Degenerative Neurological and Neuromuscular Disease

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REVIEW

Mitochondrial Toxicant-Induced Neuronal Apoptosis in Parkinson's Disease: What We Know so Far

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Abstract: Parkinson's disease (PD) is one of the most common progressive neurodegenerative diseases caused by the loss of dopamine-producing neuronal cells in the region of substantia nigra pars compacta of the brain. During biological aging, neuronal cells slowly undergo degeneration, but the rate of cell death increases tremendously under some pathological conditions, leading to irreversible neurodegenerative diseases. By the time symptoms of PD usually appear, more than 50 to 60% of neuronal cells have already been destroyed. PD symptoms often start with tremors, followed by slow movement, stiffness, and postural imbalance. The etiology of PD is still unknown; however, besides genetics, several factors contribute to neurodegenerative disease, including exposure to pesticides, environmental chemicals, solvents, and heavy metals. Postmortem brain tissues of patients with PD show mitochondrial abnormalities, including dysfunction of the electron transport chain. Most chemicals present in our environment have been shown to target the mitochondria; remarkably, patients with PD show a mild deficiency in NADH dehydrogenase activity, signifying a possible link between PD and mitochondrial dysfunction. Inhibition of electron transport complexes generates free radicals that further attack the macromolecules leading to neuropathological conditions. Apart from that, oxidative stress also causes neuroinflammation-mediated neurodegeneration due to the activation of microglial cells. However, the mechanism that causes mitochondrial dysfunction, especially the electron transport chain, in the pathogenesis of PD remains unclear. This review discusses the recent updates and explains the possible mechanisms of mitochondrial toxicant-induced neuroinflammation and neurodegeneration in PD.

Keywords: apoptosis, mitochondrial dysfunction, mitochondrial toxicant, neurodegenerative disorder, Parkinson's disease

Introduction

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder, and its symptoms appear at the age of 50 and above and worsen as aging progresses. According to the National Institutes of Environmental Health Sciences (USA), at least 500,000 Americans live with PD, although some estimates may be much higher than reported. This movement disorder results from the loss of dopaminergic neurons in the substantia nigra pars compacta of the brain. The major risk factors for PD include familial history, aging, and exposure to toxicants present in our environment. Pathogenic mutations of PARK7 (encoding DJ-1), α-synuclein, parkin, PINK1, or LRRK2 in PD cause alterations in mitochondrial dynamics.[1] PD exhibits motor symptoms, including tremors, rigidity, bradykinesia, and stooping posture. Some patients show non-motor symptoms such as constipation, loss of sense of smell, sleep, and genitourinary disorders.[2] The cellular hallmarks of PD include protein misfolding, aggregation of α-synuclein, lysosomal and proteasomal dysfunctions, neuroinflammation, neuronal cell death, calcium homeostasis, and mitochondrial dysfunction.[3,4] Mitochondrial damage-associated molecular patterns are also known to contribute to the pathogenesis of PD.[5] Even though recent research has provided many pharmacological therapies and surgeries, such as deep brain stimulation, the definitive treatment for PD is yet to be discovered.[6] Levodopa is the primary therapeutic drug in treating

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PD, whereas the other pharmacological agents used are monoamine oxidase-B inhibitors and catechol-O-methyltransferase inhibitors, amantadine, and anticholinergic agents.[7]

Several studies have shown that mitochondrial dysfunction is one of the critical factors for the selective degeneration of dopaminergic neurons in the PD model. Mitochondria are essential in maintaining normal neuronal function and viability, and their dysfunction progresses to programmed cell death[8] or necroptosis.[9] The mitochondrial electron transport chain (ETC) is the primary intracellular site for producing ATP, which is essential for the survival of neurons. Under physiological conditions, the amount of ROS generated from the ETC is insignificant.[10] However, ROS production is markedly elevated under pathological conditions or in the presence of ETC inhibitors, with mitochondrial complex III and I as the main production sites.[11,12] Several studies support the impaired function of mitochondria complex I[13] in substantia nigra, skeletal muscles, platelets, and leukocytes of PD patients.[14] Under pathological conditions, the mitochondrial membrane potential is also altered, resulting in increased mitochondrial membrane permeabilization, swelling, and release of cytochrome c, which further activates the downstream apoptotic signaling cascade. Dysfunctional mitochondria stimulate the mitochondrial damage-associated molecular patterns, which trigger inflammation and apoptosis, promoting the onset of several neurodegenerative diseases. Oxidative phosphorylation also produces highly reactive free radicals, such as superoxide anions, which cause damage to the mitochondrial components by inducing mitochondrial oxidative stress and promoting mitochondrial dysfunction.[15,16] Several natural and anthropogenic chemicals contribute to mitochondrial toxicity (Table 1), resulting in mitochondrial dysfunction. Increased production of free radicals production targets the mitochondrial genome, affecting ATP synthesis and ultimately causing cellular

