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The Role of Xenobiotics and Trace Metals in Parkinson's Disease

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Abstract
Research on the etiopathogenesis of Parkinson's disease (PD) has in the very recent years earned many insightful cues about the involvement of xenobiotics and metal pollutants in the onset and exacerbation of this neurodegenerative disorder. Furthermore, particularly for metal pollutants, the hypothesis about the role exerted by impaired mitochondrial function is gaining a leading causative role. In this review, we outline the role of environmental pollution in the pathogenesis of PD, as the prolonged exposure to xenobiotics may account for the majority of PD reported cases, expanding the debate also about some suggested therapeutic approaches.

Keywords Substantia nigra · Dopamine · Alpha-synuclein · Iron · Manganese · Oxidative stress · Chelating agents

Introduction

Parkinson's disease (PD) is a chronic, progressive neurological disorder due to the degeneration of dopamine-producing cells located in a region of the mesencephalon known as substantia nigra (SN), which is an integral element of the basal ganglia [1–3]. Dopamine synthesized in these cells takes care of essential functions as a neurotransmitter. Its precursor L-DOPA originates from the L-amino acid tyrosine (Y) via the activity of the tyrosine hydrolase (EC 1.14.16.2), which employs bivalent iron (Fe) and molecular oxygen as enzymatic cofactors. After release, specialized proteins transport dopamine extracellularly, i.e., the dopamine active transporter (DaT), to the synaptic receptors on neurons located, e.g., in the nucleus accumbens, hippocampus, striatum, spinal cord, and to the neocortex [4]. Dopamine deficiency and age-related reduction cause functional changes in the many structures of the brain controlling movement and lead to loss of muscle function [5, 6]. The condition may affect patients' mobility and independence. The term parkinsonism refers to a group of several diseases that have common symptoms and may be associated with other neurological manifestations. Among these diseases, PD is the best known. The disease is named after the English surgeon James Parkinson (1755–1824), who in 1817 described it [7]. On April 11th, Parkinson's birthday is celebrated as the yearly World Parkinson's Day, which is part of the public campaigns to create awareness about PD.

PD symptoms expand slowly over time. Initially, the most apparent are rigidity, tremor, slow movements, and problems in walking, as well as general behavioral problems. Other symptoms include sleep disturbances, altered smell sense, constipation, and depression. In the more advanced stages of PD, cognitive problems are common [8]. The disease progression in subjects with PD, as well as the response to treatment, varies from patient to patient. The exact cause of the dopaminergic cells' burnout is unknown, although both environmental and genetic factors may contribute [9]. The pathogenesis is accompanied by precipitation of Lewy bodies, i.e., abnormal protein aggregates inside neurons. Specific genetic mutations are involved in some cases of PD, although PD appears to be more commonly caused by environmental factors such as exposure to some pesticides, e.g., rotenone and paraquat [10].

As there are no specific tests to detect PD, the diagnosis is based on the patient's medical history and clinical symptoms, as well as neurological and physical examinations. Tests such as neuroimaging techniques, spinal fluid analysis, and others may

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also be addressed to rule out if other conditions are causing the symptoms. Early diagnosis depends on the awareness of the medical doctor, and a supplementary DaT-scan (SPECT imaging using ^{99m}Tc-labeled dopamine transporter) may be helpful [11].

The L-dopa-producing enzyme complex tyrosine hydroxylase uses cofactors, such as molecular oxygen and Fe(II), as a *vulnerable biochemical site* with regard to reactive oxygen species (ROS)-dependent deterioration. Toxic metals/trace elements when present at non-physiological levels, such as manganese (Mn), copper (Cu), and Fe, can trigger the production of ROS, and presumably, even impair the physiological activity of mitochondria and also the activity of detoxifying and scavenger enzymes [12]. This biochemical impairment, alongside an accelerated or exacerbated ROS generation, and subsequently, also neuroinflammation, may be components leading to nigrostriatal cell exhaustion and death. However, the precise mechanisms of cellular death, characteristically starting in pars compacta of SN and subsequently distributed to other regions of the central nervous system (CNS) in PD, are yet not completely understood [9].

In 2015, it was estimated that PD affected about 6.2 million people worldwide. PD commonly appears in people aged 60 years or older, of whom about 1% is affected [13]. More males than females are affected by PD. The disease may also appear in people below the age of 50, and it is then named young-onset PD. In general, PD patients are not expected to live more than 15 years after the diagnosis. The present review summarizes case-control and epidemiologic evidence for environmental factors related to PD.

Basic Causes Involved in Parkinson's Disease

Pathophysiologically, three findings appear to characterize the development of PD, viz. inhibition of mitochondrial complex I, oxidative stress, and abnormal protein aggregation. Although numerous studies have aimed at identifying genetic risk factors of PD, genetic background accounts only for about 10% of PD patients according to present knowledge, indicating that environmental factors play the most important role in the PD pathogenesis [14].

