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REVIEW ARTICLE

A systematic review of molecular approaches that link mitochondrial dysfunction and neuroinflammation in Parkinson's disease

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Abstract

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that affects 1% of the population worldwide. Etiology of PD is likely to be multi-factorial such as protein misfolding, mitochondrial dysfunction, oxidative stress, and neuroinflammation that contributes to the pathology of Parkinson's disease (PD), numerous studies have shown that mitochondrial dysfunction may play a key role in the dopaminergic neuronal loss. In multiple ways, the two most important are the activation of neuroinflammation and mitochondrial dysfunction, while mitochondrial dysfunction could cause neuroinflammation and vice versa. Thus, the mitochondrial proteins are the highly promising target for the development of PD. However, the limited amount of dopaminergic neurons prevented the detailed investigation of Parkinson's disease with regard to mitochondrial dysfunction. Both genetic and environmental factors are also associated with mitochondrial dysfunction and PD pathogenesis. The induction of PD by neurotoxins that inhibit mitochondrial complex I provide direct evidence linking mitochondrial dysfunction to PD. A decrease of mitochondrial complex I activity is observed in PD brain and in neurotoxin- or genetic factor-induced in vitro and in vivo models. Moreover, PINK1, Parkin, DJ-1 and LRRK2 mitochondrial PD gene products have important roles in mitophagy, a cellular process that clear damaged mitochondria. This review paper would discuss the evidence for the mitochondrial dysfunction and neuroinflammation in PD.

Keywords Parkinson's disease · Mitochondrial dysfunction · Neuroinflammation · Mitochondrial proteins

Introduction

Parkinson's disease (PD) is categorized by the attenuation of dopaminergic neurons in brain particularly substantia nigra region and the existence of Lewy bodies (LBs) is the common symptoms of PD [24]. Lewy body is produced in the presynaptic region by the α-syn expression and gets aggregated. Factors such as oxidative stress, inflammation, aging, genetic mutations, and environmental toxins may also cause PD. Off all factors, inflammation plays a major part in the introduction of PD [30]. Neuroinflammation is caused by infectious agents or neurotoxins with proinflammatory action properties that lead to the pathogenesis of PD. Previous reports have shown that dopamine-induced oxidative stress contributed to the inflammatory response in PD patients [6]. Production of ROS enhances the chronic inflammatory response by altering different biomolecules leading to the destruction of neurons [3]. Infectious substances or neurotoxins that alter glial cells include astrocytes and microglia which liberate neurotoxic factors like phagocyte oxidase (PHOX)-induced H_2O_2 and cytokines (TNFα, IL-1β, etc.) [90].

Cytokines activate receptor-mediated pro-apoptotic pathways in dopaminergic neurons and up-regulate inducible nitric oxide synthase (iNOS) and cycloxygenase 2 (COX2) by stimulating microglia. Thus the increase in generation of ROS and NO leads to DNA damage, lipid peroxidation, and protein disruption [19]. In knockout mice studies, autorecurrent factors such as PARKIN, PINK1, and DJ-1 suggested that these factors could be involved in negative regulation of neurosystem. Although mitochondrial dysfunction is well known in the dopaminergic neurons of idiopathic and

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familial PD, the mechanisms involved are unclear. Mitochondrial dysfunction is primarily due to the formation of reactive oxygen species (ROS), ATP depletion, cytochrome c-release, a reduction in mitochondrial complex I enzyme activity, and caspase 3 activation [46]. The disorder of the systemic mitochondrial complex I has been associated for a long time in the diagnosis of idiopathic PD that produces an improved level of OS (Oxidative Stress) in nigral neurons. Reduced mitochondrial activity enhances OS and ROS, accelerating the degeneration of neurons to worsen the integrity of neurons. The OS or ROS causes cellular damage and also implements signaling pathways which result in cell death [62].

Pathways and mechanisms for neuroinflammation

Cytokines

Surface markers present in both microglia and peripheral macrophages are similar which are difficult to differentiate cell types in postmortem PD brain tissue. Lipopolysaccharide (LPS) stimulated peripheral macrophages from PD patients to produce fewer TNF-α, IL-1 a/b, IFN-α, and IL-6 than healthy regulation and extent associated with disability, indicating the decreased cytokine which can develop in tandem with a disease. In different levels of multiple cytokines like TNF-α, IL-1b, IL-3, and IL-6, in postmortem striatum, SN and cerebral spinal fluid (CSF) in PD patients [21] are high, and increased levels of TNF-α receptor R1 (TNF-R1, p55), bcl-2, soluble Fas (sFas), caspase-1, and caspase-3 [55] indicate the presence of a proinflammatory/apoptotic microenvironment in PD patients. However, other regulatory cytokines, including IL-4, transforming growth factor (TGF)-α, TGF-β1, and TGF-β2 [10], also got elevated that shows its ability to control the environment during inflammation. In addition, hippocampal tissues possessed the increased level of IL-2 from PD patients compared to controls indicating that IL-2 receptors (IL-22R) on cells contained in the hippocampus is also up-regulated in PD patients [39]. Although probably expressed by both neuronal and glial cells, the location of IL-2 and IL-2R primarily for frontal cortex, septum, striatum, hippocampal formation, hypothalamus, locus coeruleus, cerebellum and pituitary, and corpus callosum fibers suggested possible regulatory interactions between peripheral tissue and CNS [57]. Most often, IL-2 acts in an auto- and the paracrine manner in the brain as in the peripheral immune system, but that reveals the characteristics of a neuroendocrine modulator under various physiological conditions. For example, IL-2 regulates neuronal and glial growth and differentiation during development and also has its effects in the modulation of sleep/excitement, memory, and cognition, dementia, and neuropsychology [9] (Fig. 1).