Table 1 Mitochondrial Toxicant-Induced Neurodegeneration in Animal Models and Humans

Mitochondrial Toxicants and Source	Disease	Cellular/ Molecular Basis of Neurodegeneration in PD
MPTP (*Industrial chemicals and contaminants of illicit narcotics*)	Parkinsonism, dystonia	Mitochondrial oxidative stress, apoptotic cell death, dopaminergic neurodegeneration.[129,130] MPP^+ inhibits NADH–coenzyme Q reductase (mitochondrial Electron Transport Chain Complex I), depletion of ATP, and neuronal apoptosis.[131,132]
Trichloroethylene *(Chronic occupational exposure, dry cleaning and paint removal agents, and typewriter correction fluid)*	Parkinsonism	Loss of dopaminergic neurons, striatonigral fibers, and mitochondrial dysfunction by inhibiting ETC complex I activity.[133–135]
Manganese (*Mining, welding, and steel manufacturing industry*)	Levodopa-resistant tremor less Parkinsonism and a "cock walk".	Degeneration of striatum, and globus pallidus, inhibits complex I and complex III activity.[71,136,137]
Iron (*Aberrant Iron metabolism*)	Neuroferritinopathy	Formation of Lewy body, non-heme iron highest concentrations in globus pallidus, substantia nigra, red nucleus, and dentate nucleus.[138,139]
Aluminum (*exposure to light and hazardous metals from air, food, and water*)	Parkinson's like conditions	Cause oxidative stress and neurodegeneration in the dopaminergic system, formation of neurofibrillary tangles, beta-amyloid plaques, tau aggregation, and neuronal dysfunction.[112,114]
Rotenone (*Pesticides*)	Parkinsonism	NADH–coenzyme Q reductase (mitochondrial ETC Complex I), depletion of ATP, neuronal apoptosis, inhibit tyrosine hydroxylation.[140–142]
Paraquat (*Pesticides*)	Parkinsonism	NADH–coenzyme Q reductase (mitochondrial Electron Transport Chain Complex I), depletion of ATP, neuronal apoptosis, inhibit tyrosine hydroxylation.[143–145]
Pyrethroid (*Pesticides*)	Parkinsonism	Mitochondrial oxidative stress, decreases dopamine uptake.[89,146,147]

Abbreviations: Ca^{2+}, calcium ion; ETC, electron transport chain; Mn, Manganese; MPP+, 1-methyl-4-phenylpyridinium ion; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NADH, nicotinamide adenine dinucleotide reduced form; PQ, paraquat; PD, Parkinson's disease; ROS, reactive oxygen species; RO, rotenone; SNpc, substantia nigra pars compacta; TCE, trichloroethylene; TH, tyrosine hydroxylase.

damage.[17,18] This review discusses the recent updates and novel insight into the cellular and molecular mechanism of mitochondrial toxicants-induced neuroinflammation and neurodegeneration in Parkinson's disease.

