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Overview on Parkinson's disease: pathophysiology, and experimental models

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ABSTRACT

Parkinson's disease, a neurodegenerative disease, is caused by dopaminergic neurons death and accompanied by rigidity, and postural instability, as well as bradykinesia. The cause of these neurons' death is still unclear. Since the dopaminergic neurons couldn't regenerate, therefore Parkinson's disease couldn't be cured. Thus, over the past decades, significant effort has been made to explore the etiology of Parkinson's disease development and ascertainment. This review aimed to highlight the progress that has been made in understanding Parkinson's disease pathophysiology. The role of oxidative stress, neuroinflammation, and apoptosis in the development of PD has been discussed. It has been noticed that oxidative stress, inflammation, and apoptosis are working together to develop Parkinson's disease, and each of these factors affects each other. Additionally, the experimental models and their drawbacks have been emphasized. Additionally, the mechanism of inducing Parkinson's disease (i.e., inducing neuroinflammation and oxidative stress) by neurotoxin has been highlighted.

Keywords: *Parkinson's disease; epidemiology; pathophysiology; oxidative stress; neuroinflammation; experimental models.*

1. Introduction

Parkinson's disease (PD) is second to Alzheimer's disease as the most prevalent neurodegenerative disorder throughout the world [1]. Paralysis agitans was first medically described as a neurological syndrome by J. Parkinson in the 19th century in the book "Essay on the Shaking Palsy" and renamed PD by Jean-Martin Charcot [2, 3].

Clinically, PD is characterized by motor dysfunction, i.e., rest tremors, bradykinesia, postural instability, and rigidity. Also, psychiatric symptoms are involved, including depression and anxiety, as well as autonomic dysfunction manifestoes, i.e., constipation and hypotension. Besides, it is characterized by paresthesia, olfactory dysfunction, and sleep disorders [4]. A review of incidence studies reported that the PD incidence rises with age to a peak occurring in the seventh decade of life and it continues to rise after this age in some studies [5].

Pathologically, PD is associated with Lewy bodies (LBs), dopaminergic neuronal cytoplasmic inclusions. These are the hallmarks of PD, as they are not detectable in healthy individuals. In 1997, LBs were reported to contain aggregates of α-synuclein (α-Syn) [6].

In this review, the pathogenesis of PD, and

neurotoxin models will be discussed.

2. The pathophysiology of PD

Pathologically, PD is characterized by hallmarked dopaminergic neurons lost in the substantia nigra and the appearance of LBs that are primarily comprised of fibrillar α-Syn [7].

Genetically, studies on familial PD have identified mutations in single genes in monogenic PD. In particular, mutations, which give rise to PD, are located in the α-Syn-encoded genes, dardarin, vacuolar protein sorting-associated protein 35, parkin ligase, deglycase DJ1, and acid β-glucosidase [8].

Despite mutations in these genes being infrequent and only exist in less than a tenth of all PD cases [9], they have discovered key processes and molecular players in the etiology of PD. This can be clarified by the gene (SNCA), which is linked to PD at a neuropathological and genetic level. Additionally, LBs and α-Syn are recognized in familial- and idiopathic- PD. Besides the mutations in SNCA and copy number variations present in monogenic PD [10], common SNCA mutations are linked to an increased risk of idiopathic PD [11].

Because there is no monogenic inheritance pattern in most PD patients (90%), the disease is considered idiopathic. Sporadic PD has a multiple-factorial etiology; environmental and genetic factors work together to determine an individual's liability to disease [12, 13].

2.1. The role of oxidative stress in PD

Mounting evidence has pointed that oxidative damage and mitochondrial dysfunction result in a cascade of events and eventually contribute to dopaminergic neurons degeneration [14]. This notion was supported by the assessment of the postmortem brain sections, in which elevated levels of 4-hydroxy-2-nominal, a lipid peroxidation by-product [15], carbonyl modifications of soluble proteins [16], and oxidation products of DNA, i.e., 8-hydroxy-deoxyguanosine and RNA, i.e., 8-hydroxy-guanosine [17, 18] have been detected.