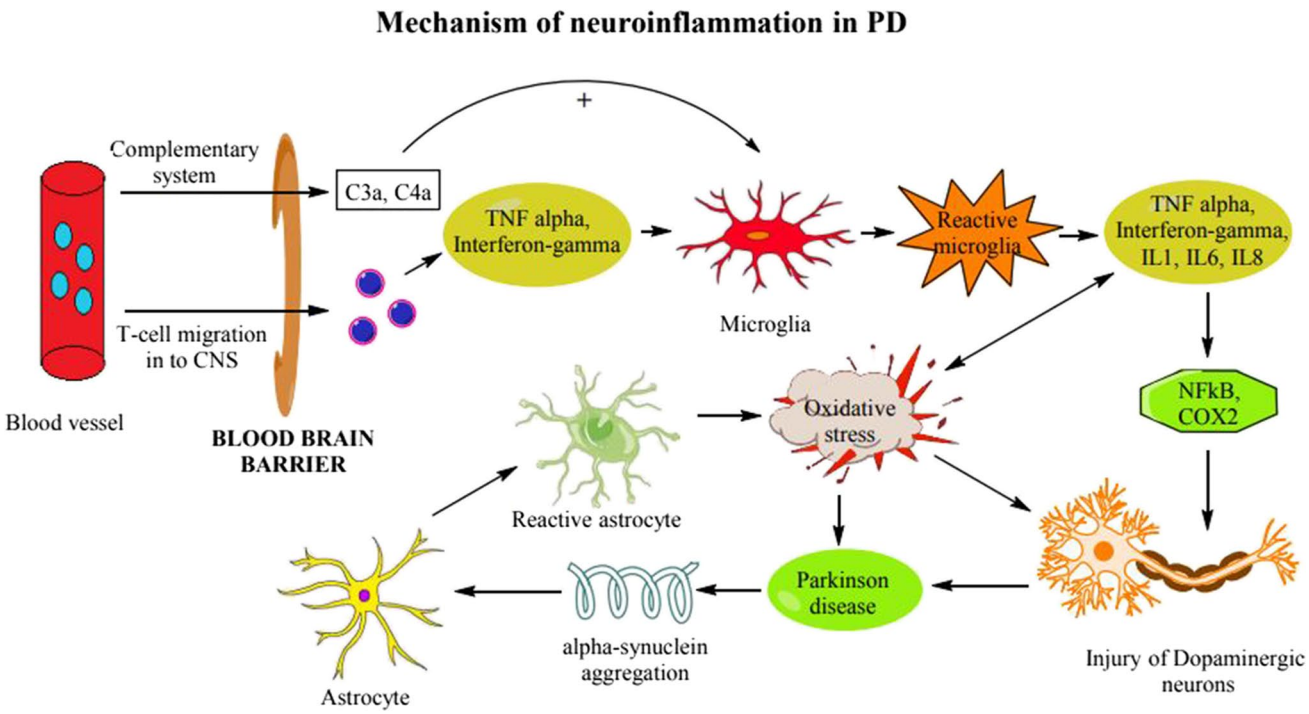

Fig. 1 Schematic representation of neuroinflammation in PD

Free radicals and reactive oxygen species

Inflammatory responses are induced by reactive microglia, macrophages, and proinflammatory T cells that provide a primary source of free radicals with the ability to modify proteins, lipids, and nucleic acids. It increases a state of antioxidant stress that increases the production of high intracranial organisms, which in turn reduces the free radical capture that leads to greater changes to survival and reductions in damaged macromolecules [81]. The most reactive nature and short half-lives of reactive species, combined with the limiting nature of neuroinflammatory foci for clinical sampling, avoid direct measurement in the pathogenic processes of these reactive species. However, changes in proteins, lipids, and nucleic acids offer substitute biomarkers, which is used to measure the extent of oxidative stress [2, 57]. Postmortem analyses of patients with PD have indicated the presence of these biomarkers for oxidative stress. Protein modifications are also a biomarker which is exhibited in the brains of PD patients. Contrasted with minds from control benefactors, elevated dimensions of nitrated proteins was found in cerebrum and CSF of PD patients [56]. Most eminent are adjustments of proteins that include Lewy bodies (LB), the neuronal considerations that are viewed as the signs of PD and comprises fundamentally of α-synuclein, ubiquitin, and lipids. Additionally, S-nitrosylated types of Parkin, an E3 ubiquitin ligase engaged with protein ubiquitination, has been separated from the transient cortex from PD patients, however not from minds of HD or AD patients [1].

