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Oxidative Stress and Parkinson's Disease: Effects on Environmental Toxicology

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Abstract

Epidemiological studies have found an increased risk of Parkinson's disease (PD) with environmental factors such as exposure to substances derived from industrial processes, use of agrochemicals, or living in a rural environment. The hypothesis that certain environmental toxins could be the source of the EP is supported by the discovery that chemicals such as herbicides paraquat, diquat, and the fungicide maneb are selectively toxic in nigrostriatal dopaminergic neurons. Also, one of the insecticides produced by plants, such as rotenone, and by-product of the synthesis of synthetic heroin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) can be reproduced in animal models where neurochemicals, histopathological, and clinical characteristic of PD can be found. Interestingly, there are similarities in the chemical structure of paraquat and MPTP. Recent evidence exhibited that inflammation and oxidative stress play an essential role in the development of PD. So, in our laboratory we found that in an animal model melatonin decreases the products of lipid oxidation, nitric oxide metabolites, and the activity of cyclooxygenase 2, which are induced by an intraperitoneal injection of MPTP. This suggests that the neuroprotective effects of melatonin are partially attributed to its antioxidant scavenging and anti-inflammatory action.

Keywords: dopaminergic neurons, melatonin, MPTP, paraquat, Parkinson, Parkinsonism

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by tremor and disruptions to voluntary movement. The main neuropathology in PD involves the death of dopaminergic cells in the pars compacta of the substantia nigra with intracytoplasmic inclusions (Lewy bodies) in the remaining intact nigral neurons [1]. Neuronal loss in the substantia nigra increases with age in PD, consistent with a worsening prognosis and increased symptom severity in older patients. The substantia nigra is an anatomical region of the brain implicated in dopamine synthesis and voluntary motor control and is a part of the basal ganglia. Neural circuits in the basal ganglia, particularly the nigrostriatal pathway, appear to be crucial to the successful execution of both innate and learned motor behaviors [2].

PD primarily affects people of ages 50 and older, and the prevalence and risk of developing sporadic PD increases substantially with age and has an incidence rate of 18 per 100,000 per year [3]. As the disease progresses, significant motor disability is seen in PD patients even when treated with symptomatic medications. Symptoms like dysphagia, sialorrhoea, microphagia, and dystonia are also well-known. Nonmotor symptoms include cognitive impairment [4], neuropsychiatric symptoms (depression, psychosis, anxiety, and fatigue), sleep dysfunction (rapid eye movement sleep behavior disorder, sleep attacks, daytime sleepiness, advanced sleep phase syndrome, and early morning awakenings) [5], autonomic disturbances (constipation, nausea, orthostatic hypotension, and urogenital problems), and sensory disturbances (restless legs syndrome, visual changes, and decreased olfaction) [6]. Interestingly, increased mortality risk has been linked with both motor and nonmotor features in newly diagnosed PD patients, especially with features like postural instability, hallucinations, and cognitive impairment [7].

No definitive diagnostic test such as magnetic resonance imaging or computed topography scans or genetic tests can confirm PD. Its diagnosis is typically based on the presence of a combination of key motor features, such as associated and exclusionary symptoms, and response to levodopa [8].

The molecular mechanisms underlying the loss of these neurons still remain elusive. Different modes of cell death, apoptotic, necrotic, and autophagic, have been described to contribute to the neuronal loss occurring in PD [9]. Oxidative stress plays an important role in dopaminergic neurotoxicity. Mitochondrial complex I deficiencies of the respiratory chain account for the neuronal degeneration in PD. Neurotoxins and other environmental factors, such as pesticides, insecticides, dopamine metabolites, heavy metals, microbial toxins, and genetic mutations, in PD-associated proteins contribute to mitochondrial dysfunction [10, 11]. A byproduct of an illicit narcotic drug, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as well as its metabolite MPP⁺, has been shown to cause the same signs and symptoms as PD. In fact, inhibitors of mitochondrial complex 1 (MPTP, rotenone, and paraquat) are able to reproduce parkinsonism with selective dopaminergic neuronal loss in mice and primate models [12]. Furthermore, a chronic infusion of either rotenone [13] or MPTP [14] in rodents induces the formation of α -synuclein positive aggregates. These data support the suggestion that sporadic PD may be caused by a combination of genetic predisposition and environmental toxins, which

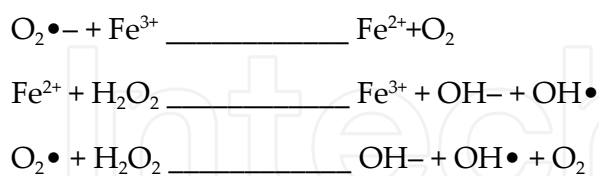
act via inhibition of the mitochondrial complex I to produce selective dopaminergic cell loss. Human epidemiological studies have implicated a higher incidence of PD in residents of rural environments with exposure to herbicides and pesticides [15].

2. Oxidative stress

The body is constantly exposed to the influence and attack of free radicals, which have been associated with various disorders of the nervous system such as Parkinson disease, the motor neuron disease, and other disorders of the central nervous system (CNS). A free radical is considered any molecule containing one or more unpaired electrons. It is produced by biochemical redox reactions occurring as a result of normal cellular metabolism (biochemical reactions with oxygen or produced as a result of oxidative stress), as well as by phagocytes in inflammatory reactions controlled in response to exposure to different environmental factors, including ionizing radiation, ultraviolet rays, smoking, air pollution, gamma radiation, hyperoxia, excessive exercise, ischemia, and toxic compounds such as cancer drugs, some anesthetics, and painkillers [16].

The main free radicals are superoxide anion ($O_2^{\bullet-}$), hydroxyl (OH^{\bullet}), nitric oxide (NO^{\bullet}), and peroxy (ROO^{\bullet}) [17]. Some of them are considered highly reactive molecules that can cause cell damage and even death. Usually, the most damaged cellular components are unsaturated fatty acids in cell membranes and proteins such as enzymes conveying ions across membranes.

It is estimated that mitochondria are the main source of oxygen radicals (**Figure 1**) [18] in which anion superoxide ($O_2^{\bullet-}$) is generated during electron transport. Superoxide dismutase (SOD) converts $O_2^{\bullet-}$ to hydrogen peroxide (H_2O_2) by the Fenton reaction; the latter in the presence of Fe^{2+} produces hydroxyl radical (OH^{\bullet}) by reacting Fe^{2+} and Cu^+ . Then, the Fenton reaction is expressed as



According to Burdon and Mattson 1995 and 1998, the $O_2^{\bullet-}$ may also interact with nitric oxide (NO^{\bullet}) to form peroxynitrite ($ONOO^-$). Of all free radicals, OH^- is the most damaging free radical, since its presence—though is only a fraction of a second—is able to destroy proteolytic enzymes causing rupture of polysaccharide and lipid membrane peroxidation (LMP) altering its permeability and associated features [19] (**Figure 2**). Peroxynitrite ($ONOO^-$) can cause direct damage to proteins and DNA, and is also a potent inducer of LMP that can destroy neurons, which are especially sensitive to this process. Oxidative stress can occur in different acute degenerative conditions such as cerebral ischemia, traumatic brain injury, and chronic degenerative processes such as Parkinson's disease [20]; it is observed, to a lesser extent, in neural circuits during normal physiological activity.