Pathophysiological Changes in the Brain of PD Patients

Parkinson's disease occurs due to the gradual loss of dopamine-producing neuronal cells in the substantia nigra pars compacta (SNpc), which consequently leads to less availability of dopamine. Dopamine is a chemical messenger that transmits signals from SNpc to the corpus striatum to regulate muscular coordination. The presence of Lewy bodies characterizes the fundamental pathophysiology of PD at the cellular level, which is an aggregate of abnormal proteins in the brain, specifically in the region of SNpc.[19,20] Lewy bodies are lamellated, eosinophilic cytoplasmic inclusion consisting of a dense core surrounded by a halo of 10 nm wide radiating fibrils. The primary structural protein of the Lewy body is α-synuclein, which localizes specifically to the nerve terminal, with relatively little in the nerve cell body, dendrites, or extrasynaptic sites along the axon in PD.[21,22] The primary function of α-synuclein is to regulate the activity of dopamine transporters. However, in pathological conditions, either abnormal levels or a mutated condition of α-synuclein contributes to Lewy bodies, which further causes neuronal cell death, consequently leading to motor dysfunctions. Since the abnormal accumulation of α-synuclein is toxic to cells, it impairs the microtubular transport and subcellular organelles.

Mutation of α-synuclein leads to aggregation, delaying the fusion of phagosomes with lysosomes during mitophagy. Recently, exosomes have been shown to play multiple roles in PD-associated inflammation that transports toxic α-synuclein oligomers into the extracellular environment causing activation of microglia and astrocytes to secrete exosomes,[23] proposing a novel mechanism for linking mitochondrial dysfunction to systemic inflammation associated with PD. Postmortem brain tissues of patients with PD support the hypothesis that mitochondrial dysfunctions contribute to the pathogenesis of PD. Further, identifying mutant genes such as PINK1, DJ-1, PRKN, and LRRK-2 involved in oxidative stress and mitochondrial dysfunction also confirms the hypotheses that mitochondrial dysfunction mediates dopaminergic neurodegeneration in PD.[24] The dopaminergic neurons of SNpc synthesize the neurotransmitter dopamine from DOPA and transport it to the axon terminals in the striatum. Neurochemical analysis shows a reduction in the striatal dopamine content by over 80% in PD patients, parallel with the loss of dopaminergic neurons from the SNpc. However, positron emission tomography shows that the symptoms of PD appear only when the striatal dopamine falls below 40% of the normal range. Experimentally-induced lesions of the nigrostriatal tract or chemically-induced dopamine depletion exhibit the triads of cardinal motor symptoms in PD,[25] such as bradykinesia, rigidity, and tremors, which are due to more complex changes in the neurochemicals, including acetylcholine, noradrenaline, 5-HT, and GABA apart from dopamine. The severity of symptoms correlates with degeneration of the dopaminergic nigrostriatal pathway and dopamine depletion in the striatum.[26] It has been shown that up to 13% of dopaminergic neurons die every decade, suggesting that more cases of age-related Parkinson's will occur as people live longer. Unfortunately, by age 80, a person may have lost at least 80% of his/ her dopaminergic neurons, but not everyone loses the cells at the same rate or develops PD.

Mitochondrial Toxicants and Neurodegeneration

Mitochondria play a crucial role in maintaining the survival of cells by regulating physiological and pathological mechanisms, including ATP generation, metabolism signal transduction, immune response, and apoptosis.[27,28] Several chemicals are well known to target mitochondria, including drugs, pesticides, and environmental contaminants (Table 1). Mitochondria are more vulnerable to exposure to toxicants due to high lipid content on membranes and negative charges of the mitochondrial matrix. Apart from beneficial effects, some pharmaceutical drugs act as mitochondrial toxicants targeting the ETC. Mitochondrial toxicants also cause direct inhibition of biochemical processes, including the oxidation of fatty acids, the citric acid cycle, and mitochondrial protein synthesis. An electrochemical gradient is established during oxidative phosphorylation, which is the primary driving force for ATP synthesis.[29,30] Under pathological conditions or exposure to mitochondrial toxicants, excessive production of free radicals occurs via oxidative phosphorylation, causing oxidative stress that leads to mitochondrial membrane depolarization and cytochrome c release, resulting in downstream activation of apoptotic signaling. Many mitochondrial toxicants have been shown to induce neuronal cell death, resulting

in various neurodegenerative disorders, including PD, AD, HD, and ALS.[31–34] MPTP, peroxynitrite, trichloroethane, paraquat, rotenone, lidocaine, carbon monoxide, and heavy metals are some mitochondrial toxicants known to induce Parkinson's or PD-like symptoms.[35]