In vitro and in vivo, S-nitrosylation of Parkin actuates an underlying increment in ligase action prompting autoubiquitination of Parkin, inevitable hindrance of ubiquitin ligase movement, and diminished activity in the E3 ligase–ubiquitin–proteasome degradative pathway [87]. Carbonyl adjustments, which are intelligent of protein oxidation, are expanded by more prominent than twofold in the SN contrasted with the basal ganglia and prefrontal cortex of ordinary subjects [83]. Increments in protein carbonyls have been found in SN, basal ganglia, globus pallidus, substantia innominata, cerebellum, and frontal post, yet not in patients with accidental LB ailment (ILBD), a putatively presymptomatic PD issue. The inclusion of the last two mind locales are surprisingly dependent on the limited neuropathology of PD, yet may mirror a result of L-DOPA treatment or an increasingly worldwide outcome of the incendiary spread of oxidative worry in PD. Other proof for oxidative harm to proteins in PD is the expanded articulation of neural heme oxygenase-1 [71] and expanded immunostaining of glycosylated proteins by nigral neurons [7]. Free radicals and nucleic corrosive adjustments change of nucleic acids by free radicals and responsive species can actuate chromosomal deviations with increase effectiveness [20], proposing that chromosomal harm showed in neurons of PD patients may be identified with a strangely increased oxidative pressure.

Among the most encouraging biomarkers of oxidative harm to nucleic acids is nucleoside 8-hydroxyguanosine (8-OHG) for RNA or 8-hydroxy-20-deoxyguanosine (8-OHdG) for DNA. 8-OHG is an oxidized base delivered by free extreme assault on DNA by C-8 hydroxylation of guanine and is a standout among the most regular nucleic corrosive adjustments seen under states of oxidative pressure [95]. The immunohistochemical portrayal of these adjustments demonstrates that the most abnormal amounts of 8-OHG changes are present in neurons of the SN and to a lesser degree in neurons of the core raphe dorsalis and oculomotor core, and at times in glial cells [95]. 8-OHG nucleic corrosive changes are once in a while recognized in the atomic region and for the most part limited to the cytoplasm, and (2) immunoreactivity is fundamentally reduced by RNase or DNase and removed with the two proteins, [95] propose that objectives of oxidative assault incorporate both cytoplasmic RNA and mitochondrial DNA. Specific notable are the discoveries that convergences of 8-OHG in CSF of PD patients are higher than in age-coordinated controls,nonetheless, serum groupings of 8-OHG show deep factor [43, 95].

Lipid peroxidation

Lipid peroxidation often occurs in response to oxidative stress, and a large variety of aldehydes are formed when lipid hydroperoxides break down into biological systems. 4-Hydroxy-2-nominal (HNE) is a responsive α, β-unsaturated aldehyde that is significant amid the oxidation of film lipid polyunsaturated fats and structures stable adducts with nucleophilic bunches on proteins [26]. HNE change of film proteins shapes stable adducts that can be utilized as biomarkers of cell harm because of oxidative pressure. Immunochemical recoloring on enduring dopaminergic nigral neurons in the midbrains of PD patients demonstrate the nearness of HNE-changed proteins on 58% of the neurons contrasted with 9% of those in control subjects. The powerless or non-coloring on oculomotor neurons was observed in a similar midbrain areas of PD patients and the nearness of HNE altered proteins in LB from PD patients [14]. HNE species are regularly more steady than oxygen species, they can without much of a stretch spread from the site of creation to impact alterations at a far off site [96]. HNE adjustments of DNA, RNA, and proteins have different unfavorable organic impacts, for example, obstruction with enzymatic responses and enlistment of warmth stun proteins, and are viewed as to a great extent in charge of the cytotoxic impacts under states of oxidative pressure [78, 92]. The cytotoxic impacts of HNE changes might be established to some extent because of the restraint of edifices I and II of the mitochondrial respiratory chain; enlistment