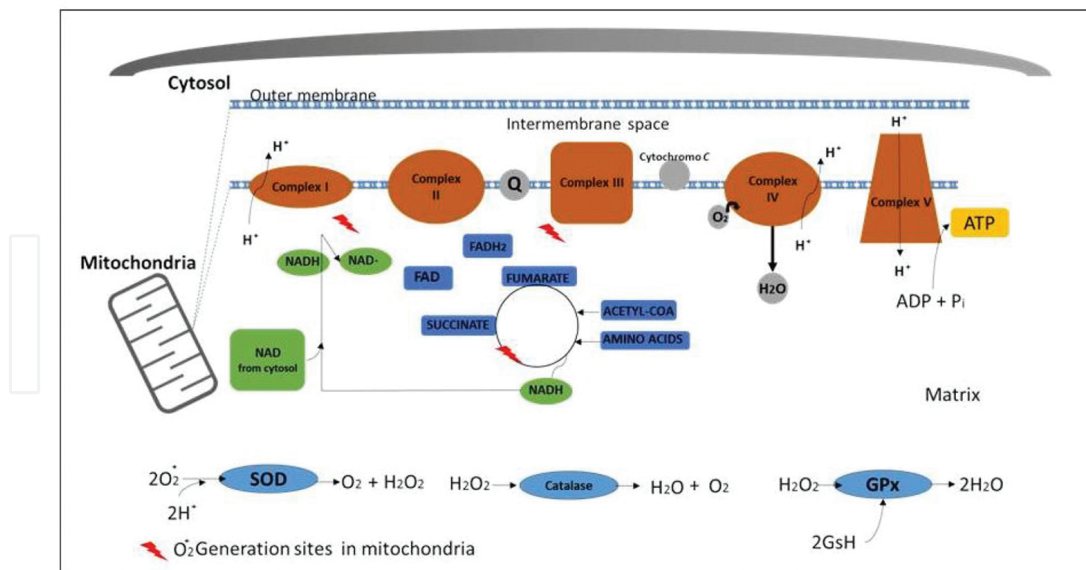


Figure 1. Mitochondria are considered the main source of free radicals, which come from the electron transport chain. Within mitochondria, $2O_2^{\cdot -}$ is produced by the one-electron reduction of O_2 . Therefore, it is the kinetic and thermodynamic factors underlying the interaction of potential one-electron donors with O_2 that control mitochondrial ROS production.

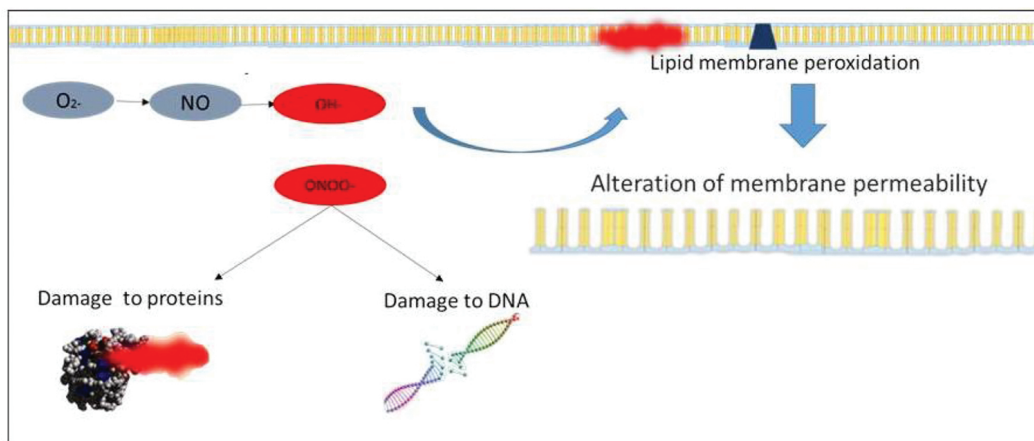


Figure 2. Damage generated by free radicals (ONOO⁻, OH[•]) directly affects proteins, membrane phospholipids, and DNA molecules. The resulting free radicals, such as superoxide anion ($O_2^{\cdot -}$) and hydroxyl radical (OH[•]), as well as the nonradical hydrogen peroxide, can damage macromolecules, including DNA, proteins, and oxidized lipids have all been related in such damages. The superoxide radical, although it is unreactive in comparison with many other radicals, biological systems can convert it into other more reactive species, such as peroxyl (ROO[•]), alkoxy (RO[•]), and hydroxyl (HO[•]) radicals.

On the other side, oxidative stress can cause the onset of a disturbance in cellular calcium homeostasis. This action is usually related to an effect on the receptor mobilizing Ca^{2+} , but the decrease of Ca^{2+} ATPase activity is also evident. Reactive oxygen species (ROS) also interfere with other transduction signal systems through the action of nitric oxide (NO) [21] (**Figure 3**). Reactive oxygen metabolites affect ligand binding to membrane receptors such as β -adrenergic, cholinergic, muscarinic, histamine, and serotonin. Some reactive oxygen species can affect enzymatic pathways such as the phospholipase A [22].

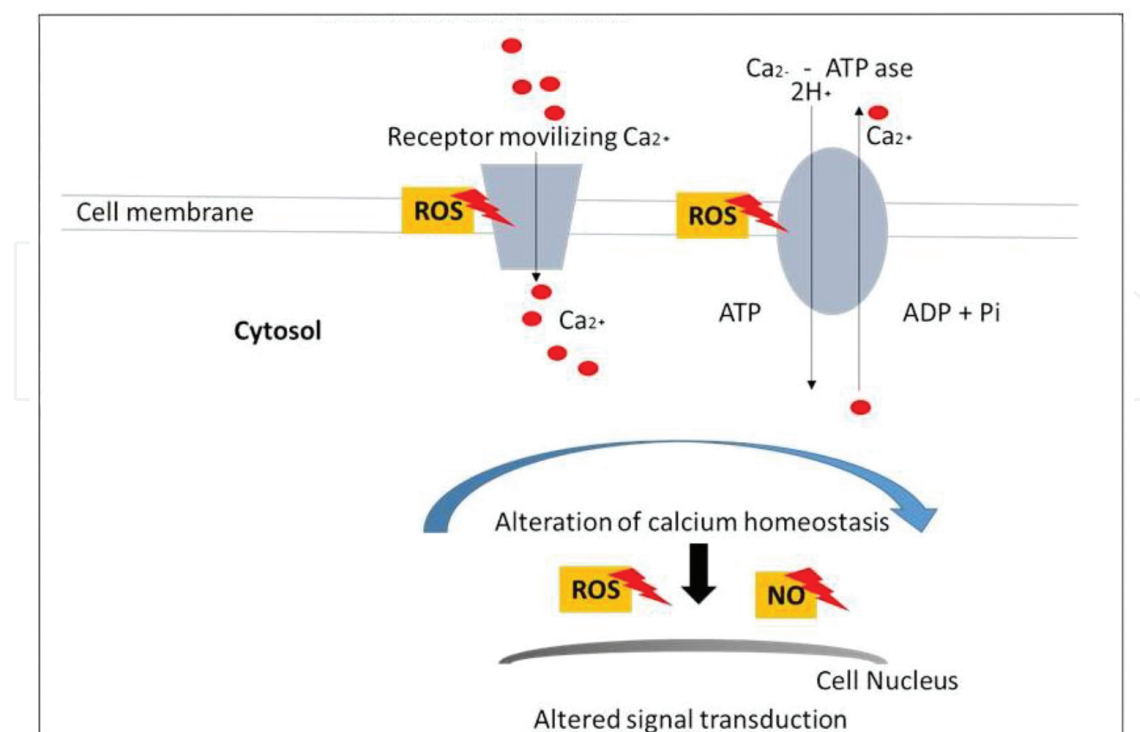


Figure 3. ROS can disrupt calcium homeostasis through its effect on receptors on the cell gate ionic membrane, calcium ATPase, and interfere with signal transduction. Interactions between Ca²⁺ and reactive oxygen species signaling coordinate signaling, which can be either beneficial or detrimental. In neurodegenerative disorders, cellular Ca²⁺-regulating systems are compromised. Oxidative stress, perturbed energy metabolism, and alterations of disease-related proteins result in Ca²⁺-dependent synaptic dysfunction.