In the presence of oxygen, metals, or enzymes, such as tyrosinase, dopamine (DA) are oxidized and form free radicals and quinones [19]. Dopamine quinones form a monochrome, a cyclic highly reactive, and cause the production of superoxide and reduction in cellular NADPH. A monochrome can also induce neuroinflammation by neuroinflammation, as it is the precursor of neuromelanin [19].

Postmortem tissues from the brain of PD patients have shown depletion in the amount of glutathione (GSH) in substantia nigra compacta compared to the controls [20]. Glutathione is generated in the cytoplasm but it is transported to the mitochondria to work as an anti-oxidant [21]. Since apoptosis is induced by oxidative stress, the mitochondrial GSH is considered a crucial marker of oxidative stress assessment. Also, mounting observations indicated that complex-I dysfunction causes higher production of ROS and subsequently a reduction in GSH. This reduction can result from a decreased synthesis of GSH by the suppressing of glutathione reductase, or rising glutathione disulfide level [22, 23]. Oppositely, reduced GSH level leads to complex-I activity impairment, and overall mitochondrial function [24].

Iron is pivotal for most human cells. Indeed, it is a cofactor for important proteins to maintain the normal neurons function, like tyrosine hydroxylase, an important enzyme for the synthesis of neurotransmitters [25]. Iron can contribute to ROS generation by the reaction of ferric/ferrous with superoxide anion radical, and hydrogen peroxide, producing the hydroxyl radicals, which trigger neurotoxicity with DA oxidation [26].

2.2. The role of inflammation in PD pathogenesis

The inflammatory process, which is a protective mechanism against any infection, damage, or injury, is mediated by several immune cells, i.e., microglia, neutrophils, and macrophages [27, 28]. Unlike other cells, damaged neurons can't regenerate [29]. The acute inflammatory response assists to fight the toxins, infectious agents, phagocytose cellular debris, and repair the affected tissues [30]. However, for a prolonged duration, the inflammatory response could be destructive, i.e., it prevents repairing of tissue, and regeneration. Thus, chronic inflammation magnifies the neurodegeneration progression [30].

The implication of neuroinflammation in PD pathology is based on quite a lot of research of evidence suggesting that neuro-inflammatory processes could possess a causal role in PD development [31]. Also, inflammation is suspected to be a melting point for genetic and also environmental factors that provoke PD pathogenesis [7].

Microglia constitute about a tenth of all glia and are usually resting in the adult brain playing beneficial housekeeping roles, as removal of toxic substances, synaptic remodeling, neuronal repair, and synaptic pruning [32]. Environmental challenges, morphological changes, intracellular molecules, and surface antigens could provoke microglial activation [33]. α-Syn and soluble molecules liberated from dying neurons could also activate the microglia [33]. In the activation state, the microglia up-regulate many receptors implicated in inflammation, and could also generate potential neurotoxins, i.e., superoxide anions [34].

Similar to microglia, the astrocytes possess primarily neuroprotective effects, associated with GSH release and scavenging of excitotoxic agents, like glutamate and calcium [35, 36]. Recent studies have linked astrogliosis with the development of PD [37]. The astrocytes and endothelial cells together with pericytes form the blood-brain barrier (BBB), which isolates the CNS from the peripheral circulation [38]. The breakdown of BBB and increase in its permeability result in secondary leukocytes movement within the brain parenchyma, reactive gliosis, and damaged neurons [39]. Thus, the immune cells invade the parenchyma of the brain and eventually induce degeneration of neurons [39].

The postmortem analyses showed accumulation of pro-inflammatory cytokines, i.e., TNF-α, and IL-6, in cerebrospinal fluid and brains of PD patients, which confirms progressing neuroinflammation [40, 41]. The serum IL-6, Normal T cell Expressed and Secreted (RANTES), and the chemokine ligand 5 (CCL5) are considerably increased in PD patients [42, 43]. The intensity of the disease is correlated with serum RANTES levels [42].

A high nitric oxide synthase level has been observed in PD patients [44] indicating that cytokines-stimulated toxicity and inflammation-stimulated oxidative stress could be implicated in the neurodegeneration, and disease ascertainment [45].