of caspase-8, caspase-9, and caspase-3; cleavage of poly (ADP–ribose) polymerase (PARP) with consequent DNA fracture; inhibition of NFκB-intervened signalling pathways [51], and reduction of glutathione levels [25, 65]. Fixations that initiate no intense change in cell in vitro at first reason is an abatement in the proteasomal reactant action to the degree that it incites collection of ubiquitinated and nitrated proteins, decreases in glutathione levels and mitochondrial action, and expanded dimensions of oxidative stress to DNA, RNA, proteins, and lipids [37]. Another receptive aldehyde species created from the peroxidation of lipids is malondialdehyde (MDA), which is shaped from the breakdown of endoperoxides amid the last phases of the oxidation of polyunsaturated fats; especially powerless are those containing at least three or more bonds. MDA can exist as free aldehydes or respond with essential amine gatherings of macromolecules to shape adducts with cell structures [2, 31]. Proof of expanded dimensions of MDA-adjusted proteins are found in the SN and CSF of PD patients, but not in controls which is a characteristic feature of expanded lipid peroxidation and supportive presence of perpetual reactions in the patients [68]. F2-isoprostane (F2-IsoP) and isofuran (IsoF) are different results of lipid peroxidation, and both are entrenched as explicit biomarkers of in vivo oxidative pressure [66]. This particular increment in IsoF species in PD patients demonstrates that the microenvironmental oxygen strain is ordinarily more noteworthy in PD than different clusters and proposes a one of a kind method of oxidant damage in PD, which might be characteristic of an expanded intracellular oxygen pressure coming about because of mitochondrial brokenness or a more prominent force of incendiary reaction in PD. This information positively show that oxidative worry in the SNpc area in PD, however, yet to be determined is whether innate immune cell activation of microglia and/or astrocytes during the progression of PD shifts the homeostatic balance towards increased protection from or exacerbation of ROS damage and whether this dynamically changes with disease progression.

Mitochondrial dysfunction

During mitochondrial respiration, the electrons of nicotinamide adenine dinucleotide (NADH) are transferred to complex I (NADH: ubiquinone oxidoreductase) and form a final product, H_2O, via the activities of complexes III and IV. During the course of electron transfer, recovery of energy is done through ATP formation which in turn enhances the production of ROS and RNS which triggers an apoptotic cascade. Previous studies shown that oxidative damage in the catalytic subunits of complex I in the frontal cortex region of PD patients, which is correlated with complex assembly and dysfunction of the complex [42]. Due to the influence of high proton motive force, the electron supplied from complex II to ubiquinone is reversibly transferred to complex I and reduces NAD^+ to NADH, resulting in an alkaline pH or high membrane, which influences the production of ROS. ROS promote single electron transfer across complexes and form a superoxide anion leading to overproduction of free radicals [85]. Increased ROS production in the mitochondria or decreased mitochondrial defense suppression results in DNA, protein, and mitochondrial lipid damage. This damage compromises the respiratory chain, thereby establishing a new link between oxidative stress and bioenergetic failure [46, 91] (Fig. 2).

Mitochondrial familial in Parkinson's disease

Mitochondria are very dynamic organelles which perform a profuse function. Apart from the versatile role of mitochondria, it possesses various cellular processes like regulation of calcium homeostasis, cell death pathway, and stress response [84]. Thus, deterioration of mitochondrial function results in cellular damage leading to neurodegenerative disorder. Many researchers evidenced that mitochondrial dysfunction plays an important role in the pathogenesis of Parkinson's disease and this might be due to the inhibition of complex I of the ETC which can induce Parkinsonism. PD-associated genes such as α-synuclein and LRRK2 are responsible for autosomal dominant forms, and Parkin, PINK1, and DJ-1 mediate autosomal recessive PD [67].

Autosomal dominant PD

α-Synuclein

α-Synuclein, a 140 amino acid polypeptide encoded by SNCA, is the main component of Lewy bodies. α-Syn present in the mitochondrial membrane had shown its effect on mitochondrial structure and functions [59]. A mutation in α-Syn with PD-related mutations such as A53T, A30P, E46K, H50Q, and G51D leads to mitochondrial fragmentation, proteasomal and lysosomal protein degradation, ER stress, and Golgi fragmentation. Recent studies showed that biogenesis of mitochondria was influenced through the regulation of PGC1α [75, 89]. Cytosolic acidification is helpful to enhance the binding of α-Syn to mitochondria [67]. The mitochondrial alteration was found in the mouse model by overexpressing wild-type or mutant α-synuclein [88]. This is due to increased α-synuclein aggregation that leads to decreased COX, complex IV activity, and mitochondrial membrane potential. α-Synuclein knockout mice were reported for abnormal mitochondrial lipid with decrease in cardiolipin content which was related with a decrease in complex I/III activity [38]. Increased α-synuclein expression and deficiency lead to mitochondrial abnormalities, thus