Free radicals formed in the organism can initiate a series of chain reactions which continue, after several reactions, until removed with other free radicals or by the antioxidant system, which protects tissues from their deleterious effects. According to the mode of action, three main types of antioxidants are known: (a) those preventing the formation of new free radicals, (b) those making them less harmful before they can react, and (c) those preventing the formation of free radicals from other molecules.

The enzymes involved in the antioxidant system are superoxide dismutase glutathione peroxidase (GPx), catalase, glutathione reductase, glutathione S transferase, and other proteins that bind metals (ferritin, transferrin, and ceruloplasmin) limiting the availability of iron necessary to form the •OH radical.

Excessive ROS reactive nitrogen species (RNS) generation may contribute to cell injury and death. In particular, accumulation of nitrosative stress due to excessive generation of nitric oxide (NO) appears to be a potential factor contributing to neuronal cell damage and apoptosis. In this process, overstimulation of N-methyl-D-aspartate-type of glutamate receptors permit calcium influx Ca²⁺ to cell, increasing NO and promoting ROS formation through a process named S-nitrosylation which consists in a reaction between NO and cysteine thiol to form S-nitrosothiols (SNOS). In addition, NO can react with superoxide to generate peroxynitrite (ONOO⁻), which is highly toxic to cell, as well [23].

3. Clinical manifestations of Parkinson's disease

PD is a common neurodegenerative disorder characterized by progressive loss of *substantia nigra* dopaminergic neurons, and the concomitant loss of dopaminergic nerve terminals in the *caudo-putamen* nuclei, which is the main neuron projection area of the *substantia nigra*. PD affects about 1% of the population over 65 years, which increases to up to 4% after the age of 80 [24]. Its main symptoms were described in 1817 by James Parkinson in an essay called the "shaking palsy." From a clinical point of view, PD is characterized by tremor at rest, slow movements (bradykinesia), rigidity, postural instability, stiffness of the muscles, serious inability to initiate movement (akinesia), and mask-like face expression. Other symptoms may be a flexed posture, freezing (motor blocks), loss of arm swing on one side, loss of smell, or a persisting glabellar tap reflex. However, the above mentioned symptoms may not all be present in one patient [25]. Bradykinesia, slowness of movement, is the most characteristic symptom. PD patients may therefore show slowness in daily activities and slow reaction times and may have difficulties in fine motor control [26].

A number of nonmotor features can precede the motor symptoms of PD. These symptoms probably arise from extra-nigral structures. For instance, olfactory deficits [27] and cardiac sympathetic denervation [28, 29] are present in a very high proportion of patients presenting with the earliest motor signs, suggesting that such features probably precede the motor signs and may be more useful in characterizing early disease status. Other nonmotor symptoms include autonomic, mood, cognitive, and sensory dysfunctions, as well as sleep disturbances [30, 31]. Depression is the most frequent psychiatric complication in PD. Although depression often precedes motor symptoms in PD [32], it may still reflect impairments of the nigrostriatal dopaminergic circuit [33]. Anxiety is also comorbid with PD [34]. These nonmotor symptoms significantly contribute to the reduced quality of life in PD patients, but are frequently undiagnosed and left untreated [35, 36].

4. Physiopathology of Parkinson disease

One of the most surprising aspects of PD is the selective vulnerability of neuronal population to damage. PD can occur when an external or an internal toxin selectively destroys dopaminergic neurons. When the neurons which connect two specific brain regions, the compact part of the substantia nigra (SNPC) and the striatum, essential to maintain the motor function die, the dopaminergic pathway progressively degenerates, and the level of dopamine in the striatum decreases causing changes in brain circuitry and motor features of PD deficiencies appear.

The main pathological findings of PD are the loss of dopaminergic neurons and formation of fibril aggregates composed of α -synuclein, called Lewy bodies, in the remaining dopaminergic neurons located in substantia nigra pars compacta [37]. DA neurons of SNPC also have a tendency to degenerate with aging at a rate of approximately 5% per decade. In contrast, the

rate of neurodegeneration in PD patients is about 10-fold faster and occurs mainly in the ventro-lateral part of SNPC [38].

The degeneration of neuronal cells may be the consequence of many pathogenic factors (toxic, infectious, genetic, metabolic, vascular, etc.) and the final consequence is apoptosis and cell death in which caspases (particularly caspase 3) and Bcl-2 protein families are central components with up and down regulatory mechanism that promotes apoptosis. Two main caspase-mediated pathways of cell death have been described in mammals: (a) the extrinsic or death receptor-mediated pathway, which has a critical role in the maintenance of tissue homeostasis, and (b) the intrinsic, mitochondria-dependent pathway that is mainly activated in response to extracellular cues and internal insults such as DNA damage, growth factor deprivation, cytoskeletal disruption, accumulation of unfolded proteins, hypoxia, and many others [12, 19–21, 39–42].

In vivo, the dysfunction of the proteasomal system in order to cleave misfolded α -syn due to lack of energy associated to mitochondrial damage, and problems with the autophagy-lysosomal degradation pathway, which disrupts damaged mitochondrial clearance, leads to the formation of protein inclusions and accumulation of damaged mitochondria, a major source of ROS, which activate the apoptotic cascade as has been mentioned. ROS accumulation may result in detrimental effects such as lipid peroxidation, protein oxidation, and further DNA damage. The maintenance of a pool of healthy mitochondria that can meet the bioenergetic demands of a neuron is therefore of critical importance; this is achieved by maintaining a careful balance between mitochondrial biogenesis, mitochondrial trafficking, mitochondrial dynamics, and mitophagy. Removal of damaged mitochondria through mitophagy can lead to the release of compartmentalized mitochondrial molecules. Once in the cytosol, some of these molecules, such as cyt-C, Smac/DIABLO, and HtrA2/OMI, are capable of activating apoptotic routines that lead to cell death. It is then reported that the failure of mitophagy results in the release of mtDNA into the cell cytosol contributing to mechanisms of cell death [43–47].

The central events in the mitochondrial-dependent cell death pathway are the activation of the mitochondrial permeability transition pore (mPTP) and the disruption of mitochondrial membrane potential, which cause the release of apoptogenic molecules and finally lead to cell death [48]. The protein α -syn is a small acidic protein containing 140 amino acids. This protein is able to undergo self-aggregation in a nucleation-dependent process to form nonfibrillar oligomers, protofibrils, and fibrillar aggregates with amyloid-like properties that are potentially cytotoxic to the neurons and it has been shown to be directly degraded *in vitro* by the 20S proteasome. Studies of the degradation of aggregated α -syn led us to suspect that oxidation of Met may play a role in α -syn degradation by the proteasome [46].

It is important to take into account that neuronal loss in PD is also associated to chronic neuroinflammation through microglial activation by some different mechanism including overexpression of inducible NOS (iNOS), COX-2, the cytokines tumor necrosis factor-alpha (TNF- α), and IL-1 β and NO or accumulation of heat shock protein 60 (Hsp60) participating in DA cell death in PD via a mechanism unrelated to cytokine release and could serve as a signal of CNS injury through activation of microglial cells. Neuromelanin is released from dying dopaminergic neurons in the SNpc and activates microglia, provoking increase in the sensi-

tivity of DA neurons to oxidative stress-mediated cell death. Parkinson's disease-associated proteins such as α -syn, parkin, LRRK2, and DJ-1 have also been reported to activate microglia, as well [11, 49].

