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REVIEW ARTICLE

Metals and Parkinson's Disease: Mechanisms and Biochemical Processes

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Abstract: Genetic background accounts for only 5 to 10% of the reported cases of Parkinson's disease (PD), while the remaining cases are of unknown etiology. It is believed that environmental factors may be involved in the causality of a large proportion of PD cases. Several PD genes are activated by xenobiotic exposure, and a link between pesticide exposure and PD has been demonstrated. Many epidemiological studies have shown an association between PD and exposure to metals such as mercury, lead, manganese, copper, iron, aluminum, bismuth, thallium, and zinc. This review explores the biological effects, the pathogenetic processes, genetic susceptibilities to metals as well as examining future strategies for PD treatment, such as chelation therapy.

Keywords: *Substantia nigra*, alpha-synuclein, beta-amyloid, glutamate, glutathione, oxidative stress, metals, dopamine

1. INTRODUCTION

Parkinson's disease (PD) is the most common muscular functioning disorder, and it is the second most common neurodegenerative disorder after Alzheimer's disease (AD). It is known as a neurodegenerative disease, characterized by neuronal cell loss in the *substantia nigra* and subsequently a reduction of dopamine secretion [1]. The prevalence of PD has increased in industrialized nations and will continue to increase alongside the longevity of the population [2, 3]. PD compromises the central nervous system (CNS), impairing the brain's ability to coordinate movements through the dopamine system in different areas of the brain, also involving many cognitive functions such as the activity of the frontal lobes [4]. Also, the induced removal of dopamine D2 receptors in adult mice impairs locomotion, motor skill learning and leads to a severe "Parkinson's-like pathology" [5]. Bradykinesia (slowness) is the most common characteristic [6], and often the first symptom of PD, followed by other symptoms such as tremor, rigidity, hypokinesia, and symptoms from the autonomic nervous system. Akinesia or muscle rigidity is also another common symptom, culminating with the loss of motility in PD patients. Other neurological complications are also very common in PD patients, such as dementia, which affects up to 90% of the PD patients [7]. In general, PD symptoms augment in complication and increase difficulties as the disease progresses [8].

The etiology of PD is largely unknown. About 25% of cases in the autonomic nervous system have been

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attributed to the consumption of medications, poisoning, cerebrospinal meningitis, and some other factors [9-11]. Also, the etiology of 75% of cases is unknown and commonly named as idiopathic PD [12]. Several studies have attempted to identify some genetic risk factors of PD, but, most cases are sporadic (>90%), and genetic background only accounts for 5-10% of PD cases, suggesting that environmental factors could play a crucial role. Additionally, in a landmark epidemiological study of nearly 20,000 pairs of twins, no definite genetic cause was identified to explain the occurrence of PD, leading the authors to conclude that PD is an environmentally influenced disorder [13]. It has also been proposed that circadian rhythm disorder is an environmental risk factor for developing PD [14]. After reports about parkinsonism caused by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) exposure in intravenous drug users, generated as an inadvertent by-product of illicit narcotic synthesis [15, 16], much attention has been given to the role of environmental factors in PD.

Furthermore, exposure to different pesticides (rotenone, paraquat i.e. N,N'-dimethyl-4,4'-bipyridine dichloride), maneb, and manganese ethylene-1,2-bis-dithiocarbamate, polymer has been associated with an increased risk of PD [17-22]. In addition to pesticides, dozens of other commonly encountered environmental toxicants have been implicated in PD, such as metals, solvents, and other pollutants [23-25].

Previous studies have shown alternations in the levels of metals in the brain of deceased PD patients compared to non-PD controls of similar age [26], and some authors suggested in the past that elevated exposure to metals might be associated with an increased risk of PD [27]. Furthermore, it has been reported that accumulation of manganese, as well as excessive intake of iron, could have contributed in the etiology of non-depressive PD [28]. A study demonstrated that elevated iron levels stimulated oxidative stress in PD and metal-induced oxidative stress is involved in the etiology of PD [29]. Also, it has been reported that prevalence rates of PD in Europe (*e.g.,* Estonia), are not significantly higher in urban areas than rural ones [30]. Considering the evidence concerning the potential role of metals on PD, in this article, we have explored the potential relationship between metal levels and PD, alongside potential mechanisms by which several metals could contribute to the development of PD.