Abnormal Protein Aggregation in Parkinson's Disease

One of the pathogenic steps leading to clinical PD is the abnormal accumulation of misfolded alpha-synuclein protein inside neurons, forming Lewy body aggregations [15]. Usually, alpha-synuclein seems to be a factor in maintaining a continuous synaptic vesicle supply, which contains the neurotransmitter dopamine in neuronal presynaptic terminals [16]. Alpha-synuclein in its physiological form is also found in neuronal mitochondria, where it may possess a regulating function on complex I [17]. However, in PD, pathological precipitates of alpha-synuclein, the Lewy bodies, appear in the SN, as well as in areas of the basal forebrain, midbrain, and in the neocortex. Lewy bodies do not necessarily lead to cell death if the abnormal protein is sequestered or removed by autophagy. In advanced cases of PD with dementia, Lewy bodies have frequently been found in the cortical areas [18–20].

Normally, aggregations of alpha-synuclein should be cleared by an adequately functioning activity of leucine-rich repeat kinase 2 (LRRK2) [21], which thereby delays the progression of PD. Gene mutations of LRRK2 are known as the most frequent cause of sporadic or familial PD. It accounts for about 5% of the patients with familial PD and about 3% of the sporadic cases. Mutations in the SNCA gene (the alpha-synuclein gene) are also a risk factor for non-familial PD since the gene encodes the protein alpha-synuclein. Moreover, mutations in other genes, including PRKN (the parkin gene), PINK1, GBA, and DJ-1, increase the risk for PD [22].

Mitochondrial Complex I and Parkinson's Disease

Numerous studies reported that the etiology of PD might be attributed to mitochondrial impairment. From those factors, the NADH-ubiquinone oxidoreductase (complex I) of the respiratory chain appears to be the most responsible [23]. Electrons from reduced cofactors are transferred during oxidative phosphorylation by a series of respiratory chain complexes (complexes I–IV) that are located in the inner membrane of mitochondria [24]. Loss of the mitochondrial complex I catalytic function in the electron transport chain (ETC) is reported in multiple tissues from PD individuals [25, 26]. Reduced nicotinamide adenine dinucleotide (NADH)-driven electron transfer rates through complex I is positively related to a reduction in PD 8 kDa subunit and inversely related to complex I protein oxidation status. Reduced complex I function in PD brain mitochondria correlates with complex I misassembly, and it seems to occur because of subunit oxidation in the internal space, not because of external oxidative stress. The auto-oxidation of complex I may result from irregularities in complex I assembly factors, or complex I toxins, or some combination [25]. Numerous laboratories have found abnormalities of electron transport complexes, in particular in complex I in different tissues of PD patients. On the other hand, questions have been raised about the debilitation of the disease process due to the drug treatments which itself may induce reduced activities of ETC. Therefore, a blinded study of platelet mitochondrial ETC activities in 18 age- and sex-matched controls and 18 early untreated PD patients and in 13 spousal controls has been undertaken, revealing that lower activity of complex I in platelet mitochondria of PD patients was also seen in early untreated disease cases, and therefore cannot be explained from drug therapy or debilitation due to prolonged suffering [26]. The crucial role of complex I in the PD pathogenesis is supported by the action of MPP^+ (N-

methyl-phenylpyridinium ion), the active metabolite of MPTP, that is a specific inhibitor of the proton-pumping complex I in the mitochondrial respiratory chain [27, 28]. The complex I inhibition can induce declined ATP production and reactive oxygen species (ROS) generation [29]. Complex I is known as a main element of the respiratory chain, and its deficiencies can represent a fundamental instability of the mitochondria and their bioenergetic functions. And it is known that complex I deterioration forms a critical step in the cascade of the process leading to dopaminergic cell death. Decreased activity of complex I has been reported in mitochondria from the frontal cortex as well as platelets and SN of the brain of patients with PD.

Moreover, the activity of complex I was reported to be lower than average in the cybrid system consisting of the mitochondria from PD patients [23]. Biochemical, behavioral, and anatomical characteristics of PD in animal models have resulted from the administration of particular inhibitors of complex I [30, 31]. These and other outcomes propose that the impairments of complex I may be critical in the dopamine neuronal death and PD pathogenesis.

Oxidative Stress and Parkinson's Disease

Oxidative stress has been presumed to represent a critical effect in dopaminergic neurotoxicity. Environmental factors, such as pesticides, dopamine itself, insecticides, and neurotoxins, in addition to genetic factors, appear to be involved in the mitochondrial dysfunction, which precedes the formation of reactive oxygen species (ROS) in PD. The abnormalities in the normal cellular processes that occur in relation to the aging process are thought to involve elevated susceptibility of dopamine neurons [32]. Selective DA degeneration of neurons in the SN pars compacta (SNpc) proposes that the levels of DA itself may be a source of oxidative stress [33]. Also, it is thought that oxidative stress is the common underlying process that induces the dysfunction of the cell as well as its death. Oxidative stress can occur because of an imbalance between cellular antioxidant activity and ROS production. Superoxide radicals and oxidants are produced as the oxidative phosphorylation products within the cell, particularly in the mitochondria as the main site of ROS production. ROS can affect mitochondrial DNA, which can induce changes in the synthesis of METC components such as the production of adenosine triphosphate (ATP) and the leakage of ROS into the cell's cytoplasm [34]. The mechanisms regarding the generation of ROS associated with PD include neuroinflammation, DA dysmetabolism, and, mitochondrial dysfunction [32]. Oxidative stress appears to trigger a cascade of reactions that lead to the degeneration of dopamine cells in PD. This cascade is intimately connected to the components of the degenerative process, which include excitotoxicity, nitric oxide toxicity, inflammation, and mitochondrial dysfunction [35]. Jenner and his colleague reported that the degenerate section of neurons in the non-pigmented and pigmented nuclei in the SN of the brain in patients with PD might be particularly sensitive to oxidative stress [36].