One of the most surprising aspects of neurodegenerative diseases is the selective vulnerability of neuronal population to damage. Parkinson's disease can occur when an external or an internal toxin selectively destroys dopaminergic neurons. When the neurons which connect to two brain regions, the compact part of the substantia nigra (SNPC) and the striatum, essential to maintain the motor function die, the dopaminergic pathway progressively degenerates and the level of dopamine in the striatum decreases causing changes in brain circuitry, and motor features of PD deficiencies appear. The high vulnerability of the SNPC neurons to oxidative agents, compared to neurons in other cerebral regions, may be explained by a combination of different factors such as reduced antioxidant activity, increased iron concentration, increased susceptible to DA oxidation, and reduced activity of the mitochondrial complex I (NADH oxidoreductase) (**Figure 4**).

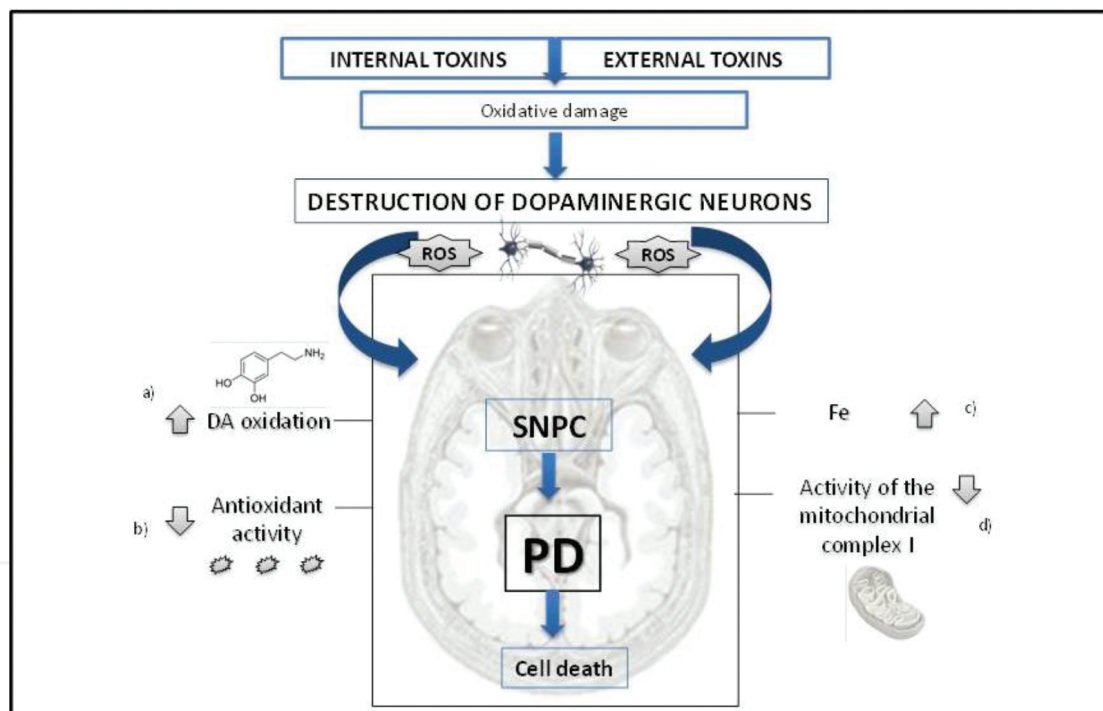


Figure 4. SNPC neurons and oxidative agents. External factors, such as neurotoxins, pesticides, insecticides, and endogenous factors such as dopamine (DA), and genetic mutations in PD-associated proteins contribute to oxidative damage and disruptions in the maintenance of the redox potential leading to destruction of dopaminergic neurons and cell death. Different pathways contribute to the substantia nigra pars compacta (SNPC) neurons vulnerability to oxidative damage including (a) high susceptibility of DA auto-oxidation, (b) reduced antioxidant activity such as glutathione, and (c) increased iron concentration d) deficits in mitochondrial complex I of the respiratory chain.

Biochemical abnormalities in the brain with PD show deficits in mitochondrial complex I, decreased extracellular thiols, increased oxidative iron in the substantia nigra, and oxidative damage, including DNA oxidation, nitration, and increased carbonyl groups of proteins. Lewy bodies inclusions contain phosphorylated neurofilaments and a protein called α -synuclein

[50]. Currently, there is evidence of properties of α -synuclein and its possible association with oxidative stress state present in PD. One such evidence is the notion that one type of amyloid aggregates of α -synuclein, similar to those observed *in vivo*, by coincubation with copper (II), Fe/hydrogen peroxide, or are induced cytochrome c/ hydrogen peroxide. Many motor characteristics defining the PD result primarily from the loss of substantia nigra neurons [28]. Deficiencies in mitochondrial function, increased oxidative stress, apoptosis, excitotoxicity, and inflammation, all of them are part of the processes that eventually result in neurodegeneration [51].

4.1. Genetic and Parkinson's disease

A relatively new theory explores the role of genetic factors in the development of Parkinson's disease. A total of 15–25% of Parkinson's patients have a close relative who had experienced parkinsonian symptoms (such as tremor).

There are many genes linked to familial forms of PD, which have produced advances in PD basic research, increasing our understanding of possible mechanism of dopaminergic cells damage in patients with this condition. These genes include those associated with α -syn, parkin, DJ-1, PINK-1, LRRK-2, ATP13A2, mitochondrial phosphatase, and phosphatase and tensin homolog (PTEN)-induced kinase gene, and they have been demonstrated to be involved in apoptosis regulation. Parkin is associated with the outer mitochondrial membrane (OMM) and prevents cell death by inhibiting mitochondrial swelling, cyt-C release, and caspase activation. Another finding in pathogenesis has been centered in the ATP13A2 gene, which regulates intracellular Mn^{2+} homeostasis, playing an important role in preventing damage induced by Mn^{2+} cytotoxicity. Overexposure of cells to Mn^{2+} may determine cell death by induction of DNA damage, oxidative stress, disruption of Ca^{2+} , iron homeostasis, and mitochondrial dysfunction. In an experimental model, monomeric α -Syn-expressing dopaminergic cells significantly attenuated Mn-induced neurotoxicity for initial exposures. However, overexposure to Mn produces precipitation of α -syn, which at the same time impairs antioxidant defense mechanism in this experimental model [39, 44, 52].

One important finding of PD is the presence of cytoplasmic inclusions containing α -synuclein and ubiquitin, known as Lewy bodies, in the SNPC and other brain regions. Some cases of familial PD are clearly attributed to mutations in the genes for α -synuclein and parkin.

4.2. Dopamine as a source of ROS in the CNS

Since the discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine infusion causes parkinsonism by selective inhibition of mitochondrial complex-1, raised the possibility that mitochondrial dysfunction is at the heart of PD [53].

In patients with PD, there is an excess amount of cytosolic DA outside of the synaptic vesicles due to damaged neurons with impaired reuptake, and a possible increased damage when an overload is related to levodopa treatment. Dopamine is easily metabolized via monoamine oxidase (MAO). Also DA suffers auto-oxidation to cytotoxic ROS producing mitochondrial impairment either by activation of the intrinsic apoptotic pathway or by inhibiting the

respiratory chain. Also, the auto-oxidation of DA produces electron-deficient DA quinones or DA semiquinones, which, at the same time, modify some PD-related proteins, such as α -syn, parkin, DJ-1, superoxide dismutase-2 (SOD2), and UCH-L1. Additionally, DA quinones can be oxidized to aminochrome, whose redox-cycling leads to the generation of the superoxide radical and the depletion of cellular nicotinamide adenine dinucleotide phosphate-oxidase (NADPH), which ultimately forms the neuromelanin, contributing to this degenerative mechanism [11, 47] (**Figure 5**).