2. RELEVANCE OF METALS IN PARKINSON'S DISEASE

Some metals with neurotoxic effects have been associated with secondary parkinsonism. Manganese was one of the major elements associated with parkinsonism [31]. In fact, a large number of metals such as mercury, copper, and others can be released from metal body implants such as dental restorations, phagocyted by blood macrophages, and transported into the brain. Additionally, mercury as vapor needs no transportations through macrophages, because it can easily penetrate through the blood-brain barrier (BBB) [32, 33]. Upon apoptosis, the metal debris is released in the brain and can be taken up by brain macrophages, such as glial cells and neuro-melanocytes. In this respect, it is interesting to note that neuro-melanocytes in *substantia nigra* are one of the cell types involved in the synthesis of dopamine [34, 35].

The role of metals in PD pathogenesis is still a great concern in neurotoxicology and medical chemistry [36-40]. This role is exerted either by metallic toxicants or by depletion in essential metals for human health. Iron deficiency, for example, when occurring as an impaired function in either the peripheral or central nervous system, may cause PD with restless legs syndrome, as it contributed to the decrease of brain dopamine and 5-HT [41]. Also, iron deposition in the deep grey matter nuclei in the basal ganglia and midbrain was associated with PD pathogenesis [42]. Cigarette smoking increases the retention of radon daughters, Pb^{210} and Bi^{210}, coming from air pollution, which are causative factors of PD [43]. Actually, some evidence exists about the correlation between cumulative lead exposure and Parkinson's disease [44], often associated with industrial toxicants or with occupational medicine [45]. Neuro-melanocytes are brain macrophages with the ability to collect toxic metal oxides [46]. Therefore, ingested metal debris could impair the viability of neuro-melanocytes and thus dopamine production.

Several epidemiological studies have shown a significant association between PD and long-term exposure to metals such as mercury, lead, manganese, copper, iron, aluminum, bismuth, titanium and zinc after two to three decades of chronic exposure to multiple metals [31, 47-53]. The main sources of exposure result from occupational exposure, environmental pollution, contaminated seafood, medications, and dental metals restorations such as amalgam fillings [27, 47, 49, 50, 54-64]. Occupational exposure to iron, aluminum, and manganese have been found to double the risk of PD [47, 65]. A 2- to 10-fold

increase in the risk of PD has also been shown in workers occupationally exposed to lead, manganese, or copper for more than 20 years. On a larger scale, a positive correlation between industrialization and the prevalence of PD was observed in China [62]. Also, in Michigan during 1986-1988, significantly higher mortality rates of PD were found in counties having elevated levels of iron, copper, or activity of chemical industries compared to counties without these industries [27]. It is a consensus that PD is not a fatal disease, but people may die from causes related to it. A high prevalence of PD was observed in Valcamonica, Italy where environmental exposure to metals occurred. After this concurrence, neuropsychological symptoms were exacerbated in PD patients exposed to metals without any detectable role of genetic factors [56]. In other parts of the world, metal exposures have also exacerbated the PD symptoms. In Canada, for example, higher ambient manganese levels in the air increased the risk of PD and shortened the age of PD diagnosis [66]. The association between PD and industrialization is of particular interest, as PD was first identified in 1817 in England by James Parkinson shortly after the beginning of the industrial revolution. This period is marked by a dramatic increase in the rate of coal burning for energy generation in all major English cities, particularly London and Manchester. Due to the lack of emission control technologies, these newly industrialized major cities experienced high levels of pollution. Additionally, during this period, mercury was extensively used as a medicine against syphilis and other diseases that resulted in intoxications [67]. As an example, calomel (Hg (I) chloride, Hg_2Cl_2) was used in teething powders [68, 69].

2.1. Manganese

Maneb, a manganese-containing fungicide, has been associated with PD risk [55]. Six patients developed parkinsonism after a ventilation failure in a ferromanganese smelter. After prolonged ingestion of 1,7 grams of manganese in microalgae nutritional supplement, a patient developed parkinsonism [70, 71]. Following occupational manganese exposure, a 51-year-old man developed parkinsonism [72].

Numerous cases of rapid-onset parkinsonism have been observed in young adult intravenous drug users exposed to manganese via ephedrone (methcathinone) abuse [73-76]. Permanganate is used as a catalyst when preparing ephedrone from pseudoephedrine, and manganese dioxide remains as a contaminant in the drug [74]. This resembles earlier reported cases of drug users developing rapid-onset parkinsonism induced by intravenous MPTP [77], which is produced when the opioid MPPP is incorrectly synthesized.

2.2. Mercury

Parkinson's disease onset has been associated with exposure to elevated levels of mercury [58]. In fact, mercury has not only been associated with the incidence of PD, but several similarities between the effects of mercury exposure/ingestion, and the symptoms/consequences of PD have been identified (Table **1**). Detectable blood mercury levels were six times more frequent in individuals with PD than in healthy controls [78]. In another larger study, significantly higher blood Hg levels were seen in PD patients compared to controls, and mercury exposure was associated with an 8-fold increase in the risk of developing PD [57]. After adjusting for sources of mercury exposure such as dental amalgam, long-lived fish consumption (such as tuna), medications, and occupational exposures. A robust dose-response relationship between blood mercury levels and PD was found [79].