Dopamine Function—the Vulnerable Target in the PD Pathogenesis: the Case of Mercury

Dopamine is produced from tyrosine and acts as a monoamine neurotransmitter. It is well known that the major function of dopamine is to regulate motivation and cognition as well as to assist in the modulation of brain activity and to distribute information into different regions of the cortical brain. However, molecular interactions of the dopamine circuitry with xenobiotics and pollutants may account for disturbances leading to the PD onset [37]. For example, Cu dyshomeostasis can induce dopaminergic degeneration, particularly if induced by intrastriatal administration [38]. Metals cause dramatic impairments in the redox signaling, causing neuroinflammation and neurodegeneration.

Moreover, monoamine oxidases (MAO), which catalyze the oxidation of dopamine to dihydrooxphenylacetyldehyde, can exacerbate the redox status [39]. Deficiency of antioxidant defense enzymes such as glutathione peroxidase may then lead to the formation of highly reactive and toxic hydroxyl radicals [40]. It is widely known that dopamine-related neurotoxicity is characterized by increased aggregation of α-synuclein, which is accumulated selectively in the SN in PD [41, 42]. It has been found in studies on the brain of ray-finned fishes that MAO activity is triggered by the mercury (Hg) exposure [43]. In this perspective, it is of interest that MAO inhibitors have been used therapeutically with some effect in PD [44]. In river otters, it has been demonstrated that brain Hg levels are inversely associated with the activity of MAO in the cerebral cortex [45]. In the presence of Hg, an abnormal uptake of dopamine by synaptosomes in rats has been reported. It has been found that dopamine D2 receptors are negatively correlated to Hg exposure in wild mink's brain [46]. And reduced dopamine D2 receptor binding was demonstrated in the caudate–putamen region in methylmercury (MeHg)-exposed animals [47]. MeHg exposure during development affected both cortical and striatal dopamine D1 and D2-like receptor density [48]. Further reports have shown that MeHg exposure resulted in increased striatal dopamine levels [49].

Moreover, the observed effects on dopamine levels and functions were age-dependent [50]. These outcomes are in agreement with the results reporting a substantial elevation of extracellular dopamine levels in response to intrastriatal Hg salt injections [51, 52]. Chronic low-dose MeHg exposure induces a remarkable decrease in dopaminergic neuron differentiation from murine embryonic stem cells [53]. Using nematodes as a model of chronic Hg exposure, it was found that MeHg induces degeneration of dopamine neurons [54]. These

studies reported similar findings as the previously reported data from animal experiments, which indicated MeHg-induced neuronal shrinkage and nucleic chromatin condensation in dopaminergic mesencephalic cells [55].

The role of Hg is only one of the hypothetic causative agents in the dopamine-related dysfunctions leading to PD [56, 57]. And the activity of mixed exposures to toxic metals is particularly complex, as it may not be described merely by a classical dose–response mechanism [58]. Therefore, further research is requested to elucidate the etiopathogenetic role of metal pollutants in PD.

Environmental Factors in Parkinson's Disease

PD is considered to involve a multifactorial etiology, including a variety of environmental factors [59]. While about 5–10% of the patients have a type of PD that occurs due to gene mutation, these mutations do not necessarily lead to PD. Usually, the mutations represent susceptibility factors elevating the risk to develop PD, whereas other factors influence the severity and the age of onset [60]. Typically, the Fe accumulation reported in SN is related to inclusions of misfolded proteins. The Fe accumulation may be associated with oxidative damage, which is accompanied by neuroinflammation and misfolding [61]. One theory claims that exposure and accumulation of Fe, Cu, Mn [62], or Hg [63] may aggravate the oxidative damage and thus be involved in the pathogenesis of PD.

After reports on parkinsonism caused by the contaminant MPTP in illegal opioid drugs taken intravenously by abusers [64], much attention has been paid to the role of environmental pollutants in the PD pathogenesis. Pesticide exposure, e.g., to paraquat, rotenone, and maneb, have been associated with increased risk of PD development [65–67]. Paraquat is also a well-known catalyst for ROS formation. In vivo paraquat undergoes a redox cycling, which leads to ROS generation [68]. In rats, toxicity induced by paraquat has been associated with Parkinson-like neurodegenerative mechanisms [69]. Also, a study found a positive connection between combined exposure to Fe and paraquat in mid-life and infancy Parkinson's mice in the laboratory [70].