2.3. The role of apoptosis in PD pathogenesis

Apoptosis starts with specific internal/external signals and plays a substantial role in aging, neoplasm, and neurological disorders [46]. Based on the postmortem recognition of fragmentation of DNA, and apoptotic chromatin alterations in dopaminergic neurological cells of PD suffer, it is evident that apoptosis is the primary mechanism of neurons demise in PD [47].

Additionally, the implication of apoptosis in

PD etiology has been confirmed in postmortem, *in vivo,* and *in vitro* studies that revealed increased apoptosis markers in Substantia nigra compacta [48-51]. Despite the extrinsic apoptotic pathway could be implicated in PD, the intrinsic dopaminergic neurons apoptosis pathway is still believed to be the predominant [52].

Several inherited forms of PD develop because of genes (LRRK2, PINK1, and DJ-1) mutations related to mitochondrial function [53]. Although these mutations are uncommon within the PD patients, they provide some supporting evidence to the susceptibility of mitochondria damage-mediated apoptosis, and to these relevant processes in idiopathic PD [53].

Parkin possesses many roles that could be relevant in PD pathogenesis, as it can induce mitochondrial- biogenesis, genes transcription, and DNA replication [54]. Furthermore, Parkin performs as an E3 ubiquitin-protein ligase involved in the degradation by the ubiquitin-proteasome system, i.e., the glycosylated form of α-Syn [55]. The impairment in Parkin activity is believed to increase protein aggregates causing PD [55].

Additionally, mutations in leucine-rich repeat kinase 2 (LRRK2) have been considered as the main cause of hereditary PD [56] and can lead to defective dynamic/morphology of mitochondria, and exaggerate generation of ROS [57]. These mutations are also proposed to cause neuronal demise by apoptosis caused by mitochondrial malfunction. Cell death could be experimentally triggered by the up-regulation of mutant LRRK2 with apoptosis being inhibited by caspase inhibitors [58].

Additionally, DNA removals have been previously reported in dopaminergic neuronal cells in both elderly and PD suffers, possibly heightening their vulnerability to apoptosis [59]. The anticipatory mechanisms of DNA removals

are unidentified with the possibility of oxidative stress involvement [60]. Depletion and deletion in mitochondrial DNA lead to a decrease in the performance and integrity of mitochondria, consequently exaggerating the release of cytochrome c and apoptosis [61]. Furthermore, a rare type of inherited PD could develop because of variation in POLG, a gene that is involved in the expression of many genes encoded in mitochondrial DNA [62].

3. Neurotoxin-based model of PD

Epidemiological studies have affirmed that prolonged exposure to rural chemicals, i.e., paraquat and rotenone elevate the risk of PD development [63]. Dopamine structural analogs, like MPTP, and 6-hydroxydopamine (6-OHDA), have been reported to selectively damage dopaminergic neurons and induce parkinsonism.

3.1.   The 6-hydroxydopamine model of PD

6-Hydroxydopamine is the first neurotoxin used to induce PD because it could induce mitochondrial dysfunction of dopaminergic neurons [64]. Since 6-OHDA cannot cross BBB, it has to be injected intra-cerebrally. 6-Hydroxydopamine is transferred into the neurons by the DA transporter and then suppresses the activity of mitochondrial respiratory chain complex-I [65, 66]. In mitochondrial, 6-OHDA can also suppress the complex-IV activity and reduce membrane potential [67].

Once inside the neurons, 6-OHDA produces H_2O_2, and superoxide from its metabolic degradation or oxidation. ROS cause protein- and DNA oxidation, and lipid peroxidation, and eventually lead to oxidative stress and mitochondrial impairment [68, 69]. 6-Hydroxydopamine could increase glutamate, and lower the striatal glutamine, resulting in an imbalance between excitatory and inhibitory brain processes, causing long-term irregularities in activities of the glutamate system and

GABAergic system **[70]**.

The severity of symptoms induced depends on the injection site, as 6-OHDA administration into the striatum induces relatively mild symptoms with a slow progression; while, the direct 6-OHDA administration into the medial forebrain and SN, induces severe symptoms with fast and significant severe dopaminergic cell death **[71]**. However, the 6-OHDA-based model lacks Lewy pathology **[72]**.