After being occupationally exposed to mercury in a chlorine factory for 30 years, a patient developed parkinsonism [52]. A 47-year-old dentist with parkinsonism was found to be intoxicated with mercury. Following chelation treatment, he regained health [80]. In dentists and dental assistants who are occupationally exposed to mercury from dental amalgam, an elevated mortality of PD and dementia has been described [60]. Among several professions, dentists were the most common among PD patients [81]. In one retrospective case-control study, PD patients had a significantly higher number of amalgam fillings before the onset of the disease compared to controls [61]. It has also been demonstrated that patients exposed to dental amalgam fillings were ~1.6 times more likely to have PD in comparison with their non-exposed counterparts after adjusting for comorbidities and Charlson-Deyo Comorbidity Index (CCI) scores [1].

In industrialized countries, dental amalgams are the single largest source of mercury exposure [82, 83]. For the general population, amalgam fillings also are the primary source of mercury in the CNS [84]. The uptake of mercury from amalgams follows mainly two pathways. First, mercury vapors released from the amalgam are inhaled and subsequently absorbed (80% in the airways), and secondly, eroded or abraded amalgam particles are swallowed. A small amount of the ingested mercury particles is potentially oxidized during digestion. About 10% of the ingested mercury is reab-

Table 1. Similarities between the effects caused by mercury (Hg) exposure/ingestion and the consequences of Parkinson's disease.

Mercury Exposure/Ingestion	Parkinson's Disease
Loss of dopamine receptors	Significant loss of dopaminergic neurons occurs before onset of PD symptoms
Tubulin degeneration	Degeneration of tubulin, high tubulin content in dopaminergic neurons
Axon degeneration	Degeneration of axons
Glutathione depletion	Appears to be a central event, first biochemical event in the substantia nigra
Glutamate increased	Increased glutamate, results in a loss of dopaminergic neurons
Amyloid-β increased	Increased amyloid-β, promotes α-synuclein aggregation
Tau phosphorylation	Phosphorylation of tau is a crucial abnormality, promotes α-synuclein aggregation
Mitochondrial dysfunction	Mitochondrial dysfunction appears to play a major role
Glutathione susceptibility	Increased risk of PD, earlier onset of PD
APOEe4 susceptibility	Increased risk of PD, PD with dementia (PDD), earlier onset of PD, and an earlier onset of psychosis in PD

sorbed as Hg^{2+} [84, 85]. Mercury can also be taken up in the nerve endings and transported in a retrograde direction to ganglia and central nerve cells [86, 87]. Mercury increases in the brain in proportion to the number or the surface area of the subjects' amalgam fillings [88]. Removal of amalgam fillings in mercury-sensitized patients has been shown to improve general health in patients with chronic fatigue syndrome, fibromyalgia and various autoimmune diseases [89-91]. It is also worth mentioning that bismuth, thallium, and metal tin also rarely damage the basal ganglia and have been linked with myoclonus, tremor, chorea, and ataxia, accompanied by psychiatric symptoms - psychotic or behavioral disorders or depression [92, 93].

2.3. Synergistic toxicity

Metals may increase the toxicity of other metals and pesticides. Synergistic effects were seen between metals and PD with combined exposures of iron-copper, lead-copper, and lead-iron compared to the effects of single metals [47, 49, 50]. Mercury exhibits synergistic effects when combined with other metals such as lead, aluminum, manganese, cadmium, and zinc, exacerbating mercury toxicity even at low and non-toxic doses [94-99]. In animal and cell studies, pesticides and metals were also found to have synergistic effects when combined [100-102]. When a solution of mercury which kills 1 in 100 rats (LD1Hg) is combined with a solution of lead which also kills 1 in 100 rats (LD1Pb), all of the rats die when exposed (LD100Hg+Pb) [98]. In another animal study involving rats, synergistic effects were seen when low levels of mercury, lead, and manganese were combined [97]. Mercury combined with safe levels of aluminum hydroxide or the antibiotic neomycin significantly increased neuronal mortality in an *in vitro* study [96]. Zinc also exacerbated the toxicity of mercury, by increasing cytotoxicity and the inhibition of tubulin [94, 95, 99]. Interestingly, a DJ-1 protein that is known as a PD-associated protein protects cells from toxic stresses and can bind both mercury and lead [102]. Genetic variants of DJ-1 protein exert no protective effects on mercury toxicity and, therefore, increase the risk for PD [102, 103].