Xenobiotics

General Aspects

A xenobiotic can be defined as exogenous chemicals or any foreign substance presented within an organism that the body does not recognize such as pollutants, drugs, and cosmetics, as well as some food additives. It is not naturally generated or expected to be found within the organism [71, 72]. These substances are rare or unknown in nature and usually found as synthetic chemicals [73]. Examples of such structural elements are rotenone, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), maneb, and paraquat. The PD etiology has been elucidating as a complex interaction of environmental and genetic agents.

Rotenone

Rotenone is a natural plant-derived pesticide that is regularly applied for the killing of fish in the pool and as an insecticide. Although it is known as an organic substance that commonly proposes to be human non-toxic, it has been reported to be a toxin for mitochondria that control the electron transport chain in complex I [74], inducing progressive oxidative damage and neurodegeneration of non-dopaminergic and dopaminergic neurons. The auto-oxidation of complex I may result from irregularities in complex I assembly factors, rotenone-like complex I toxins, nuclear or mitochondrial encoded subunits, or some combination [25]. The toxic effect of rotenone and the toxic metabolite of MPTP are attributed to their effect on complex I in the mitochondrial electron transport chain. Both these agents inhibit the electron transfer from NADH in the Fe–sulfur center of complex I to ubiquinone (coenzyme Q10). This transport block in the mitochondrial matrix leads to a back-up of electrons that will generate ROS and disrupt DNA, alpha-synuclein, and other integrates of the mitochondria [75, 76]. Rotenone also can damage mitochondria and give typical symptoms of PD [77]. The administration of rotenone by daily intraperitoneal injection (IP) in rat models created postural instability, rigidity responsive to dopamine, and bradykinesia. Postmortem studies of rats showed that nearly half of striatal neurons and the substantia nigra were lost. Furthermore, polyubiquitin-positive aggregates and alpha-synuclein were found in the enteric nervous system, and dopamine neurons in the substantia nigra, similar to the Lewy bodies reported in PD [78, 79]. Also, the aggregation and phosphorylation of amyloid and tau proteins can be induced by rotenone [80, 81]. In a study, during treatment with rotenone, it has been shown that the overexpressing of Mul1 and Park genes that are known to encode mitochondrial ligases protects neurons. Overexpressed *mul1* or *park* in the *Drosophila* strains revealed a remarkably decreased degeneration of normal motor activity and dopaminergic neurons during exposure to rotenone. In addition, rotenone can affect synaptic proteins such as Disk Large1, Synaptotagmin, and Synapsin, as well as the structure of synaptic vesicles in the nervous system [77]. Furthermore, human epidemiological studies have shown that PD may develop commonly in people with regular application of rotenone [10, 82]. Moreover, the Farming and Movement Evaluation (FAME) study showed that rotenone was related to PD regardless of the use of protective gloves [83]. Therefore, with the controversially mixed

laboratory outputs, many supportive laboratory results and supportive human epidemiologic studies propose that PD is likely correlated with rotenone [84, 85].

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was the first-described agent that can induce an animal model of Parkinson's syndrome and/or parkinsonism, although it is not a frequent environmental exposure. It has been reported that different biological properties such as mice strain may lead to insensitivity to the administration of MPTP, reproducibility of lesions in mice, and differing rates of mortality, although there is no documentation on its associated pathological lesions and the possible sensitivity of C57BL/6 mice from various origins to MPTP [86]. MPTP was correlated with the rapid onset of PD in a young victimizer of the drug presented in Northern California [87]. Studies on the mechanism of action of MPTP and its functions may significantly increase our knowledge on the effective role of the nigrostriatal system and dopamine and expand our understanding about the basic mechanisms of cells and about the role of the substantia nigra in health and PD. Among the different models of pharmacological PD, the model of MPTP-stimulated PD has been regularly applied because of no requirements for experimental technology, reproducible and reliable lesions in the nigrostriatal dopaminergic pathway, and similar clinical symptoms with PD patients [88]. MPTP can damage neurons through inhibiting complex I of the electron transport chain [89]. Non-human primates and studies of rodents have reported that MPTP induces depletion of striatal dopamine with selective eradication of dopaminergic neurons in the substantia nigra. Also, other areas of the brain, such as the locus ceruleus, and other non-dopaminergic regions, are significantly spared in MPTP-stimulated parkinsonism. Also, not progressive and stable symptoms, as well as no Lewy Body pathology, may be seen in postmortem analysis after MPTP exposure in developed parkinsonism individuals [64].

Furthermore, postmortem tissue evaluation has also reported ongoing, active inflammation with the presence of extracellular melanin, microglia, and neurodegeneration, after some years of MPTP exposure, suggesting to the concept of "long-latency neurotoxicity" after first exposure [64]. It has been hypothesized that ongoing inflammation and oxidative stress can lead to nigral cell loss and are proposed as the mechanism for the continued and progressive degeneration [90].

Maneb and Paraquat

The fungicide maneb and the herbicide paraquat are known as the oxidative stressor that was correlated with PD [10, 65, 91, 92]. The chemical structure of paraquat is closely similar to the active metabolite of MPTP. Maneb and paraquat also likely have synergistic effects [93]. Paraquat induces tissue damage through the subsets of the redox cycle that produces toxic superoxide free radicals. In *Drosophila* flies, a mimetic enzyme of superoxide dismutase has been reported to decrease the mitochondrial damage induced by paraquat [94].