MPTP and Parkinson's Disease

Accidental exposure to synthetic drugs contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) by intravenous street drug abusers exhibited symptoms remarkably similar to idiopathic PD.[36] MPTP is a lipophilic compound that can cross the blood-brain barrier and reach the central nervous system, which is taken up by the glial cells. The 1-methyl-4-phenyl pyridinium (MPP^+) is an active metabolite of the neurotoxin MPTP that causes parkinsonian syndrome in humans and animals. MPP^+ is well known to inhibit NAD(H)-linked mitochondrial oxidation, acts as a selective dopaminergic neurotoxin, and induces superoxide anion and hydroxyl radicals, which causes oxidative stress-mediated neuronal cell death.[37] MPTP metabolism is a complicated multistep process; it is converted into MPP^+ in the astrocytes and released into the neuronal microenvironment, where they specifically bind to the dopamine transporter to enter the dopaminergic neurons. Astrocytes contain MAO-B, which is actively involved in converting MPTP to MPP^+. Once within the dopaminergic neuronal cells, MPP^+ enters the mitochondria and interferes with the complex I of the ETC, which ultimately leads to apoptosis of the dopaminergic neuronal cells,[38–40] suggesting that mitochondria are the preferential target for MPP^+ in causing neurodegeneration. MPTP is capable of causing clinical symptoms in humans and monkeys indistinguishable from PD.[41] MPTP exerts its effect by inducing oxidative stress and the formation of inclusion bodies with abnormal α-synuclein proteins, thereby causing accelerated neurodegeneration in the substantia nigra pars compacta and striatum.[42,43] Since MPTP induces selective neuronal cell death of dopaminergic neurons, it is also considered the standard mouse model for PD research. Interestingly, the C57BL/6 strain is more vulnerable to MPTP-induced mitochondrial dysfunctions, perturbations in energy metabolism, and motor defects than the BALB/c strain.[44] One of the characteristic features of PD which is not reproduced in animal models is that the SNpc lesion does not coincide with the Lewy body formation in the brain.[45]

Peroxynitrite and Parkinson's Disease

Nitric oxide reacts with superoxide anion, forming peroxynitrite ($ONOO^-$), a highly reactive oxidizing and nitrating agent causing adverse biological effects.[46] Peroxynitrite reacts with the cellular DNA to cause single-stranded breaks.[47] Due to its ability to cause oxidation and nitration of various biomolecules, it is implicated in the pathogenesis of various diseases, including neurodegenerative diseases.[47,48] The origin of peroxynitrite is either in extramitochondrial compartments or directly produced within the mitochondrial matrix. The diffusion of peroxynitrite into the mitochondria leads to alterations in calcium homeostasis and mitochondrial energy production, resulting in increased membrane permeability.[49] In addition, $ONOO^-$ is an effective inhibitor of enzymes in the mitochondrial respiratory chain, resulting in decreased ATP synthesis.[50–52] Several studies have shown that peroxynitrite inhibits most components of the electron transport chain, including complex I,[53] complex II,[54] complex III,[55] and complex V,[56] by oxidation or nitration of complex proteins.[50,51] Peroxynitrite also leads to DNA damage, inactivation of enzymes, ionic pumps, proteins, and disruption of cellular membranes, which contribute to mitochondrial dysfunctions and promote apoptosis.[51] In the postmortem brain of PD patients, peroxynitrite-mediated oxidative and nitrative stresses contribute to the pathogenesis.[57,58] As this compound is highly reactive with protein molecules, some modified proteins accumulate and are involved in the onset and progression of PD.[59,60] Impairment of mitochondrial complex I is also consistently observed in the postmortem PD brain, and peroxynitrite is suspected to be involved with the inhibition via nitrosylation and nitration of mitochondrial complex I.[61] Nitration of tyrosine hydroxylase, the initial and rate-limiting enzyme in the biosynthesis of dopamine, is inhibited by peroxynitrite, leading to failure in the synthesis of dopamine.[62] Peroxynitrite also targets the intracellular glutathione in substantia nigra by inactivating glutathione reductase, the enzyme responsible for the regeneration of glutathione from its oxidized form.[63]