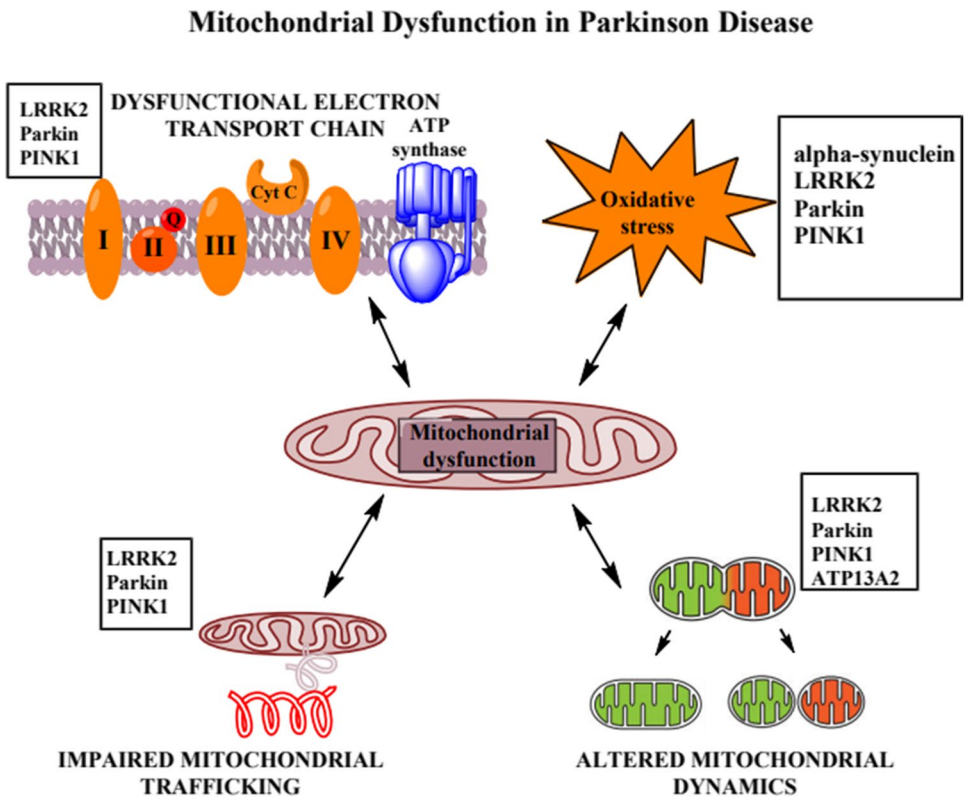

Fig. 2 Schematic representation of mitochondrial dysfunction in PD

from the above evidence that α-syn has effects on mitochondria indirectly influencing its mitochondrial function.

LRRK2

LRRK2 (leucine-rich repeat kinase 2) is a multirole protein kinase that exerts its pathogenic role by enhancing the kinase activity [67]. PD-associated mutations in LRRK2 include p.G2019S, p.R1441C/G/H, p.Y1699C, p.I2020T, and p.N1437H [60]. By overexpressing WT or mutant LRRK2 showed increased vulnerability to mitochondrial toxins that cause defects in mitochondrial dynamics and increased ROS production. Several proteins (mitochondrial fission protein, dynamin-related protein 1, mitofusin (MFN) 1/2, and optic atrophy 1) interact with LRRK2 which are responsible for pathological effects on mitochondria. UCP2 and UCP4 up-regulation lead to increased proton leak and loss of mitochondrial membrane potential [70]. Overexpression of LRRK2 leads to loss of DA neurons in *Drosophila* and *C. elegans*. PD can contribute to the immune system by directly disabling LRRK2 immune system cells. The strong stimulation of the LRRK2 protein is found in microglia cells of the mouse [54]. However, in LRRK2 p.R1441G knock-in mice, LPS-activated microglia cells showed the highest exposure of pro-inflammatory cytokines and decreased expression of anti-inflammatory cytokines compared with wild-type control microglia cells [48, 64].

Parkin

Parkin, a gene that encodes a cytosolic 465 amino acid protein with the ubiquitin-like domain at N-terminal and RBR domain of C-terminus, has two RING finger motifs which flanks a cysteine rich between RING finger domain [45]. Mutation in Parkin leads to autosomal recessive PD. Mitochondrial morphology and their functions are greatly affected by Parkin deficiency. Major Parkin targets located in mitochondria were found by ubiquitous examination. Parkin has a different function in managing healthy mitochondria by organizing their biogenesis and degeneration through mitophagy [77]. In the early phase of mitochondrial deterioration, Parkin leads to damage of mitochondria, and PTEN is stimulated [8]. Mitophagy removes the process to mitochondria from the healthy mitochondrial pool and enhances their degradation through the autophagy-lysosomal pathway. In the recent past, the in vitro models revealed the pathophysiological significance of Parkin-mediated mitophagy in PD [27]. Under stable conditions, Parkin mediates the destruction of Parkin interacting molecule, a repression of the PGC1α activity, leads to nuclear transfer of PGC1α and transcriptional implementation of mitochondrial related genes. Loss of Parkin function permits PARIS to accumulate and suppress mitochondrial biogenesis and results in decreased mitochondrial mass and functional defects [15]. These findings focus on the key role of Parkin which plays

in restructuring the balance of mitochondrial production and destruction.