Several epidemiological studies have shown a strong association between pesticide exposure and PD [104-106]. On the other hand, pesticides and metals promote the aggregation of α-synuclein, a small, highly abundant and conserved presynaptic protein with neurodegenerative effects. Its aggregation is an important step in the etiology of PD [107,108]. For example, ions of Cu(II) are efficient in the aggregation of α-synuclein at related physiological contents without changing of the resultant fibrillar constructions [109, 110]. It has been shown that since some divalent metals such as manganese and iron bind with C-terminus of α - synuclein with low-affinity, non-specific binding interface, copper interacts at the N-terminal region of α - synuclein at a high affinity and it is the most potent metal in the aggregation of α-synuclein filament assembly [111]. Iron combined with the herbicide paraquat synergistically accelerates the age-related loss of nigral dopaminergic neurons [100]. In an animal

experiment, developmental exposure to paraquat or the manganese-containing fungicide maneb produces minimal changes in the nigrostriatal dopamine system alone. However, a significant reduction in striatal dopamine levels is seen when both maneb and paraquat are combined.

There is also some evidence suggesting a gender effect, males having a twice as high risk of developing PD than women [112]. This can be due to the fact that estrogen protects neurons from mercury while testosterone synergistically enhances the toxicity of mercury [96, 113].

2.4. Effect of Metal Exposure on Dopaminergic Neurons

Parkinson's disease is characterized by a significant and selective loss of dopaminergic neurons in the substantia nigra of the brain, which occurs before the appearance of the first symptoms. Oxidative stress contributes to the process leading to dopaminergic neuron degeneration [114]. A depletion of glutathione in the substantia nigra occurs before this, which is the earliest biochemical effect reported [115]. This loss is believed to play a crucial role in PD, with a 40-90% reduction of glutathione seen in the substantia nigra as the disease advances [116-118]. This loss of glutathione correlates with the severity of the disease and the loss of dopaminergic neurons [116]. Increased lipid peroxidation and impaired mitochondrial function are also seen in the substantia nigra of PD patients, and in other areas of the PD brain, evidencing oxidative stress.

Substantia nigra dopaminergic neurons have long axons containing microtubules, consisting of tubulin molecules [119]. Tubulin formation is inhibited by very low doses of inorganic mercury while other ATP- or GTP-binding proteins are not [120, 121]. Tubulin has at least 14 sulfhydryl groups (SH-), and mercury binds to sulfhydryl with a very high affinity. Therefore, it is postulated that mercury could interact with in functional loss of tubulin and the formation of neurofibrillary tangles. On the other hand, the effect of wild-type α-synuclein on the partitioning between microtubules and tubulin dimers revealed that Parkinson's disease-linked mutants lose this capability [122]. Other metals such as aluminum, iron, lead, and zinc are not able to inhibit binding of tubulin to GTP [123,124].

Analysis of brain tissues from PD patients showed elevated levels of aluminum, iron, and zinc in the substantia nigra compared to controls [125-129]. In the substantia nigra of PD patients, the accumulation of iron was twice as much compared to controls [125]. This was confirmed in other studies. Thus, high levels of trivalent iron were found in Lewy bodies and dopaminergic neurons of the substantia nigra of PD patients. In adult rats, unilateral injection of Fe (III) chloride into the substantia nigra resulted in a selective decrease in striatal dopamine (95%) and impairment of dopamine-related behavioral responses indicating that iron may initiate the loss of dopaminergic neurons in PD [130]. The uptake of 11C-nomifensine, a potential ligand for the evaluation of monoamine re-uptake sites at the presynaptic dopaminergic terminals, was reduced within the striatum following subcutaneous injections of manganese oxide, showing that exposure to manganese may lead to a loss of dopaminergic neurons as well [131,132]. The exposure to metals with a high affinity for sulfhydryl groups such as Hg, Cd, Cu, and Zn resulted in the reduction of D2 dopamine receptor sites. Low concentrations of Hg (1 mM) were able to abolish completely D2 dopamine receptors while the administration of 3 mM of copper or cadmium only caused a 40-60% reduction in dopamine receptors [133].

Mercury targets areas of the brain which are not able to detoxify mercury [134-136]. Even at the lowest levels, inorganic mercury causes neurodegeneration within minutes of exposure. Very low levels of inorganic mercury lead to the destruction of intracellular microtubules and the degeneration of axons. This dramatic neurodegenerative cascade is specific for mercury and was not found with other metals such as aluminum, cadmium, lead, or manganese [137]. Mercury depletes glutathione [113, 138] and impairs mitochondrial function [139-141].