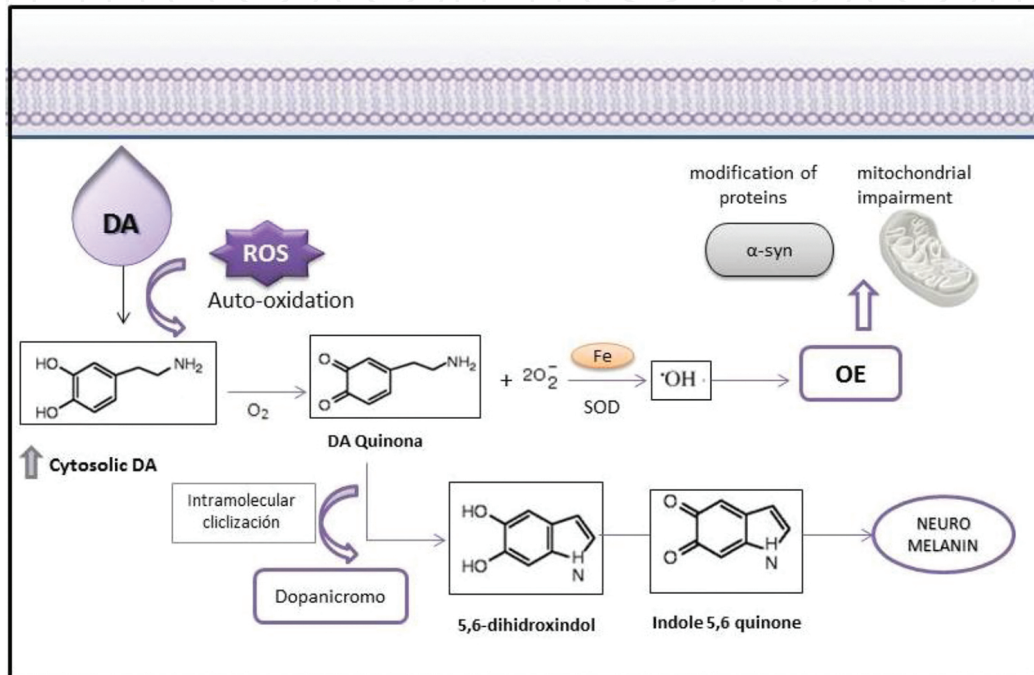


Figure 5. Dopamine as a source of ROS in the CNS. In patients with PD there is an excess amount of cytosolic dopamine (DA), this molecule is unstable and undergoes auto-oxidation to form dopamine quinones and free radicals that leads to modification of PD-related proteins such as α -syn and mitochondrial impairment. The products of dopamine oxidation, dopamine quinones, can also contribute to neurodegeneration. Dopamine quinones can cyclize to form dopaminocromo who is the precursor of neuromelanin, a brain pigment that may contribute to neurodegeneration.

The microtubule (MT) system may play an important role in PD pathogenesis, as well. It is crucial for many aspects of neuronal function, including motility, differentiation, and protein and organelle trafficking. In experimental models, both acute and chronic sub-lethal settings, 6OHDA-induced oxidative stress elicited significant alterations in microtubule (MT) dynamics; very important for axonal transportation; these includes reductions in MT growth rate, increased frequency of MT pauses/retractions, and increased levels of tubulin acetylation [54].

DA metabolism act as proneurotoxins in the development of PD. Certain components of snuff smoke can react with these proneurotoxins preventing its activation. This may explain the possible beneficial effect of smoking on the incidence of PD. The ROS generated by the auto-oxidation of dopamine have been implicated in the neuron loss; related to age and other neurodegenerative disorders such as PD. To date, there have been proposed two mechanisms

by which the DA stimulates the production of ROS. These depend on the presence or absence of enzymatic mediators [55]. The DA in the substantia nigra and striatum is spread by the enzyme monoamine oxidase (MAO), located in the outer membrane of mitochondria [56], from this reaction results the superoxide and hydroxyl radicals plus hydrogen-peroxide production. Another derivative compound is 1,2,3,4 tetrahydropapaverolin DA (THP) obtained from enzymatic catabolism. TTP itself is capable of inducing necrosis in neuroblastoma cells and is related to the pathogenesis of PD [57].

DA is a molecule with a catechol group which cannot be easily enzymatically oxidized to form an array of electrochemical species (quinone type). First, the initial step in the oxidation of DA involves a reaction with molecular oxygen to form DA quinone and two molecules of superoxide anion. Second, the superoxide anions formation during autoxidation of DA leads to the production of hydrogen peroxide by the dismutation of superoxide. Third, in this way, iron mediated in substantia nigra showed high amounts of oxidative stress. Last, the total iron increased but does not necessarily mean an oxidative stress state as excess iron always store into the proteins, such as ferritin, which leaves the iron inert and harmless [58].

However, that state of iron stability can change by continuing entry and release of iron from ferritin to more active form entering the Fenton reaction generating the hydroxyl radical. The iron accumulates in astrocytes in the substantia nigra (experimental data), increasing the rate of Fe(III)/Fe(II) and reduced glutathione. Aging may be a factor which predisposes the brain to the PD, due to, according to our interpretation, the kidnapping by the mitochondria of Fe(II) in astroglia in the substantia nigra. Furthermore, there is evidence that the intracellular loss of redox balance results in aberrant dopamine oxidation in 6-hydroxydopamine, which in turn can undergo auto-oxidation to quinones and simultaneously generate superoxide. This cascade reaction, either by itself, or amplified by the generation of ROS, may explain the neuronal loss as an end result. The DA-o-quinone then undergoes intramolecular cyclization to form 5,6-dihydroxyquinoline, which is subsequently oxidized by the DA-o-quinone to form dopaminocromo; this compound undergoes a rearrangement to form 5,6-dihydroxyindole, which in turn is oxidized into a quinone indole. The following polymerization process finally leads to the generation of a dark pigment called neuromelanin. The dark appearance of the black substance is due to the presence of this pigment containing oxidation products of the cysteinyl-DA.

Dopaminergic neurons are particularly exposed to oxidative stress due to the metabolism of dopamine that causes a series of molecules that are potentially toxic if they are not adequately removed. Dopamine acts as a free radical generating compound, and can oxidize itself at physiological pH, generating dopamine-forming toxic quinones, superoxide radicals, and hydrogen peroxide [40]. It can also be enzymatically deaminated by monoamino oxidase (MAO) to 3,4-dihydroxyphenylacetic, a nontoxic metabolite acid (DOPAC), hydrogen peroxide [41], and by other oxidative processes. Thus, the metabolism of dopamine generates high concentrations of ROS, which can activate and induce apoptotic cell death cascades [19, 20]. ROS accumulation is toxic *per se*, and generates oxidative stress as a result of depletion of cellular antioxidants (e.g., vitamin E and reduced glutathione), increase the membrane lipid peroxidation, DNA damage, and oxidation alteration of protein folding [20]. Besides the

general oxidative damage, there is evidence that the interaction between α -synuclein and dopamine metabolites determines the preferential neurodegeneration of dopaminergic neurons. Along with a number of possible changes, abnormal protein aggregates could also act as irritants, causing a chronic inflammatory reaction which can induce synaptic changes and neuronal death. Findings which suggest the existence of a chronic inflammation process include the presence of microglial activation and astrogliosis in the brain of these patients, particularly in the vicinity of protein aggregates. In PD, along with several toxic and genetic mechanisms producing neuronal damage, the compounds released from damaged neurons can induce microglial release of neurotoxic factors aggravating neurodegeneration [36]. Among those released is neuromelanin compound which is a strong iron chelator. The neuromelanin-ferrous complex activates microglia *in vitro*, causing the release of neurotoxic compounds such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and nitric oxide (NO). Increased total iron concentration had been described in the substantia nigra of PD severe cases, although the underlying mechanism is not known [59]. Iron also contributes to increasing the generation of oxygen radicals (ROS), oxidative stress, and increased protein aggregation, including α -synuclein aggregation. The rapid aggregation of α -synuclein protein in turn can induce the formation of ROS. Lastly, dopamine stabilizes the protofibril form of α -synuclein, which would be toxic. Thus, in the oxidative atmosphere of a dopaminergic neuron, α -synuclein is involved in generating a vicious circle, which leads to neuronal death [59] (Figure 6).