Trichloroethane and Parkinson's Disease

Trichloroethylene (TCE) is a chlorinated hydrocarbon used in the industrial degreasing of metals and as a secondary solvent in adhesive paint and polyvinyl chloride production. TCE is detected in air, soil, and food and enters the human body through inhalation, ingestion, or skin. Hence, it breaches the central nervous system due to high lipid solubility and slowly induces anesthesia.[64]

TCE is transformed to chloral by cytochrome P450, converting it to a trichloroethylene oxide intermediate.[65] Chloral is one of the precursors of 1-trichloromethyl-1,2,3,4-tetrahydro-b-carboline, also known as TaClo,[66,67] which is readily produced from the biogenic amine tryptamine and chloral under physiological conditions.[67] TCE is structurally similar to the MPTP has led to speculation that it could cause PD.[68] TaClo, one of the mitochondrial toxicants, is cytotoxic to the primary culture of dopaminergic neurons,[69] which further induces apoptosis by blocking the transfer of electrons from complex I to ubiquinone in both rat brains homogenates and liver submitochondrial particles.[70,71] Similarly, animal models exposed to TCE have shown nigrostriatal degeneration, which led to the mitochondrial dysfunction and the development of parkinsonian features.[64,72]

Paraquat and Parkinson's Disease

Paraquat (PQ) is a bipyridyl compound commonly used as a contact herbicide and is poorly absorbed when inhaled, but when ingested orally, it causes severe sickness and death. PQ exposure leads to cytotoxicity by inducing oxidative stress and mitochondrial dysfunction.[73] PQ induces the production of superoxide in the complex I of ETC, thereby causing extensive mitochondrial oxidative damage in mammalian systems.[74] PQ exposure decreases the activity of mitochondrial complex I and mitochondrial transmembrane potential and induces the release of cytochrome c from mitochondria.[75] Paraquat is a well-known neurotoxicant associated with an increased risk of developing PD and PD-like symptoms.[76,77] In experimental animals, PQ induces oxidative stress, resulting in the death of dopaminergic neurons and causing behavioral abnormalities similar to patients with PD.[78] The production of free radicals and activation of cholinergic and glutamatergic transmission is also connected to PQ-induced neurotoxicity.[79] PQ significantly increases the in vitro rate of α-synuclein fibril formation and aggregation, with dose-dependent accelerating effects.[80] Furthermore, the amount of α-synuclein increases considerably in the brain of mice exposed to PQ.[80]

Rotenone and Parkinson's Disease

Rotenone (RO) is an isoflavone insecticide obtained from the roots and stems of various plants, including Derris, Tephrosia, Lonchocarpus, and Mundulea. According to WHO, rotenone is a moderately hazardous substance; however, it is mildly toxic to humans and other mammals but highly toxic to insects and fishes. After intravenous injection in mouse or rat, rotenone is metabolized in the liver by NADP-linked hepatic microsome enzymes to rotenolone I and II, hydroxy-, and dihydroxy-rotenone, which is used as a biomarker for rotenone poisoning in blood, urine, feces, and liver.[81] Due to its lipophilicity, rotenone enters the cells without transporters and can readily cross the blood-brain barrier. Rotenone then enters the brain and is accumulated in the cellular organelles such as mitochondria.[82] The mode of action of rotenone includes the inhibition of oxidation of NADH to NAD as well as the mitochondrial respiratory chain. Rotenone induces mitochondrial dysfunction by inhibiting the complex I of the ETC, which leads to oxidative stress, and apoptosis.[83,84] Rotenone induces apoptosis by enhancing the production of mitochondrial reactive oxygen species, cytochrome c release, and activation of caspase-3, followed by DNA fragmentation.[85] Chronic exposure to rotenone increases the risk of PD-like features in various animal models. In vivo experimental model shows RO induces loss of dopaminergic neurons in the substantia nigra, one of the characteristic features of PD neuropathology.[86] Rotenone also replicates the clinical features of PD, including the aggregation of α-synuclein and the formation of Lewy bodies.[87]