Autosomal recessive PD

PINK1

Mutation in PINK1 is the main cause of autosomal recessive PD [29]. PINK1 is a mitochondrial serine/threonine kinase which plays an important role in managing mitochondrial homeostasis. Defects in PINK1 may cause deformities in mitochondria like a change in morphology, trafficking etc. [40]. PINK1 activate the Parkin by direct phosphorylation of Parkin at S65 and transactivation by phosphorylation of ubiquitin at S65 thus in turn helpful in clearance of damaged mitochondria [58]. Nuclear Dot protein and optineurin help PINK1 to mediate mitophagy. Similarly, LRRK2 and PINK1 promote mitophagy by aborting the mitochondrial trafficking through phosphorylation [4]. Various researchers have proved that loss of PINK1 leads to mitochondrial dysfunction in vitro and in vivo models (*Drosophila* and mice) [61]. PINK1 regulates mitochondrial homeostasis, for example, PINK1 deficiency is found to be effective in mitochondrial Ca^{2+} overload and a specific depletion in mitochondrial complexes I and III [32]. Increased mitochondrial fission has increased protein kinase A (PKA)-mediated DRP1 activation and modified mitochondrial biogenesis through Parkin-mediated destruction of PARIS [72].

DJ-1

DJ-1 protein is largely present in the cytosol and a little part in the nucleus and mitochondrial matrix and intermembrane space and decreases degradation [34]. Upon OS, DJ-1 transfer easily to mitochondria and nucleus and plays a vital role and act as a neuroprotector [79]. A decrease in mt DNA, ATP level, and respiratory control ratio was observed in DJ-1 knockout in fly and mice [76]. Further, DJ-1 and its mutant are highly related to Hsp 70 in mitochondria. During OS, wild-type DJ-1 with mitochondrial Hsp 70 was increased, and translocation happens with the help of mitochondrial chaperones [97]. DJ-1 interacts with Parkin and PINK1 under OS conditions and activates Mn-SOD gene responsible for the mitochondrial antioxidant enzyme. Furthermore, decreased DJ-1 leads to reduced MMP, increased mitochondrial fragmentation, autophagy, OS, and mitochondrial fusion [86].

Mitophagy in PD

Autophagy is a highly conserved cellular degradative pathway that is essential for survival, differentiation, development, and homeostasis [94]. The specific autophagic elimination of mitochondria is defined as mitophagy [94]. Previous studies have reported that autophagosomes accumulate due to aggregation of misfolded proteins in the brains of patients leading to diverse neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and Huntington's disease [73]. Defects in mitophagy have been shown to summarize a number of reported PD features, namely impaired motor coordination, tremor, and the accumulation of protein aggregates/inclusion bodies in residual neurons. In general, the autophagy process involved in the suppression of many neurodegenerative processes by degrading unfolded proteins and also inhibits a few types of PD by degrading damaged mitochondria. Parkin (PARK2) and Pink1 (PARK6) are the genes involved in eliminating damaged mitochondria by autophagy in familial PD [62]. During the process of mitophagy, first Pink1 accumulates on the outer mitochondrial membrane from the cytosol succeeding mitochondrial depolarization. Later, Parkin, a cytosolic E3-like ligase, binds with Pink1 on the outer mitochondrial membrane, which then leads to ubiquitination of depolarized mitochondria by the ubiquitin ligase activity of the Parkin followed by employing numerous autophagy components such as p62 [41]. Autophagic molecules recognize ubiquitinated mitochondria and are digested by autophagy. Thus, genetic mutations in these genes Parkin and Pink1in familial and sporadic PD becomes inefficient in the elimination of damaged mitochondria, which results in the degeneration of dopaminergic neurons.

Mitochondrial fission and fusion in Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder with characteristic symptoms. The most compelling research platform in PD or any other neurodegenerative disorders is the underlying pathology as they are potential therapeutic targets and beacon for the better understanding of the disease. In the case of PD, dysfunctional mitochondrial dynamics and the resultant incapacitation form the basic driving force for the cause and progress of disease as indicated by scientific studies [5, 12, 18]. The most notable and compelling evidence on the role of mitochondrial dysfunction in PD is the exposure of the chemical 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its metabolite MPP^+ on the complex I activity of mitochondria. MPTP mice model is one of the most widely used mice models for PD research and scientific study for therapeutic interventions [63].

Within the nerve cell, the mitochondria (Mt) generate energy for the active functioning of the cell. These mitochondria often undergo specific dynamic changes with respect to the number, size, and shape by the process of mitochondrial fission or fusion. Fission of Mt results in multiple smaller organelles and fusion results in on larger

Mt. These processes are supported by the fission/fusion proteins and by the cells demand. Dysfunctions in mitochondria will disrupt the integrity of the nerve cell network and metabolic efficiency. Genetic and biochemical studies on the model organisms such as *Drosophila melanogaster* and *Saccharomyces cerevisiae* along with human cells have vividly accounted for the regulation of Mt fission and fusion mechanics by conserved proteins and dynamin-GTPases [16, 52]. Also, the Mt biogenesis is not de novo which means that Mt cannot be made; hence, the fission and fusion process are quintessential for the biogenesis process.