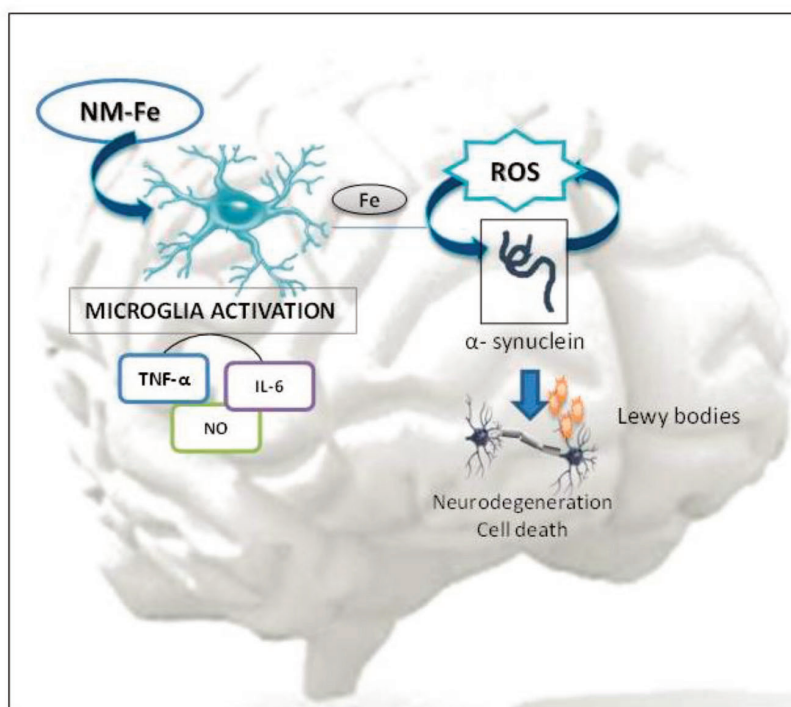


Figure 6. Interaction between α -synuclein and dopamine metabolites. Dopamine metabolites such as neuromelanin-Ferrum complex produce microglial activation that leads to chronic inflammation process, causing the release of interleukins, and free radicals. The reactive oxygen radicals interact with total iron concentration in the substantia nigra and increase the propensity of the α -synuclein to aggregate. This protein is present in Lewy bodies and the formation of aggregates is associated with increased oxidative stress, neurodegeneration, and cell death.

Finally, till date there have been at least five different mechanisms of death in neurons with dopaminergic dysfunction associated to oxidation of the dopamine (DA): (1) proteasome dysfunction, (2) mitochondrial dysfunction, (3) oxidative stress, (4) α -syn oligomers precipitation, and (5) lysosomal autophagy dysfunction.

Another possible mechanism implicated in neuronal destruction and death is associated with diminished neuroprotection due to the dysfunction of neuromelanin and diaphorase enzyme [45, 56].

4.3. MPTP and Parkinson's disease

In 1982 (California, USA), a group of recreational drugs were developed which severely causes parkinsonian syndrome days after injection; 1-methyl-4-phenyl-4-propionoxipiperidina (MPPP), a synthetic analog of meperidine, was used for that purpose. This analog-product, according to the analysis of samples provided by the seller, was contaminated by 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine, which was discovered to cause parkinsonism at a concentration of 2.5–2.9% by weight. Initial clinical symptoms shown by these patients were treated with carbidopa/L-dopa. In the following years, the clinical treatment was insufficient to halt the progression of the disease and died 12 and 16 years, respectively, after injection. Pathological analysis of their brains showed moderate to severe decrease of neurons in the substantia nigra without Lewy bodies. Besides, gliosis and clumping of microglia around nerve cells were found [60].

In 1991, an individual, 39 years old, tried to produce the MPPP following the instructions of a chemistry textbook and obtained, without knowing, the by-product MPTP. Approximately, 45 g of the drug in the course of a week were injected. At the end of this period, he had language problems, remained lethargic, and developed rigid posture. These symptoms worsened over the next week, so he had to be admitted to a hospital. In the next two weeks, he was treated with selegiline and carbidopa/L-dopa, which greatly improved their symptoms. Over the next 3.5 years, the patient responded transiently to treatment with carbidopa less/L-dopa and bromocriptine; however, his condition progressed to severe parkinsonism immobility and a significant hypophonia and died. Neuropathological analysis of this patient showed similar findings to those found in the brains of those patients studied from California. Besides, large amounts of extraneuronal melanin were found indicating a progressive death of nerve cells in response to a brief temporary aggression the nigrostriatal system. The above data show that the acute phase of parkinsonian syndrome is completed within a few days after administration of MPTP; however, neurodegeneration caused by MPTP silently continue for several years or even decades [61, 62].

From a neurochemical point of view there is a great similarity between the MPTP-induced parkinsonism and PD. The neurotoxic action of MPTP involving dopaminergic transmission produces a variety of neurochemical changes: (1) decrease in the concentration of dopamine and its metabolites (3,4-dihydroxyphenylacetic acid and homovanillic acid), (2) decrease activity of the enzyme tyrosine hydroxylase, and (3) alteration in the density of dopamine receptors.

Since the discovery of the effect of MPTP in human, extensive research in animal models, cell cultures, etc. was initiated to characterize in more detail the effects of the toxin.

MPTP produces selective death of dopaminergic neurons and parkinsonian syndrome in several species, including Rhesus monkeys, squirrel monkeys, and beagle dogs. The effects of MPTP, presented in a variety of nonhuman primates, consist in a very significant reduction in spontaneous activity, rigidity, tremor, and bradykinesia. Very few human subjects develop resting tremor characteristic of PD. MPTP initially produces temporary parkinsonian symptoms but become permanent with repeated administration of the toxin. The mechanisms involved in spontaneous recovery experienced by these animals are not known, but may be related to a transient alteration of other neurotransmitter systems other than nigrostriatal. On the other hand, rats and guinea pigs do not show permanent impairments of DA in the striatum nor they present movement disorders such as those observed in primates. In mice of the C57BL/6 strain MPTP induces toxic changes, but at higher concentrations.

There is no evidence that MPTP induces alterations in the cholinergic, GABAergic, and glutamatergic systems in primates. However, the levels of various neuropeptides, substance P, dynorphin, and enkephalin in striatum, substantia nigra, and globus pallidus are reduced in animals chronically treated with MPTP. These same abnormalities have been described in patients with PD. However, it is not known whether they are due to the degeneration of neurons containing these peptides or represent adaptive nigrostriatal denervation to changes.

The susceptibility of different animal species to MPTP may be related to differences in the metabolism of MPTP, cerebral distribution, and retention of the final metabolite [63].

4.4. Metabolism of MPTP

MPTP metabolism is a complex process, after systemic administration it readily crosses the blood brain barrier due to their lipophilicity. Once in the brain, it is transformed extraneuronally in astrocytes, a monoamine oxidase B rich cells, into the intermediate, 1-methyl-4-phenyl-2,3-dihydropyridinium (MPDP⁺). This is a very reactive ion undergoing autoxidation to the radical 1-methyl-4-phenyl pyridinium (MPP⁺) with the formation of superoxide anion (O₂[•]). Besides, the MPDP⁺ readily crosses the cell membrane and into the extracellular space to form MPP⁺ and O₂[•]. Extracellular MPP⁺ is leaking from astrocytes and used by the presynaptic DA system uptake, resulting in an energy-dependent concentration in dopaminergic neurons [64].