Pyrethroid and Parkinson's Disease

A pyrethroid is a class of synthetic insecticides, which targets the nervous system of insects and other species, and is widely used due to its high efficacy and low environmental persistence. There are different types of pyrethroids, such as deltamethrin, cypermethrin, and permethrin, and exposure to such pyrethroids leads to progressive neurodegenerative

diseases. Exposure to pyrethroids affects the mitochondrial membrane potential and inhibits the complex I function.[88,89] Deltamethrin causes mitochondrial dysfunction with decreased membrane potential, increased permeability, and cytochrome c release.[90,91] Rats exposed to cypermethrin exhibit changes in the mitochondrial proteome profile of the substantia nigra and striatum.[92] Deltamethrin has been shown to cause apoptosis in the cerebral cortex, hippocampus, and striatal neuronal cells.[88,93] Permethrin raises α-synuclein, decreases striatal dopamine levels, causes oxidative stress, and inhibits ETC's mitochondrial complex I.[88]

Iron and Parkinson's Disease

Iron is necessary for almost all living species and is essential in heme-containing proteins and iron-sulfur clusters, which are involved in various physiological processes, including oxygen transport, mitochondrial respiration, and DNA synthesis.[94] Free iron enters cells and accumulates in mitochondria, inhibiting oxidative phosphorylation, promoting free radical generation, catalyzing lipid peroxidation, and ultimately causing cell death.[95] Iron accumulation within cells and tissues impairs the redox equilibrium, forming lipid peroxide through ferroptosis. Ferroptosis is a non-apoptotic, and iron-dependent form of cell death mainly occurs in the brain due to high lipid content. Due to compromised blood-brain barrier in older adults, poor recycling or redistribution of iron in the brain, and prolonged neuroinflammation,[96,97] have been shown to increase iron buildup in the substantia nigra, globus pallidus, putamen, and caudate nucleus.[98] The pathogenesis of many neurodegenerative disorders is implicated with the buildup of iron in specific brain locations in the CNS.[99] Iron accumulation in the SNpc has been recognized as one of the key pathological features of PD[100] and in the experimentally-induced mouse models of PD.[101]

Interestingly, iron chelation ameliorates neuronal cell death and alleviates motor deficits in animal models,[102] and decreases the progression of PD in patients.[103] Further, rotenone exposure to rats or monkeys has been shown to cause iron accumulation in the nigral dopaminergic neurons and microglial cells,[104] suggesting that the increased iron content of microglia in the PD brain comes from phagocytosis of iron-laden dopaminergic neurons.[104] In animal models and patients with PD, transferrin accumulates in dopaminergic neurons, and much of the iron transport protein primarily localizes to mitochondria, and a large proportion of the nigral transferrin is oxidized at cysteine residues, forming an intermolecular disulfide bond in close proximity to the iron-binding site.[104] Iron also appears to contribute to the formation of the pathological hallmarks of PD, such as Lewy bodies, intraneuronal proteinaceous inclusions that contain the aggregation-prone protein, the α-synuclein. Neurodegeneration with brain iron accumulation has been reported due to mutations in pantothenate kinase type 2 that also exhibit Lewy pathology labeling for α-synuclein and neuroaxonal spheroids labeling for β- and γ-synuclein.[105,106] Specifically, iron associates with α-synuclein, increasing its aggregating and thereby potentiating neurotoxicity.[107] Conditions such as neuroferritinopathy and Friedreich ataxia are associated with mutations in genes that encode proteins involved in iron metabolism, and as the brain ages, iron accumulates in regions affected by AD and PD.[108] Under the pathological condition, the non-heme iron is in higher concentrations in globus pallidus, substantia nigra, red nucleus, and dentate nucleus,[109] and upregulation of iron-related protein, Divalent Metal Transporter Iron Responsive Element (DMT1+IRE), has been observed in dopaminergic neurons and microglia in patients with PD and mouse model of PD.[101] Iron metabolism occurs in the mitochondrial matrix, where the Fe-S cluster assembles and incorporates into the electron transport complexes. Under pathological conditions, disproportionate cellular iron is observed due to disruption of Fe-S clusters, resulting in the mitochondrial dysfunction observed in the early pathogenesis of PD.