3. METAL-INDUCED OXIDATIVE STRESS IN PARKINSON'S DISEASE

Oxidative stress is considered one of the major causes of the Parkinson's disease pathogenesis [142]. Oxidative stress causes mitochondrial dysfunction [143]. Patients with PD have an upregulation in ROS production and oxidative stress [144]. Furthermore, these subjects have impaired mitochondrial functionality [145]. The increased level of oxidative stress in PD patients is reflected by elevated iron levels [127], nucleic acid oxidation [146], elevated lipid peroxidation [127, 147] and low contents of the antioxidant glutathione (GSH) in the dopaminergic zones of the brain [148]. In *substantia nigra* of PD patients, increased contents of nitrated and oxidized proteins are found [149]. Exploration of substantia nigra pars compacta as well as by postmortem studies

have indicated nigral cell degeneration as a result of oxidative stress [150]. The impact of oxidative stress in neurodegeneration in animal models of PD has also been demonstrated [151]. Furthermore, it has been demonstrated that iron induces oxidant and oxidative stress to the dopaminergic nigrostriatal system, that shows an important effect in the PD pathogenesis [152].

Moreover, the post-translational modifications of α-synuclein and other neuronal proteins such as tau could be as a result of the redox metal ions and oxidative stress [153].

4. THE ROLE OF METALS IN GLUTATHIONE DEPLETION AND GLUTAMATE NEUROTOXICITY IN PARKINSON'S DISEASE

4.1. Selenium and Selenoproteins

Selenium is an essential trace element for humans and is an integral part of the enzyme glutathione peroxidase (GPx), which protects the organism against oxidative damage by reducing lipid peroxides and hydrogen peroxide in the presence of glutathione. Selenium is found in GPx as the amino acid selenocysteine.

Selenium has been found to be a very good antidote for mercury poisoning in animal experiments [154-156]. However, selenium intake is less than optimal for much of the world population [154, 155]. When the dietary selenium intake is less than optimal, selenium-antagonistic toxic metals, such as mercury, cadmium, and silver, bind selenium in a biologically inert form as heavily soluble selenides. The toxic metals concerned cannot do any harm after they have been precipitated as selenides inside the cells, but they reduce the number of selenide ions available for the synthesis of selenophosphate and selenocysteyl-tRNA, as well as for incorporation in the iron-sulphur groups of enzymes in the mitochondrial respiratory chain [154, 155].

Reduced selenium plasma levels in PD patients have been found to be significantly associated with decreased performance in neurological coordination tests [157]. It is thought that dopaminergic neurons may be more sensitive to oxidative stress than other cells in the brain because they contain dopamine, which is a molecule that can be oxidized to form the electrophilic molecule dopamine quinone, which can covalently bind nucleophilic amino acid residues such as cysteine [158]. It has been hypothesized that selenoproteins, which contain a highly nucleophilic selenocysteine residue and often play vital roles in the maintenance of neuronal viability, are likely targets for dopamine quinone [158]. Subfamilies of selenoproteins include GPx, iodothyronine deiodinases (DIO), and thioredoxin reductase (TrxR) [159].

The expression of GPx4 has been studied in postmortem human brain tissue from PD individuals and controls [160]. In both control and PD samples, GPx4 was found in nigral dopaminergic neurons, co-localized with neuromelanin [160]. Overall GPx4 was found to be significantly reduced in the substantia nigra in PD compared to control subjects but was increased relative to the cell density of surviving nigral cells [160]. In the putamen, GPx4 was found to be concentrated in dystrophic dopaminergic axons in PD subjects, although overall levels of GPx4 were not significantly different compared to control putamen [160]. The upregulation of GPx4 expression that was found in surviving neurons of the substantia nigra and the association of this protein with dystrophic axons in the striatum of PD brain were considered to indicate a possible neuroprotective role for GPx4 [160].

Exposing intact rat brain mitochondria to dopamine quinone resulted in decreases in GPx4 activity and monomeric protein levels as well as detection of multiple forms of dopamine-conjugated GPx4 protein [158]. Evidence of both GPx4 degradation and polymerization was observed following quinone dopamine exposure [158]. A dose-dependent loss of mitochondrial GPx4 was found in differentiated PC12 cells treated with dopamine [158]. These observations suggest that a decrease in mitochondrial GPx4 monomer and a functional loss of activity may be contributing factors to the vulnerability of dopaminergic neurons in PD [158].