Intraneuronal concentration of MPP⁺ increases by binding to neuromelanin and then brought into the mitochondrial matrix through active transport system, which acts as a potent inhibitor of complex I of oxidative phosphorylation system. This effect is due MPP⁺ binding to complex I at a distal sulfur iron site core and near the binding site of ubiquinone Q10. This leads to the cessation of oxidative phosphorylation, ATP level is depleted and decreases the concentration of the major cellular antioxidant, reduced glutathione. This also leads to changes in cellular calcium, altered transmembrane potential, and ultimately neuronal death is manifested [65].

The inhibition of mitochondrial complex I can increase oxidative stress induced by MPP⁺, since the electrons inside the mitochondria may contribute to the toxic effects of MPTP. For example,

it has been demonstrated that MPP⁺ induced lipid peroxidation in cultured cells and the DA is blocked by specific inhibitors of lipid peroxidation [66] (see **Figure 2**).

4.5. Toxicology of paraquat

The LD₅₀ of paraquat in humans is about 3–5 mg/kg, which represents only 10–15 ml in a 20% solution. Although paraquat is regarded as moderately hazardous substance and the Environmental Protection Agency classifies it as a possible human carcinogen and weakly genotoxic, the toxic potential of this herbicide is very high [67].

The genotoxic potential of paraquat has been studied in our research group through induced micronuclei in erythrocytes and bone marrow of mice. Paraquat (15 or 20 mg/kg) was injected intraperitoneally at an interval of 24 hours and then every 6 hours until completion of the study (72 hours). We found that treatment with paraquat increases the number of polychromatic erythrocytes micronucleus cells in blood and bone marrow. Also in this work, it was found that the administration of melatonin, an efficient free radical scavenger, at doses of 2 or 10 mg/kg, 30 min before injection of paraquat partially reverses micronucleus formation [68].

The widespread use of paraquat carries great risk potential for misuse and also for accidental and intentional poisonings. Therefore, the label for minimum safety should be increased because recommendations for its use are not strictly followed. Particularly to protect the skin, equipment is required for face and hands. Poisoning usually occurs in the first instance through the skin when in direct contact with the backpack spray of the herbicide. The eyes and nose may also be exposed to the herbicide. Toxic effects include mild irritation, blistering, peeling, necrosis, dermatitis, and dermatitis of hands and sometimes of the scrotum. Severe exposure to the hands causes localized discoloration or temporary loss of nails. Splashes in the eyes can cause irritation and inflammation of eyelids and decreased visual acuity. Although the intact human skin is relatively impermeable to paraquat, some fatalities as a result of dermal exposure are documented. The presence of scratches, cuts, wounds, or severe dermatitis can substantially increase the risks [69].

The lungs are the first target of paraquat, and pulmonary effects represent the most lethal and least treatable manifestation. The inhalation toxicity is rare. The main mechanism of cell damage is the generation of free radicals that oxidize lung tissue. Although acute pulmonary edema and lung damage after several hours of severe acute exposures may occur, delayed pulmonary fibrosis is the usual cause of death that commonly occurs 7–14 days after ingestion. In some patients, ingestion of a large amount of concentrated paraquat form (20%) died more rapidly due to circulatory failure (within 48 hours). Lung cells appear to selectively accumulate paraquat which generates free radicals causing lipid peroxidation and cell damage. Hemorrhage, fluids, and leukocytes infiltrates into the alveolar spaces, followed by fibroblast proliferation. There is a progressive decrease in arterial oxygen tension and diffusion capacity of CO₂. Such deterioration in gas exchange causes progressive proliferation of fibrous connective tissue in the alveoli eventually causing death by asphyxiation and tissue anoxia [70].

In the gastrointestinal tract, toxicity first occurs at the mucosal layers after paraquat ingestion. This causes swelling, edema, and painful ulceration of the mouth, pharynx, esophagus,

stomach, and intestine. At high doses of paraquat, hepatocellular damage occurs, which is manifested by increased serum liver enzymes. Also, the deterioration of renal function may play an important role in determining the outcome of paraquat poisoning. Normal tubular cells secrete paraquat in urine quickly, efficiently removing it from the blood. However, high blood concentrations of poison affect the secretory mechanism and may destroy the cells.

Ingestion or accidental or deliberate exposure to paraquat has been responsible for many deaths. In one study, done in 1989 in Sri Lanka, found that out of 669 cases of poisoning, agrochemicals were responsible for 59% of toxicity and paraquat was the most common agent with a fatality rate of 68%. Even in the United Kingdom, in the years 1990–1991 there were 44 deaths with paraquat.

In Sweden, Denmark, Finland, and Austria, the use of paraquat is prohibited. In 2003, Syngenta pursued the Standing Committee on the Food Chain and Animal Health of the European Commission to include the authorization policy of EU pesticides. Subsequently, in August 2005, Austria, Finland, and Denmark opposed the use of paraquat. This is because it has sufficient evidence linking chronic use of paraquat with Parkinson's disease (PD) as described below. Moreover, paraquat residues in food are usually not detectable, except when this herbicide is used before getting the harvest of crops such as cereals, pineapple, etc. These foods have been reported to have levels of up to 0.2 mg/kg, whereas the acceptable daily intake is 0.004 mg/kg.

In the case of smoking marijuana contaminated with paraquat, the toxic effects are rare or nonexistent. Most paraquat that contaminates marijuana is pyrolyzed during the combustion of cigarette becoming bipyridyl, which is known to be very less toxic [71].

4.6. Toxicology of diquat

In humans, diquat is not systemically selectively absorbed nor concentrated in the lung tissue, as paraquat do, therefore, lung injury caused by diquat is less. However, diquat has severe toxic effects on the central nervous system that are not typical of paraquat poisoning. In many cases of human diquat poisoning, the medical signs and symptoms of neurological toxicity are the most important. These include nervousness, irritability, restlessness, combativeness, disorientation, nonsensical statements, diminished reflexes, and inability to recognize friends or family members. Neurologic effects may progress to coma, accompanied by tonic-clonic convulsions resulting in death. Also, parkinsonism was reported after skin exposure to diquat.

Another interesting aspect is the recognition of the role of inflammation and oxidative stress in the pathogenesis of PD. For example, in postmortem studies of some patients who were exposed to MPTP activation of microglia around neurons was found. So in our laboratory, we investigated the effect of MPTP over the activity of cyclooxygenase 2 (COX-2) using mice from the C57/BL6 strain. Our data indicate that a single dose of MPTP in mice had the following effects: a significant increase in the peroxidase activity of COX-2 in midbrain, compared with controls and increased nitrite levels and lipoperoxides in serum. These effects were presented after 24 hours of treatment. We also found that melatonin partially reverses the effects of MPTP on the activity of COX-2 and levels of nitrites and lipoperoxides in serum. The oxidative stress

induced by MPTP in the mouse midbrain is also reflected in the serum, suggesting a systemic MPTP damage, which is reversed by melatonin, due to its antioxidant action. The action of melatonin can be attributed to the decrease of oxidizing species like dopamine-quinone. It has been further suggested that the cytotoxicity of neuronal COX-2 can come from the formation of reactive oxygen species generated during the catalysis of peroxidase activity of the enzyme [72].

4.7. Herbicides and Parkinson's disease

Structural similarity of the MPP⁺ and paraquat suggested that this herbicide could be toxic to dopaminergic neurons. In 1985, it was found that paraquat produced a parkinsonian behavior in leopard frogs (*Rana pipiens*). Whereas in mice of strain C57BL/6 systemic administration of paraquat resulted in a loss of dopaminergic neurons, degeneration of striatal dopaminergic fibers, and a reduction in ambulatory activity. Subsequently, in humans, the incidence of PD positively correlates with exposure to pesticides, including paraquat, in patients from some regions of Canada, Taiwan, and elsewhere.

Paraquat neurotoxicity is associated with their ability to induce the formation of free radicals, to induce the fibrillation α -synuclein, and to induce cell death by apoptosis [72].