Moreover, in vivo animal investigations reported that paraquat induced the glutamate efflux initiating excitotoxicity regulated by reactive nitrogen species [95]. Other studies also have reported that paraquat stimulates the upregulation of alpha-synuclein [96], microglial activation, and aggregate formation [97, 98]. Dopaminergic neuronal cell death in the basal ganglia also can be induced by systemic subchronic exposure to paraquat in mice, although the levels of dopamine remained unchanged [99]. Furthermore, elevated doses of chronic paraquat exposure did induce delayed decrease of dopaminergic neurotransmission and slow progressive degeneration of nigrostriatal neurons, indicating that paraquat may induce "subclinical" results and additional genetic or environmental agents may be demanded if PD develops. Also, an epidemiologic study revealed a significant decrease in the glutathione transferase gene that induces cellular protection against oxidative stress was associated with an elevated risk of PD when male subjects were exposed to paraquat [100]. Also, dopamine transporter susceptibility alleles may be seen in exposure to paraquat and maneb and led to a higher PD risk [101]. The results of a study also showed that NADPH oxidase is involved in maneb- and paraquat-stimulated dopaminergic neurodegeneration by ferroptosis, suggesting a new potential mechanism for pesticide-stimulated dopaminergic neurotoxicity [102].

Furthermore, the rapid influx of extracellular zinc (Zn^{2+}) into dopaminergic neurons by transient receptor potential melastatin 2 (TRPM2) cation channel activation induced by paraquat can accelerate the degeneration of nigrostriatal dopaminergic in aged rats. It is possible that vulnerability to paraquat-induced pathogenesis in the aged substantia nigra pars compacta is due to accelerated dysregulation of intracellular Zn^{2+} [103]. This area needs more human studies since our knowledge was restricted by exposure to multiple pesticides in addition to paraquat and small sample size.

β-Methylamino-L-alanine

β-Methylamino-L-alanine (BMAA) is an excitotoxin that allegedly globally contributed to neurodegenerative diseases such as the Parkinson–dementia complex (PDC), a neurological disorder with motor neuron disease symptoms [104]. Numerous in vitro studies performed on leeches, rats, mice, and human cells have reported the detrimental effects of BMAA on neurons [88]. It has been reported that the most commonly involved mechanism for the action of BMAA is the process of cell death-inducing because of excitatory amino acid (EAA) receptor activation (particularly glutamate receptors). BMAA is correlated with the three potential approaches of degeneration in PD, including excitotoxicity, mitochondrial

dysfunction, and non-cell autonomous death [105]. Also, BMAA exposure induces CNS cell death in the mice through the examining glial response and neuronal numbers in the brain and the spinal cord. No motor, neuropathological, or cognitive outcome resulted from this feeding pattern, indicating a lack of neuropathological and behavioral effects of dietary BMAA in mice [104].

Furthermore, another investigation reported that BMAA might be involved in human neurodegenerative diseases [106]. Following numerous exposure, BMAA can accumulate in the brain. However, in the male rats, BMAA was slowly eradicated from other tissues and blood (half-lives ≥ 48 h). On the other hand, there is no higher affinity for accumulation in the brain compared with the other tissues and organs [106]. Numerous studies on BMAA effects showed conflicting effects, although some in vitro data are revealing a neurotoxic effect, and experimental animal evidence failing to replicate the neurodegeneration pattern of these human Parkinson–dementia complex (PDC), even at very high exposures.

Metals and Parkinson's Disease

General Aspects

The role of dopamine in PD is well established. However, its wide activity in many regions of the midbrain makes the toxic role of xenobiotics as promoting ROS exacerbation of the utmost role not only in PD but in many degenerative neurological diseases (Fig. 1). The effective function of metals in the pathogenesis of PD is known as a great concern in medical chemistry and neurotoxicology [56, 107]. This role is known either by a decrease in essential metals or by metallic toxicants for human health. For example, numerous epidemiological researches also have reported a positive relevance between long-term exposure and PD to metals such as Mn, Hg, Cu, lead (Pb), Zn, Fe, bismuth (Bi), aluminum (Al), and titanium (Ti) after chronic exposure to multiple metals [108–110]. The important sources of exposure comprised occupational exposure, contaminated seafood, environmental pollution, dental metal restorations such as amalgam fillings, and medications [56]. Occupational exposures to Al, Mn, and Fe have been reported to double the risk of occurrence of PD [109, 111]. Synergistic effects also were reported between PD and metals with combined exposures of Pb–Cu, Pb–Fe, and Fe–Cu in comparison with the effects of single metals [112, 113]. Also, metals stimulate the α-synuclein aggregation that is a highly abundant, small, and conserved presynaptic protein with neurodegenerative function in the PD etiology [114, 115]. Finally, it has been demonstrated that Hg and other metals may be involved in PD development.