The expression of selenoprotein P (SelP) has also been studied in postmortem PD brain tissue [161]. Selenoprotein P in midbrain was present in the neurons of the substantia nigra mainly within the centers of Lewy bodies, the pathological hallmark of PD [161]. Similar to GPx4 expression, SelP-1 expression was significantly reduced in the substantia nigra from PD subjects compared with control [161]. In the putamen, SelP-1 was found in cell bodies, dopaminergic axons, and terminals, although levels of SelP-1 were not altered in PD subjects compared to controls [161]. Expression levels of SelP-1 and GPx4 were found to correlate strongly in the putamen of control subjects but not in the putamen of PD subjects [161]. These observations indicate a role for SelP-1 in the nigrostriatal pathway, suggesting that local release of SelP-1 in the striatum may be important for signaling and/or synthesis of other selenoproteins, such as GPx4 [161].

4.2. Glutathione

Glutathione is crucial for many cellular processes and owing to that, it has been associated with the etiology of several human degenerative diseases (see Ballatori *et al.* 2009 [162] for an excellent review). Glutathione also plays a central role in the detoxification of infectious and non-infectious xenobiotics, which have been associated with some cases of Parkinson´s disease. Depletion of glutathione increases the retention and toxicity of mercury as the metal is not being adequately detoxified in the body and/or excreted out of the body. Levels of glutathione in the midbrain decrease prior to clinical symptoms of PD [117, 163], impairing the function of GPx and promoting an increased oxidation [159]. Among the elderly, who are primarily affected by PD, glutathione levels are considerably decreased [164]. Therefore, PD patients may have an impaired ability to detoxify mercury and other xenobiotics due to glutathione depletion, leading to increased susceptibility.

Genetic depletion of glutathione and glutathione S-transferase (GST) is also a known risk factor for PD [116, 165-169]. In a study of 349 PD patients and 611 controls in a Chilean population, the frequency of the double-deleted genotype (-/-) of GST M1 (Glutathione S-transferase M1) was significantly elevated in PD patients and it was revealed that GST M1 plays an important role in the conservation of astrocytes against toxic dopamine oxidative metabolism [167]. This relation was found to be the strongest among patients with an early onset of PD [165]. The most accepted mechanism, by which mercury would cause degenerative diseases, is by affecting glutathione balance and activity, then triggering oxidative stress and disrupting several cellular processes [162, 170]. In a cell culture, low doses of mercury have been demonstrated to inhibit glutathione activity and to cause an increase in oxidative stress [113].

4.3. Glutamate

Glutamate-induced neurotoxicity due to overactivity of glutamatergic neurotransmitters results in a loss of dopaminergic neurons while a loss of dopaminergic neurons leads to increased glutamate toxicity. This is due to a balance between nigral inhibitory dopamine and excitatory cortical glutamate, which regulates the discharge activity of striatal neurons [171-173]. When protective mechanisms fail, glutamate accumulates and becomes toxic. Additionally, glutamate has a greater neurotoxic effect on dopaminergic neurons than other neurons [173]. In primate and rodent models of PD, the inhibition of glutamate transmission with glutamate antagonists demonstrated decreased PD symptoms. This effect was greatly increased when glutamate antagonists were administered in conjunction with the PD medication levodopa [171, 174].

The reuptake of glutamate in astrocytes and other cells in the nervous system is inhibited by mercury, which results in extracellular accumulation of glutamate [175, 176]. Mercury and lead inhibit glutamine synthetase, which converts glutamate to non-toxic glutamine [177]. Therefore, the inhibition of glutamine synthetase leads to an increase of glutamate.

4.4. Apolipoprotein E, Amyloid-β, and α-Synuclein

Parkinson's disease is the primary disease associated with the presence of intracellular, insoluble Lewy bodies that are composed of highly stable α-synuclein, the causative protein of PD, which forms Lewy bodies [178, 179]. Patient brains with Lewy bodies reveal α-synuclein aggregation in pre-cerebellar brainstem structures, indicating resting tremor, unstable gait and impaired balance which may be associated with cerebellar dysfunction [180]. Lewy body diseases (LBD) could induce PD, PD with mild cognitive impairment (PD-MCI), PD dementia (PDD), and dementia with Lewy bodies (DLB) [181]. Accumulation of α-synuclein in dopaminergic neurons leads to apoptosis mediated by reactive oxygen species, although α-synuclein is not toxic to non-dopaminergic cortical neurons where it exhibits a neuroprotective activity [182]. Soluble α-synuclein is believed to be a possible mediator of neurotoxicity, and the selective neuronal loss of dopaminergic neurons may be explained by the fact that neurotoxicity of soluble α-synuclein seems to be dopamine-dependent [183]. Authors have suggested that α-synuclein may be involved in the regulation of dopamine biosynthesis by reducing the activity of tyrosine hydroxylase [182, 184]. Metals and pesticides promote the aggregation of α-synuclein and yield synergistic effects when combined [107]. Aluminum, cadmium, cobalt, copper, iron, and manganese accelerate the fibrillization of α-synuclein, with aluminum having the most pronounced effect [107]. Since mercury and lead have not been investigated in this respect, further research is urgently needed.

