004, 279, 32333–32338.

196. Alaimo, A.; Gorojod, R.M.; Miglietta, E.A.; Villarreal, A.; Ramos, A.J.; Kotler, M.L. Manganese induces mitochondrial dynamics impairment and apoptotic cell death: A study in human Gli36 cells. Neurosci. Lett. 2013, 554, 76–81.