Manganese

Several studies of rapid-onset parkinsonism have reported that exposure to Mn of young intravenous drug users through ephedrone (methcathinone) abuse can be the critical factor of PD [116–118]. Manganese also is known as a basal ganglia toxin related to PD, although there are controversial results about its relevance with idiopathic PD [119, 120]. The neurotoxicity mechanism of Mn is the globus pallidum degeneration regulated through the disruption of the apoptosis and cell death mitochondria by the formation of elevated ROS [121]. Manganese can inhibit glutamate transport, inducing the elevation contents of glutamate and therefore induce cytotoxicity [122]. Also, Mn is rapidly absorbed by the mitochondria and stimulates the accumulation of calcium and controls oxidative phosphorylation, leading to ATP depletion [123]. The exposure to a low concentration of Mn was related to elevation of contents of astrocytosis in the motor and striatum as well as specific motor symptoms similar to PD, indicating Mn is a great neurotoxicant. The toxicity of Mn is reported in the central nervous system, particularly in the nigrostriatal neuronal circuitry, and consequences include motor and behavioral impairments [124]. Also, there is a rare understanding about neurobehavioral mechanisms among patients with idiopathic PD and patients with manganism, although there is a study with 13 patients with PD, 34 patients with manganism, and 43 healthy workers as the reference group. In this study, it was revealed that PD patients had greater postural tremor intensity with narrower frequency dispersion compared with the patients with manganism. However, the asymmetrical neurobehavioral performance was reported commonly in PD patients compared to manganism patients, particularly science testing for static steadiness, tremor intensity, and grooved pegboard suggesting lateralized impairment in the PD patients [125]. Therefore, it has been reported that Mn can be described as a neurotoxic substance because of neuroinflammation mitochondrial dysfunction and oxidative stress, and protein trafficking and misfolding [125]. Furthermore, despite the distinction between idiopathic PD and Mn neurotoxicity, there are some supportive studies that highlight the exposure with Mn can be a risk factor for PD [113].

Mercury

Remarkably elevated blood levels of Hg were reported in patients with PD regarding controls, and it has been demonstrated that Hg exposure was correlated with an eightfold increase in the PD risk [126]. However, particular neurodegenerative effects and neuronal modifications that have been seen in PD are only detectable with the Hg exposure at the lowest contents. Particularly, nigral dopaminergic neurons are very sensitive to Hg because of elevated glutamate toxicity and their high content of tubulin [56]. PD onset has been