Mercury causes an increase in the production of amyloid-β proteins, which form amyloid plaques in the brain [113, 138]. Amyloid-β is believed to be the causative protein of AD [185], and amyloid-β has also been implicated in PD [186-192]. There is increasing evidence that amyloid-β promotes the aggregation of α-

synuclein to form fibrils [186, 188, 189, 191, 192]. Amyloid-β and α-synuclein may directly interact *in vitro* [188], and amyloid-β promotes the toxicity and aggregation of α-synuclein *in vivo* [189, 192]. This is of particular interest since several authors have confirmed that the pathology of AD and PD overlap in a heterogeneous group of syndromes recognized as Lewy body disease (LBD) [193-198]. Furthermore, increased consumption of whale meat and blubber, resulting in exposure to methylmercury and polychlorinated biphenyls (PCBs), was significantly associated with PD in a much larger study [59].

Dementia in PD strongly correlated with the amyloid-β burden, which is significantly higher in the striatum [187]. The brains of PD patients have significantly more vascular amyloid-β deposits than the brains of controls [190].

The APOEe4 allele is associated with an increased risk of developing either AD and PD [199-203] in addition to PD with dementia (PDD) and familial PDD [199, 204-209]. In fact, the presence of some clinical features in PD patients has been associated with the APOEe4 allele [199]. An earlier onset of PD and an earlier onset of psychosis in PD have also been associated with an elevated expression of the APOEe4 allele [200, 202, 205, 207, 209]. Cortical Lewy body burden is significantly associated with amyloid plaque burden, which increases a 50% further in PD patients with a higher amyloid plaque load. The apolipoprotein E e4 (APOEe4) allele is also overrepresented in this subgroup [186].

The APOEe4 also appears to increase susceptibility to the neurotoxic effects of lead and mercury [210, 211]. These associations may be explained by the fact that APOEe4 allele has reduced detoxifying capabilities compared to the other two subtypes (APOEe2, APOEe3). Unlike these two subtypes, the APOEe4 allele does not contain any sulfhydryl- groups, which may have the ability to bind to and detoxify metals such as lead and mercury [121, 212].

4.5. Tau Protein Hyperphosphorylation

Phosphorylated tau in Lewy bodies is a characteristic abnormality of PD, AD, and LBD. Phosphorylated tau is found in synaptic-enriched fractions in the frontal cortex in PD and LBD, which indicates increased tau phosphorylation at the synapses [213]. *In vitro* and *in vivo*, the increase of tau phosphorylation has been found to be strictly dependent on the presence of aggregated α-synuclein, which parallel each other and indicate that they modulate the pathogenicity of one another [214-216].

Mercury promotes tau protein hyperphosphorylation in neuronal cell cultures within 24 hours, even at very low doses [113]. Although cobalt reduces glutathione levels and stimulates the secretion of amyloid-β in neuronal cell cultures, it does not hyperphosphorylate tau-protein. These changes caused by cobalt are, however, only observable at concentrations considerably higher than mercury (~1700 fold higher) [113,138]. Both aluminum and iron (III) promote the aggregation of hyperphosphorylated tau *in vitro*. Again, this has only been demonstrated at concentrations much higher than those required for mercury [217, 218].

5. CHELATION THERAPY

Chelation therapy is the medical use of chelating agents (chelators) to remove, through complex formation, metals from looser chemical compounds in the body [219]. After receiving only a week of chelation treatment for metal intoxication, clinical improvements of parkinsonism were reported in a patient intoxicated with mercury. During a 5-year follow-up period after the initial improvement from treatment, the patient's neurological status remained stable [66]. In a patient with PD induced by manganese, chelation treatment led to a dramatic improvement of MRI abnormalities in the brain and a gradual improvement of symptoms [71].

Similar observations were made in workers who developed parkinsonism after manganese exposure. The symptoms resemble the symptoms of PD. Herrero Hernandez and colleagues (2006) applied calcium EDTA chelation therapy in seven workers with parkinsonism, who had deposition of manganese in their basal ganglia. Excellent clinical outcome and reduction on manganese in the blood were observed in four out of seven patients; one patient showed mild improvement of symptoms [220].

Calcium EDTA is a fairly safe drug if used by a trained health professional [219]. It seems to be helpful in the treatment of manganese-induced parkinsonism [220]. As opposed to PD, manganese-induced parkinsonism affects the globi pallidi mostly. However, in some cases of manganese-induced parkinsonism, MRI detects manganese deposits also in the substantia nigra. Thus, EDTA chelation therapy could be useful in patients with PD as well, especially since cardiovascular problems are a frequent comorbidity in PD. EDTA has been used in the treatment of cardiovascular disease for many years [221].