The implications of Mt fission and fusion in PD pathogenesis are described as follows. Pink1 is a serine/threonine kinase that is present in the mitochondria and cytosol, and Parkin is a cytosolic E3 ubiquitin ligase. These two proteins are mostly associated with PD. Scientific research on these proteins have given solid evidence that loss of Pink1 in the neuronal cell cultures resulted in abnormal Mt morphology [28]. Further, the knockdown of Pink1 in SH-SY5Y cells can lead to the fragmentation of Mt and is reversible by the overexpression of Parkin [22]. This evidence suggest that a strong interaction exists between these two protein and act downstream of each other [44, 93]. A genetic study on the Pink1/Parkin mutant *Drosophila* flies has proven that overexpression of *Marf/Mfn2* (a fly homolog of mammalian Mfns) or *Opa1* can ameliorate the phenotypes such as the flight muscle degeneration, defects in flying, or abnormal wing position [23]. Taken together, the mitochondrial fission and fusion have quite a significant effect over the functionality and quality of the nerve cell integrity, subsequently contributing to the pathogenesis of PD. Currently, the genetic testing kits for the proteins, SNCA, Parkin, PINK1, and LRRK2 are available commercially [33] along with animal models. Given the heterogeneity and complexity of the disease, more suitable underlying principles and their respective biomarkers have to be investigated deeply to win over PD.

The experimental model of neuroinflammation and mitochondrial dysfunction

There is widespread evidence that PD is caused by neurotoxins particularly 6-hydroxydopamine, rotenone, paraquat, diquat, and MPTP. All these chemicals act through various mechanism (Fig. 3).

6-Hydroxydopamine

6-Hydroxydopamine serves as a well-formed animal model for PD to induce neurodegeneration and stimulation. 6-OHDA is the neurotoxic effects of entering the cytosol via the complex electron transporter chain, the complex I-preventing DA transporter, which enhances the ROS productivity, where it can automatically carry oxidation. Despite the 6-OHDA, it does not penetrate into the blood–brain barrier, which requires its local injection in SNpc or the striatum. The local injection of 6-OHDA in SNpc was first reported by Ungerstedt [80]. The researchers used a bone sample to stimulate the neurons-containing disorder in the rodent brain, in which the SNpc or brain was used to decompose the dopamine levels in the tyrosine after using the stereotaxic injection of this compound, which is the TH positive terminals of the striatum [11]. This functional procedure, like human, provides a gradual improvement of the neurological process. Therefore, 6-OHDA stimulates the most repetitive and reliable brain SNpc injury, which is shown to be very helpful in finding novel treatment techniques for neurological effects.

Rotenone

It is a natural compound present in various plant species such as Derris, Lonchocarpus, Tephrosia, and Mundulea. It is broadly used as an insecticide and pesticides which possess a neurotoxic effect. Rotenone is lipophilic and has the tendency to cross the blood–brain barrier, neuronal cells, and organelles such as mitochondria without the help of transporters. It blocks the mitochondrial ETC via inhibition of complex I that lead to free radical generation in the mitochondrial matrix and ROS formation. The mechanism of action of rotenone is unclear, but evidence from in vitro and in vivo PD models suggest that this may cause delayed decrease in glutathione leading to oxidative damage to protein and DNA. Administration of rotenone modify the DJ-1 and leads to α-syn aggregation causes PD. Rotenone exposure to rats leads to cytoplasmic inclusions in the brain; thus it has linked with mitochondrial dysfunction and PD. This may also cause damage to neurons in the striatum.

Paraquat and diquat

After the identification of MPTP, MPP^+ as a functioning metabolite of MPTP model and analysts have discovered a structure like MPP^+ in forming synthetic substances. Subsequently, herbicide paraquat was recognized as a specialist that used to think about PD in mice. Paraquat was infused into mice to initiate engine shortfalls and loss of nigral dopaminergic neurons in a portion subordinate way. Uversky [82] revealed that paraquat administrated fundamentally, have been appeared to repeat highlights of PD in rodents. Somayajulu-Niţu et al. [74] also detailed that paraquat-led neurodegeneration speaks to a beneficial rodent model of PD that is reasonable for thought-out and neuroprotective