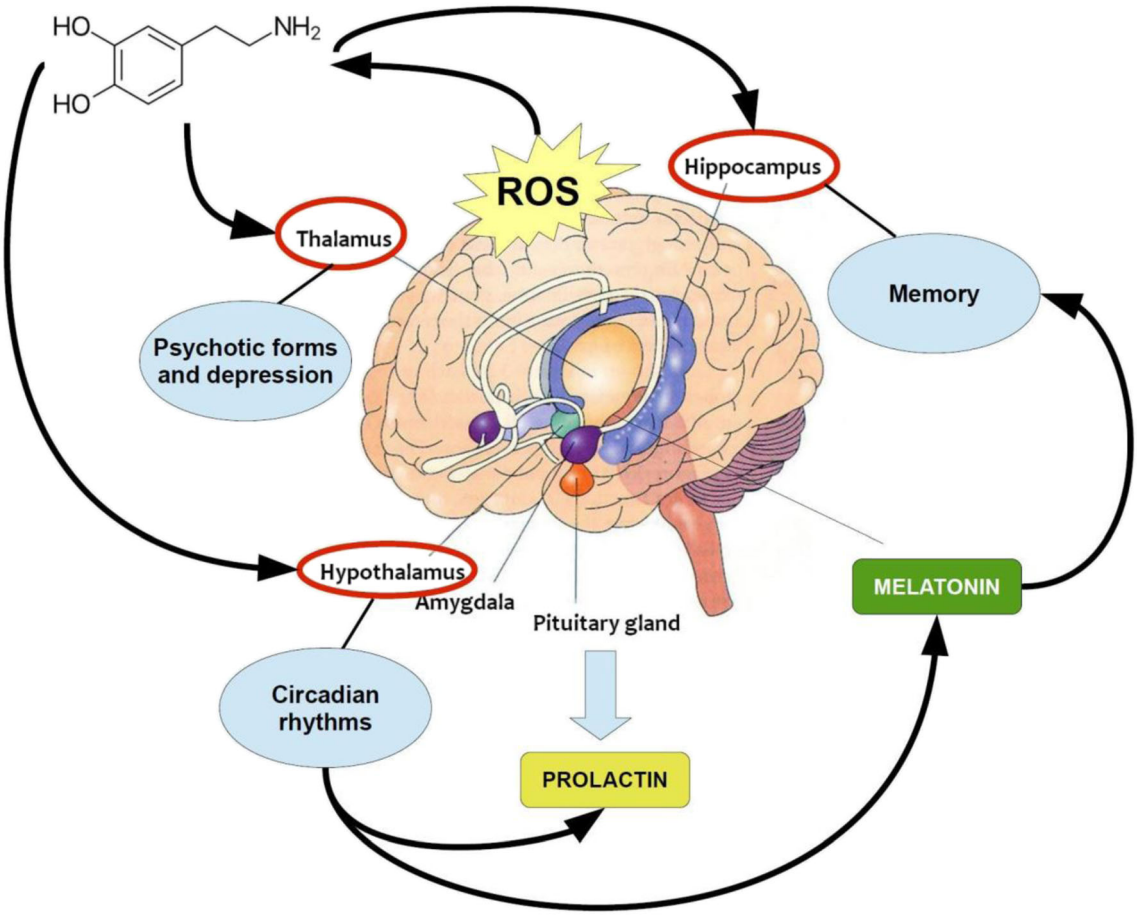

Fig. 1 The possible major pathways involved in the dopamine-related actions causing neurodegeneration. Considering that the impaired signaling of reactive oxygen species (ROS) provoked by metal pollutants and xenobiotics induces a dopamine activity disorder, this may involve thalamic response to dopamine, with the onset of psychotic and cognitive impairments, and the hypothalamus, with circadian regulation. Toxic metals can also modulate or exacerbate the relationship dopamine/prolactin, while melatonin can modulate the impairment of dopamine in circadian and seasonal rhythms acting on the dopamine circuitry in the hippocampus. Many of these activities are included in several signs of neurodegenerative and aging-related neurological disorders. This should give suggestions about the widest role of the dopamine signaling in neurodegenerative diseases

associated with exposure to elevated levels of Hg [58]. Numerous similarities between the effects of Hg ingestion/exposure and the consequences/symptoms of patients with PD have been reported, although Hg has not only been related to the PD incidence [56]. It has been reported that in patients with PD, the detectable blood Hg contents were six times more frequent compared with healthy individuals [127]. The sources of Hg exposure comprised long-lived fish consumption (such as tuna), dental amalgam, occupational exposures, and medications. A significant dose–response relevance was found between PD patients and blood Hg levels [128]. It has been found that intoxication with Hg can induce parkinsonism in a 47-year-old dentist, and consequences chelation treatment, induced health [129]. Methylmercury can cross through placental barriers and the blood–brain barrier, inducing neuronal damage in the central nervous system. Also, Hg vapor, being highly lipid-soluble and volatile, can pass through the lipid cell membranes and the blood–brain barrier and can be stored into the cells in its inorganic forms [130]. In vitro studies reported that exposure with Hg was importantly contributed in apoptotic processes and oxidative stress. Furthermore, neural loss and cognitive and motor impairment have been showed in different studies carried out in animal models [41, 130, 131]. Finally, observational investigations on PD patients with neurodegenerative diseases reported conflicting data on the possible involvement of Hg [132, 133].

Iron

Iron has been reported to be possibly connected with the PD pathophysiology in numerous laboratory investigations, although the documented data of human exposure is rare [134, 135]. Some studies have reported that increased dietary Fe is associated with PD [97, 98], while there are conflicting data on serum Fe levels and their relevance with PD [136, 137]. A deficiency of Fe can impair the function of the central or

peripheral nervous system, which may induce restless legs syndrome with PD [138]. Also, in a case–control study with idiopathic PD and controls, the effective role of occupational exposure to Fe, Mn, Cu, Zn, Pb, and Hg as potential risk factors for PD has been investigated. The result of this study reported that chronic exposure to each or a combination of these metals is related to PD [113]. Substantia nigra neurons have some neuromelanin that can link with the Fe and generate free radicals that affect cell death and lipid peroxidation [139]. Iron also can induce dopamine oxidation in substantia nigra neurons, which led to the release of further free radicals [140]. Higher concentrations of Fe in the substantia nigra of patients with PD also have been reported in pathological studies [141]. Also, animal experiments have reported that in MPTP-stimulated parkinsonism, Fe chelation has shown therapeutic effects [142]. A total of 135 patients with PD were divided according to the ratio of mean tremor score to the mean bradykinesia/rigid score of the Unified Parkinson's Disease Rating Scale (UPDRS) III and showed the interaction between relevant inflammation and disturbed metabolism of Fe might regulate clinical phenotypes of PD [143]. Abnormal accumulation of Fe is correlated to a host of neurodegenerative diseases, such as PD through a malfunction of Fe homeostasis or the abnormal deposition in specific brain regions [144]. Most of the investigations with PD patients focus on the Fe overload of the brain in regions, including the putamen, globus pallidus, and substantia nigra neurons [145, 146]. A study also has confirmed that the Fe depositions in the red nucleus dentate and the nucleus of the cerebellum are associated with tremor in patients with PD [147]. However, more studies need to be done on the relevance of Fe and its metabolism-related proteins in both the peripheral and central systems, and different motor PD phenotypes. Finally, whether the accumulation of Fe can stimulate the substantia nigra neuron injury or occurs as a subsequence of neuronal degeneration needs clarification.