In mouse models of PD, neuroprotective and neurorestorative effects were seen with iron chelators such as apomorphine, clioquinol, deferoxamine, M30, and VK-28 [222-227]. In lactacystin-induced dopaminergic neurodegeneration, both M30 and VK-28 significantly improved behavior, microglial activation in the substantia nigra, iron accumulation, and attenuated the loss of dopaminergic neurons [227]. Pretreatment with subcutaneous injections of apomorphine (5-10 mg/kg protected against nigrostriatal dopamine neurodegeneration induced by MPTP (24 mg/kg administered intraperitoneally) [222, 223].

In rat models of PD, iron deposition occurs in several parts of the brain, including substantia nigra and the globi pallidi [228]. Iron chelators, baicalin, and deferoxamine, substantially inhibited iron accumulation and had a protective effect on dopaminergic neurons. Iron chelation in PD has been previously reviewed [229].

In a study of Febbraro and colleagues (2013), chronic intranasal deferoxamine ameliorated motor defects and pathology in the α-synuclein Parkinson's model [230]. Recent research on the so-called metal protein attenuating compounds (MPACs) has reported that these small molecules are useful to prevent abnormal interactions of metals (such as copper, zinc, iron) in the brain with endogenous metal-binding proteins (such as amyloid-beta peptide [Abeta] or neuromelanin) that may lead to oxidative stress and neurodegenerative disorders and showed promising therapeutic effect on several pathologies [231-234]. These molecules are different from traditional chelators and due to their chemical properties and hydrophobicity (such as clioquinol) they can cross the blood-brain barrier [235, 236]. MPACs improve irregular interactions of metals and remove metals from tissues. Furthermore, they promote the clearance (and solubilization) of beta-amyloid and control redox interactions that produce neurotoxic hydrogen peroxide. Actually, MPACs named 8-hydroxyquinoline-2-carboxaldehyde isonicotinoyl hydrazone have been reported as an alternative approach in the pharmacological treatment of PD [237].

Metal ion chelators were assumed to solve the great concern of metal toxicants in the pathogenesis of neurodegenerative disorders such as Alzheimer disease or PD [238, 239]. Particularly, facilitating iron homeostasis, chelation therapy may bear some advantage in PD affected patients [184, 229, 240, 241]. The use of the iron chelator deferiprone ameliorated the iron levels, reducing its accumulation in the central nervous system (CNS) of patients with PD, particularly in those subjects having the lowest ceruloplasmin-ferroxidase activity [242]. Currently, in PD subjects with a very common iron-chelator, deferiprone is widely used and ceruloplasmin activity considered as a prognostic marker of chelation [243]. Other iron chelators, such as desferal and the VK-28 class of chelators appeared as particularly effective in reducing iron accumulation in the substantia nigra (pars compacta) [225]. While even in PD-induced animal models (such as lesions in the striatal dopamine neurons induced by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or by 6-hydroxydopamine), desferal is not able to affect dopamine metabolism and the related striatal tyrosine hydroxylase activity. Evidence suggests that VK-28 iron chelators are more neuroprotective than desferal as well as more effective in ironing iron out from PD brains [225]. In summary, the iron chelator 5-[4-(2-hydroxyethyl) piperazine-1-ylmethyl]-quinoline-8-ol, or VK-28 shows high efficacy in chelating iron without inducing a stress response and in the level of 6-hydroxydopamine [244, 245].

CONCLUSION

Numerous epidemiological studies have demonstrated significant associations between PD and exposure to metals, with several potential mechanisms of action being described. While most metals might contribute to the pathology of PD, mercury seems to be the most toxic metal. Mercury is neurotoxic in every chemical form and appears to be of particular importance in the development of PD. There are many similarities between the effects of mercury exposure/ingestion and the symptoms/consequences of PD. Specific neuronal changes and neurodegenerative effects, which are typical of PD, are only observable with the presence of mercury at the lowest concentrations. Especially nigral dopaminergic neurons are very sensitive to mercury due to their high tubulin content and increased glutamate toxicity. Furthermore, heavy metal pollution might play another fundamental and major role in the onset of neurodegenerative diseases. Metals such as iron, copper, and lead do exert a synergistic effect when in combination with mercury. Taken together, mercury, as well as other metals, may contribute to the development of PD.

The research findings presented in this study suggest that in addition to standard treatment, the removal of Hg-containing dental amalgams, supporting body's detoxification mechanisms with glutathione and antioxidants as well as suitable chelation therapy might

contribute to the optimal treatment of PD. Properly controlled large clinical trials addressing these issues are clearly indicated.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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