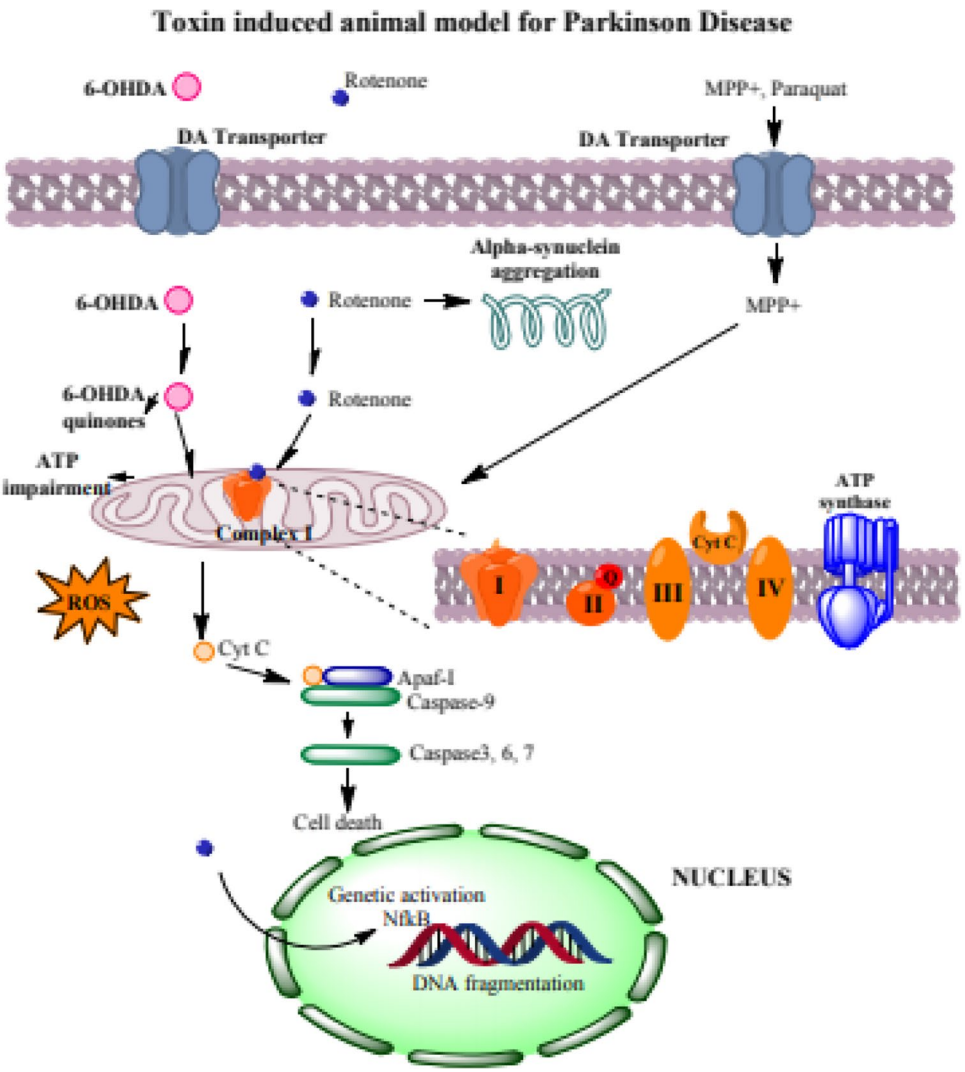

Fig. 3 Schematic representation of various toxin-induced animal model of PD

studies to recognize new medication that focuses on the treatment of PD.

MPTP

MPTP is a primary toxin that connected with mitochondrial complex I inhibition and PD. MPTP is produced as a byproduct of the synthesis of meperidine simple with heroin-like properties [36]. It has additionally been appeared to intently repeat the DA degeneration and manifestations of PD in different models and has been the most generally utilized toxin-induced models of PD [47]. MPTP promptly crosses the blood–brain barrier and is changed over to the lethal 1-methyl-4-phenyl-2,3-dihydropyridium particle (MPP+) (Fig. 3) by monoamine oxidase B in astrocytes toxin [17]. Furthermore, it is then taken up into DA neurons by DAT decrease in MPTP danger in DAT lacking mice [53]. MPP^+ is taken up into mitochondria by means of uninvolved transport because of the expanded mitochondrial transmembrane angle, where MPP + restrains mitochondrial complex I [13, 29]. This restraint of complex I prompts cell passing by means of vitality deficiencies, free radical, and ROS age [49], and perhaps excitotoxicity [35]. In an MPTP mouse model of PD, α-synuclein is nitrated [50], giving another connection between MPTP and PD. In any case, regardless of the majority of the proof of connections among MPTP and PD, there are contrasts between MPTP models of PD and idiopathic PD with varieties in sickness movement, an intense beginning, and the absence of normal LB development [69].

Conclusion

PD is a complex neurodegenerative disorder with various etiological factors involved in the pathogenesis. There are many pathways that play a vital role in modulating pathogenic events that lead to the death of the dopaminergic

neurons in PD. Curiously, these pathways affect the neuronal dopaminergic cell function and survival. The role of neuroinflammation and mitochondrial dysfunctions is the overall inability of available animal models to predict accurately the outcomes of trials that test neuroprotection in human beings.

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Author contribution SM, AK, and SS drafted the manuscript MS and SM reviewed and edited the manuscript.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval None.

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