3.2.   1-Methyl-4-Phenyl-1,   2,   3,   6-Tetrahydropyridine (MPTP) model of PD

The PD model induced by MPTP is an experimental model based on the systemic treatment of MPTP, which has a high toxically affinity to dopaminergic neurons **[73]**. Langston et al. have described parkinsonism in a group of drug abusers mediated by intravenous injection of MPTP with an illegal neurotoxin-containing drug **[74, 75]**.

After crossing the BBB, MPTP is converted by MAO-B into 1-methyl-4-phenylpyridinium ion (MPP$^+$), its active form, and then carried by the DA transporter inside the dopaminergic neurons, where it suppresses the mitochondrial complex-I activity **[76]**. It has been re-assessed following MPTP treatment through the intranasal route, resulting in depletion of striatal DA, accompanied by PD symptoms **[77]**.

The main limitation of the MPTP-based model is that it lacks Lewy pathology. Therefore, myriads of studies have attempted to solve the missing of this crucial neuropathological PD hallmark by changing treatment regimens. It has been induced of ubiquitin and α-Syn formation by a 30-day administration of MPTP via osmotic minipumps **[78]**; while Shimoji et al. has not succeeded to detect LBs in mice treated with different regimens of MPTP treatment without using osmotic minipumps **[79]**.

Additionally, the dopaminergic nigrostriatal deficits resulting from acute or sub-acute administration of MPTP are reversible, however, the chronic coadministration of MPTP and probenecid has been demonstrated to overcome this limitation **[80]**.

3.3.   The paraquat model of PD

Paraquat is an herbicide that has been got great interest due to its chemical structural similarity to MPP$^+$ **[81]**. Paraquat has been used to induce the PD model as it can penetrate the BBB by the neutral amino acid transporter since the L-valine treatment significantly reduced the paraquat penetration of BBB **[82]**. Paraquat impairs the redox recycling of GSH and thioredoxin inducing oxidative stress **[83]**.

However, paraquat administration causes acute toxicity in many organs, particularly lung tissues; thus, it may affect motor performance and cause a high mortality rate **[84]**. Additionally, the use of the paraquat model in examining neuroprotective therapies is limited due to the lack of paraquat-induced striatal DA depletion **[85]**.

3.4.   The rotenone model of PD

Rotenone is an isoflavone found in the roots and stems of the Lonchocarpus and Derris, and due to its high lipophilicity, it can cross BBB **[86]**. As soon as ROT is in the dopaminergic neurons, it inhibits the complex-I activity, resulting in an elevation in ROS production and mitochondrial dysfunction **[87]**

Lipid and also glutamine metabolism alterations by rotenone play a pivotal compensatory role in PD modeling **[88]**. ROT has become of high interest following the seminal paper by the Greenamyre group in 2000, it was continuously IV infused into the back of Lewis rats at a concentration of 3 mg/kg/day **[89]**. Rotenone induces α-Syn accumulation and aggregation replicating the neuropathological hallmark of LBs seen in PD **[51]**; another reason

for the ROT-based model of PD to outweigh other neurotoxin-based models and qualify this model to closely simulate human PD.

The main limitations of the ROT-based model are low reproducibility in the animals, i.e., they develop varied dopaminergic lesions, size and location of lesions, and mortality **[90]**. These limitations have been overcome to some extent by using different routes of ROT administration **[86]**.

Conclusion

Significant advances in understanding the pathogenesis of PD have been concluded from the epidemiological findings, experimental methods, and pathological manifestations. Signaling pathways have been detected, accompanied by mitochondrial homeostasis impairments, and protein accumulation, and are likely to be involved in PD etiology. Additionally, a substantial advance has been made in PD modeling. However, each model has advantages and limitations. Further research is needed to develop the currently used models or new models to recapitulate the human PD.

List of abbreviations

6-OHDA, 6-Hydroxydopamine; α-Syn, α - synuclein; BBB, blood-brain barrier; DA, Dopamine; GSH, Glutathione; LBs, Lewy bodies; MPP+, 1-Methyl-4-phenylpyridinium ion; MPTP, 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine; PD, Parkinson's disease; ROS, Reactive oxygen species; ROT, Rotenone

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

Data analyzed during this study are all included in the main manuscript.

Competing interests

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