Aluminum and Parkinson's Disease

Aluminum (Al) is one of the most prevalent elements since it has only one oxidation state, and it can combine with other metals present in the environment to form a complex. In the experimental animal model, Al has been shown to accumulate in all regions of the brain, with the highest concentration in the hippocampus, the memory and learning center of the brain.[110] Al is known to induce ROS, which impairs mitochondrial functions, leading to cellular damage and apoptosis. Al induces cell death by various other mechanisms such as the generation of ROS, the release of intracellular Ca^{2+} deposits, and perturbation of mitochondrial function.[111–113] Al exposure due to high amounts of this element in the environment leads to the formation and accumulation of neurofibrillary tangles, β-amyloid plaques, tau aggregation, and

neuronal dysfunction in the central nervous system.[114] Al concentrations are also higher in the substantia nigra pars compacta of the PD patients' brain, indicating a link between PD and Al exposure. Al also promotes the ability of 6 OHDA to cause oxidative damage and neurodegeneration in the mouse model of PD.[115]

Manganese and Parkinson's Disease

Occupational exposure to manganese causes Manganism, a cognitive disorder with muscle weakness, bent posture, whispering speech, limb tremor, and salivation, symptoms very similar to PD that occur due to the accumulation of Mn in basal ganglia, targeting dopaminergic neurons. Occupational exposures occur mainly in welding and mining as miners are surrounded by dust of Mn and airborne Mn particles, alloy production and processing, and ferromanganese operations, especially in which Mn ore or compounds are turned into steel, and work with agrochemicals. Overexposure to Mn in the ionic forms mainly influences the central nervous system, causes symptoms that increase the possibility of irreversible hippocampal damage, and shows involuntary extrapyramidal symptoms associated with PD. Apart from divalent metal transporter 1 (DMT1), Mn is transported across the cell membrane by voltage-gated Ca^{2+} channel, Ca^{2+} coupled ionotropic glutamate receptor, solute carrier 39 (SLC39), ZIP8, and ZIP14. Elevated levels of Mn in the brain also impair iron homeostasis and cause a synergistic effect. Histopathological analysis shows Mn^{2+} at a low dose induces apoptotic neuronal cell death through a mitochondrial-dependent pathway.[8,116] Mn overexposure in rodent and non-human primates results in Mn accumulation in brain regions, including the basal ganglia, further disrupting the GABAergic and dopaminergic neurotransmission and activating glial cells and eventually causing neuronal loss.[117] One of the impending mechanisms underlying Mn neurotoxicity is the induction of ROS generation and subsequent oxidative damage to the dopaminergic neurons,[8] especially in the globus pallidus, striatum, and substantia nigra,[118–120] and antioxidants have been shown to ameliorate the deleterious neurotoxic effects of Mn.[121] Mn^{2+} interferes with oxidative phosphorylation by inhibiting ETC complex activities, especially mitochondrial complex I and III (Figure 1), or decreasing the production of ATP.[121–123] In an in vitro study, dopaminergic neuronal cells, not the glial cells exposed to Mn, show inhibition of mitochondrial ETC,[122] whereas in vivo exposure to $MnCl_2$ inhibits cytochrome c oxidase.[124]