4.8. Other pesticides and Parkinson's disease

Another class of chemicals associated with PD in humans is certainly having dithiocarbamates, such as maneb. *In vitro* studies show that neurotoxicity induced by maneb is related to the enzymatic inhibition of mitochondrial complex III and the oxidation of catecholamines. Systemic administration of paraquat and maneb induce a synergistic decrease in the content of DA in the striatum, SNPC degeneration, and motor abnormalities. Moreover, neonatal exposure of both pesticides increases the susceptibility of nigrostriatal dopaminergic system in maturity [73, 74].

Several plants (*Derris elliptica*, *Lonchocarpus*, and *Tephrosia*) contain the insecticide rotenone, which is a specific inhibitor of mitochondrial complex I. Its exposure to humans has been associated with PD. In rats, continuous systemic administration of rotenone reproduces the key aspects of PD including the selective degeneration of the nigrostriatal dopaminergic system, like the formation of cytoplasmic inclusions, Lewy bodies, and movement disorders. The effect of rotenone is mediated by the enzyme activity of microglial NADPH oxidase, which is the main source of O₂• radical [75, 76].

Also, organochlorine insecticides such as dieldrin are associated with motor disorders observed in ducks, pigeons, and rats. Furthermore, dieldrin residues detected in brains of PD patients, in cultured cells *in vitro*, shows selective dopaminergic neurotoxicity, which is mediated by the formation of oxygen-free radicals, lipid peroxidation, and fibril formation, α -synuclein. Also, some organophosphorus insecticides are associated with PD in humans.

It remains to be determined whether exposure to pesticides explains some cases of PD. A valuable tool to help determine this has been studies in which high doses of the pesticide are used for short periods and chronic application of these toxic in animal models [77].

4.9. Medical treatment of Parkinson's disease

Medical treatment of PD is usually based on anticholinergics, amantadine, levodopa, and other dopaminergic drugs. These agents maintain a good quality of life for most patients; however, when the disease progresses, it usually becomes ineffective and can cause adverse effects. So far, the most potent treatment of PD is L-dopa. However, L-dopa motor complications of chronic administration have emerged as a major limitation in response to treatment. That is why, in the future, neuroprotective therapies would slow the progression of the disease and delay the L-dopa need. There is insufficient evidence that L-dopa therapy prevents the progressive death of nigrostriatal neurons, but instead there is speculation that it may contribute to the progressive disease course. In the past years, they have contributed new knowledge about the mechanisms of neurodegeneration present in the PD [78].

4.10. Mitochondria and Parkinson's disease

Mitochondria participate in numerous cellular functions including ion homeostasis, heme and steroid synthesis, calcium signaling, and apoptosis [79, 80]. The well-known role of this organelle is to generate energy for cellular metabolism by the oxidative phosphorylation system. Electrons derived from cellular metabolism reach the mitochondria through two key coenzymes. Then they undergo a passage throughout the electron transport chain that consists of five protein complexes located in the inner mitochondrial membrane. Electrons pass through complexes I, III, and IV thanks to a proton gradient generated by the transport of these complexes to the outer side of the inner mitochondrial. In this process, the electron leakage from the respiratory chain induces the conversion of oxygen (0.4–4%) in superoxide radicals. As a consequence mitochondria are the primary source of ROS [81].

In the mitochondrial respiratory chain, the complexes I and III are the major sites of superoxide production. Partially reduced forms of oxygen are highly active; they chemically interact with biological molecules, resulting in oxidation of protein, DNA and RNA, and peroxidation of lipids. The damaging effects of ROS are counteracted by endogenous antioxidant enzymes such as catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase, and by molecules such as glutathione, metallothionein, and vitamins A, C, and E. Then cell death may be as well associated with decreasing capability to clear ROS by mitochondria [82–84].

Complex I of the respiratory enzyme is decreased in substantia nigra in patients with PD, possibly causing electron leakage from the electron transport system and increasing in the generation of peroxide anion (O_2^-). This produces increasing activity in the manganese-superoxide dismutase (Mn-SOD), which is demonstrated in autopsied parkinsonian brains. Therefore, it indicates an increase in the generation of O_2^- in the mitochondria, resulting in an increase in the generation of hydrogen peroxide. Levels of cytokines, such as TNF- or, interleukin-1/3, and interleukin-6, are elevated in the striatum, indicating activation of astrocytes and/or microglial cells. The activation in the microglial cells increases the nitric oxide (NO^-) formation through the diaphorase system, and diffused to nerve terminals and dopaminergic cells in the central nervous system. NO^- reacts with O_2^- to produce peroxynitrate. On the other hand, iron is accumulated in astrocytes and microglia and NO^- provokes ferric

ion conjugation with ferritin, which is slowly released from cells to the intercellular space. Other proposed mechanism of oxidation is union of iron to oxygen and L-DOPA to iron (or copper) in the complex 27 of the mitochondrial chain, possibly initiating a lipid peroxidation in the cell membrane [85].

The genes linked to familial forms of PD include those associated with α -syn, parkin, DJ-1, PINK-1, LRRK-2, ATP13A2, mitochondrial phosphatase, and phosphatase and tensin homolog (PTEN)-induced kinase gene, between others, and they have been demonstrated to be involved in apoptosis regulation. Parkin is associated with the outer mitochondrial membrane and prevents cell death by inhibiting mitochondrial swelling, cyt-C release, and caspase activation. Another finding in pathogenesis has been centered in the ATP13A2 gene, which regulates intracellular Mn^{2+} homeostasis, playing an important role in preventing damage induced by Mn^{2+} cytotoxicity. Overexposure of cells to Mn^{2+} may determine cell death by induction of DNA damage, oxidative stress, disruption of Ca^{2+} and iron homeostasis, and mitochondrial dysfunction. In an experimental model, monomeric α -Syn-expressing dopaminergic cells significantly attenuated Mn-induced neurotoxicity for initial exposures. However, overexposure to Mn produces precipitation of α -syn, which at the same time impairs antioxidative defense mechanism in this experimental model [86–88].

Other findings suggested that mitochondrial dysfunction is at the heart of PD. For instance, MPTP infusion causes parkinsonism by selective inhibition of mitochondrial complex-1 [89]. In patients with PD there is an excess amount of cytosolic dopamine outside of the synaptic vesicles due to damaged neurons with impaired reuptake, with a possible increased damage when an overload is related to levodopa treatment. Dopamine then is easily metabolized via monoamine oxidase or by auto-oxidation to cytotoxic ROS provoking mitochondrial impairment by activating the intrinsic apoptotic pathway or by inhibiting the respiratory chain. Also, the auto-oxidation of DA produces electron-deficient DA quinones or DA semiquinones, which at the same time can modify some PD-related proteins, such as α -syn, parkin, DJ-1, superoxide dismutase-2, and UCH-L1. Additionally, DA quinones can be oxidized to aminochrome, whose redox-cycling leads to the generation of the superoxide radical and the depletion of cellular nicotinamide adenine dinucleotide phosphate-oxidase (NADPH), which ultimately forms the neuromelanin, contributing to this degenerative mechanism [11].

5. Conclusion

There are many proposed mechanisms that may produce damage to dopaminergic neurons, but all of them finally converge in a common pathway involving ROS/RNS and mitochondrial dysfunction that promotes apoptosis. Exposure to environmental factors or mutations in PD-associated genes of patients with either sporadic or familial PD may cause mitochondrial dysfunction that ultimately results in PD. In the near future, neuroprotection may coincide with reductions in intracellular reactive oxygen species, lipid peroxidation, and DNA damage in the effort to save neurons from death avoiding neurodegeneration to advance until the point of neither manifesting PD symptoms nor producing advanced symptoms in a patient with evident motor PD.

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