Metal Chelators and Neurotoxicity

Chelators bind to some substances such as metals in different degrees. The mechanism of chelators is composed of the construction of chelator–metal complexes (chelates) that are secreted in urine [148]. A chelating antidote may be used orally or intravenously in cases of metal toxicity. Depending on the chemical affinity for the toxic metal, some compounds such as 2,3-dimercaptopropane-1-sulfonic acid (DMPS, Dimaval, Unithiol), ethylenediaminetetraacetic acid (EDTA), or meso-2,3-dimercaptosuccinic acid (DMSA, Succimer) are given as intermittent courses or continuously for several days. Some studies proposed that oral DMSA is the safest and efficient chelation treatment regimen directly available in moderately Pb-poisoned cases. Human and animal data suggest that DMSA should be evaluated as the approved antidote to move Pb from soft tissues [149]. Also, DMPS treatment can increase the urinary excretion of Zn and Cu [150, 151], in which case deficiency symptoms may be reported in some patients. Also, it has been identified that the combination of DMSA and Monensin, a polyether antibiotic, is even more effective in Pb mobilization from the kidneys and brain in comparison with their being used alone. The proposed pathways for this is that Monensin can act as a Pb shuttle in exchange for external sodium [152]. Numerous studies have reported the concerns of the Pb–EDTA complex that might be redistributed in the brain. Therefore, they suggest that DMSA is safer than CaEDTA because of extracellular scavenging of Pb [153]. It has been reported that EDTA can induce greater losses of essential minerals such as Fe, Zn, Mg, and Ca in comparison with DMPS and DMSA [154]. Other reported side effects of EDTA chelation include lacrimation, mucocutaneous lesions, glucosuria, nasal congestion, and hypotension [148]. Therefore, a promising chelating agent can generate less toxic metal complexes and reach the body's metal storage sites. Also, a good chelator should have a high affinity for the toxic metals at the pH of the body fluids, be easily soluble in water, and be resistant to biotransformation [155, 156].

Deferiprone, other iron chelators, and PD

In the PD brain, a feature is the crucial accumulation of Fe in degenerative regions [157]. Although Fe levels in the PD brain may be moderately increased in several regions, in early PD is neuronal loss limited to SN [158] where a pronounced Fe deposition is reported in PD brains [159]. An interaction between an extra-vesicular fraction of dopamine and electrophilic Fe ions is thought to have an important role in SN progressive degeneration, which initially creates an unstable complex that increases the neurotoxic products particularly in sensitive regions of the brain [160]. One theory involves the production of dopamine-quinones (DA-quinones), o-quinones, and 6-hydroxydopamine (6-OHDA) [161]. The latter is in animal PD models, a frequently used neurotoxin [160]. In the cell, DA-quinones interact with the protein thiols and sulfhydryl groups of glutathione (GSH) to produce changed proteins [162] that induce cellular toxicity [163]. It has been suggested that 6-OHDA formation initiates a cascade of mechanisms that increase the labile e pool in the cell, therefore great protective antioxidant pathways [160].

Devos et al. (2014) studied the effect of Fe chelation with deferiprone in both mice and minor clinical trials of patients with early-stage PD [164]. In mice, dopaminergic dysfunction after chelation treatment was shown to be reduced due to subsequent administration of MPTP. MRI was used to quantify the deposition of nigral Fe, and the improvements of the patients after deferiprone treatment were assessed using the Unified Parkinson's Disease Rating Scale. It has not yet evidently been reported in PD that chelation therapy of Fe

restores the dopaminergic system integrity. However, these data support the hypothesis that deferiprone may modify the PD progression. It is possible that chelation of Fe can be even more useful if initiated in a subclinical or early stage of PD. Experimental studies by the same or other research group support the observations of a therapeutic effect of Fe chelation with deferiprone or deferasirox in PD [165]. It has been reported that after 6 months of chelator deferiprone therapy, it can be effective through the improvement of gait and reduction in dyskinesias in neurodegeneration associated with brain Fe overload [166]. It can cross the blood–brain barrier in effective concentrations and lead to progress in the phase II trial for deferiprone to evaluate its efficacy and safety as an Fe chelator for excess contents of Fe in the PD treatment [167]. In a pilot, double-blind, placebo-controlled randomized clinical trial study, deferiprone remarkably decreased biological damage and labile Fe in oxidation-stressed animals and cells at 30 mg/kg/day through the improvement of motor functions in increased striatal dopamine [164].

Concluding Remarks

The present paper has highlighted the role of environmental factors in the pathogenesis of PD since lifestyle factors, exposures to metals, pesticides, and drugs, seem at least to account for 90% of the cases. Preventive measures in PD have to take into consideration that primary causes in the development of the disease are abnormal protein aggregation and inhibition of mitochondrial complex I, and in particular pathological oxidative stress in the nigrostriatal neurons. Since excesses of Fe that have been identified in SN regions can speed up the oxidative stress, mobilization of this element from the vulnerable areas is anticipated to slow down the progression. Such mobilization can be obtained by chelating agents (deferiprone or deferasirox).

Early clinical signs of PD are reduced ability to move with slow movements, and the steps of these patients may become shorter when walking. Muscle stiffness may occur in any part of the body, often distally in extremities. Some tremor may occur already in the early stages. Similar symptoms are also described in another neurological disease, the so-called Skogholt disease, characterized by neuroinflammation and concomitant notable increases in levels of Fe and Cu in CSF. And it has been suggested that the latter disease is also caused by combined toxicity of Fe and Cu accompanied by oxidative stress, i.e., in regions in basal ganglia.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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