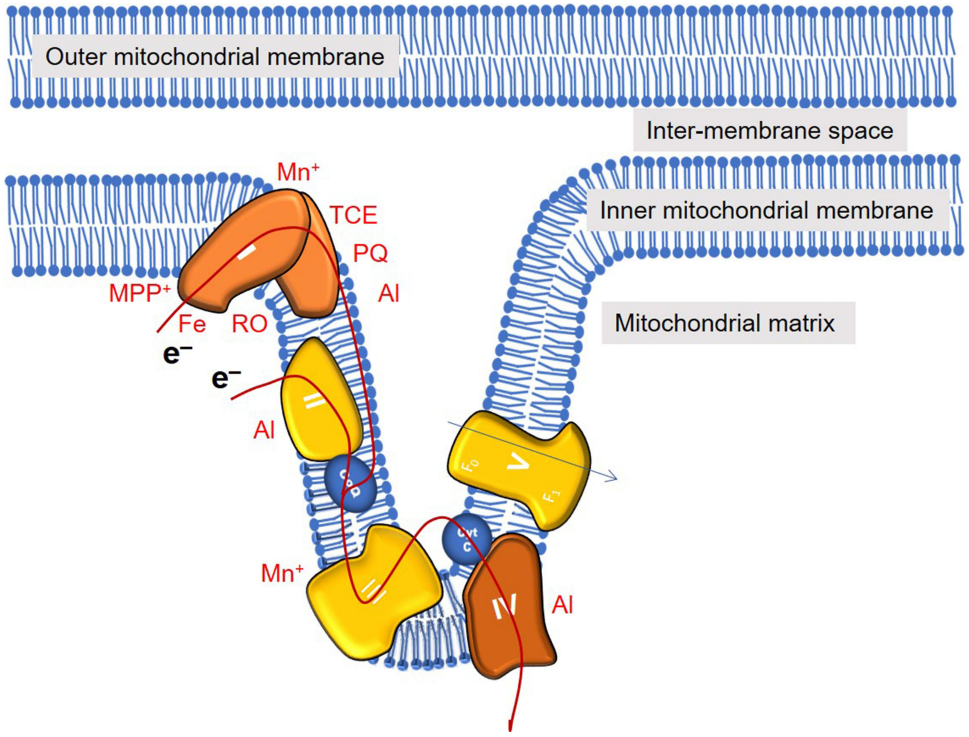

Figure 1 Mitochondrial toxicants and electron transport complexes. The above figure shows the flow of electrons during oxidative phosphorylation and the toxicants targeting various electron transport complexes. Most of the toxicants inhibit complex I, causing mitochondrial dysfunctions and neurodegeneration.

Mn exposure further mediates nonenzymatic autoxidation of catecholamines, dopamine to 6-hydroxydopamine that further potentiate neurotoxicity and also explain the reason for the depletion of dopamine from the specific regions of the brain following Mn exposure.[125,126] Accumulation of Mn in the striatal regions inhibits tyrosine hydroxylase activity, affecting dopamine synthesis.[127] Mitochondria sequester intracellular Mn through the Ca^{2+} uniporter,[128] and the specificity for Mn accumulation in GP and striatum is likely correlated with Mn transporter distribution.

Conclusion

Besides providing beneficial effects to society, pesticides, heavy metals, drugs, and natural and anthropogenic chemicals present in our environment pose a significant threat to our health. Although some serve a vital purpose, exposure to these chemicals causes cellular toxicity, contributing to the pathogenesis of many diseases, including neurodegenerative diseases. Several of these chemicals have different mechanisms in causing pathogenesis; however, most chemicals directly or indirectly target the mitochondrial electron transport system. At the organelle level, mitochondria are involved in fundamental processes, including energy production, reactive oxygen species generation, calcium signaling, mitochondrial dynamics, and apoptosis. This review elaborates on the molecular mechanism of mitochondrial toxicant-induced neurodegeneration and its role in the pathogenesis of PD (Figure 1), signifying the need to develop innovative strategies for studying this organelle at the cellular and molecular levels. Remarkably, mitochondria are unintended drug targets of many pharmaceutical and therapeutic agents that can cause mitochondrial dysfunction by altering the membrane potential and electron transport chain. The brain heavily depends on oxidative phosphorylation for survival and appears to be the main target for many mitochondrial toxicants. Interestingly, each chemical does not induce the same effect on the population in developing neurodegenerative diseases, which varies on the time of exposure, duration of exposure, and the metabolic conditions of an individual. Furthermore, all the individuals exposed to pesticides or mitochondrial toxicants do not have, or develop the symptoms or neurodegeneration similar to Parkinson's disease at the same rate due to genetic diversity. Due to predisposition, some individuals are more prone to react when they are exposed to mitochondrial toxicants even at a lower concentration. However, it is inconclusive about the specific dose of exposure that correlate with neurodegeneration. Understanding the mechanism of action of chemical agents contributing to neurodegeneration is essential to developing a neuroprotective strategy.

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Disclosure

The authors report no conflicts of interest in this work.

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