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PRECLINICAL MODELS OF PARKINSON'S DISEASE: TOOLS FOR UNDERSTANDING AND ADVANCING NEUROPROTECTIVE STRATEGIES

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ABSTRACT

Parkinson's disease (PD) is commonly identified in many individuals, making it a prominent neurodegenerative disease, and likely the second most prevalent neurodegenerative disease affecting millions of people worldwide. PD manifests with both motor and non-motor symptoms disrupting everyday functional abilities. While the understanding of PD has advanced greatly over the years, including the understanding of genetic, environmental, and neurobiological factors contributing to the pathophysiology of PD, the etiology of PD is still unclear. Treatment options for PD mainly rely on symptomatic therapies. Although dopamine-replenishing drugs (i.e., levodopa) are the principal symptomatic treatment for PD, the use of levodopa, for example, is often associated with damaging side effects (i.e., dyskinesias) and does not alter the course of the disease. This review provides an overview of the various experimental models of PD (like pharmacological, neurotoxin, genetic, etc.) and outlines the advantages and disadvantages of each in their ability to represent the potential mechanisms of the disease in humans. Perhaps more importantly, it highlights the need for more organisms that can capture the complexity of the disease, such as including models of neuroinflammation and non-motor aspects of the disease, to improve preclinical predictive validity. This work hopes to build from the knowledge of previous models in this area while highlighting the importance of integrative models to inform future investigations and lead to the discovery of novel therapeutics. Indeed, by better understanding PD using integrative models, we may improve treatments and quality of life for people with this disease.

KEYWORDS: Parkinson's disease, Levodopa- Carbidopa, Pharmacological model, Neurotoxin model, Genetic model.

INTRODUCTION

Parkinson's disease is a common and complex neurological condition. marked by a range of motor and non-motor symptoms, including cognitive deterioration, muscle rigidity, and tremors.[1] Parkinson's disease (PD) is identified as the most rapidly increasing neurological ailment globally regarding death, disability, and age-standardized prevalence. According to data from the World Health Organization (WHO) in 2019, the global prevalence of individuals with Parkinson's Disease (PD) exceeded 8.5 million.[2] Parkinson's disease impacts approximately 0.3% of the global population, affecting around 1% of individuals aged 60 and older. Among those aged 85 and above, about 4-5% are affected by the condition. After Alzheimer's disease, it is the second most common neurodegenerative disease and is linked to significant functional impairment and a lower quality of life.[3] The pathological hallmark of Parkinson's disease (PD) is the gradual degradation of dopaminergic neurons in the substantia nigra pars compacta, which leads to the development of Lewy bodies and the motor impairments that are characteristic of PD. Numerous molecular pathogenic processes and signaling pathways, such as alpha-synuclein proteostasis, oxidative stress, calcium homeostasis, axonal transport, neuroinflammation, and mitochondrial function, are associated with Parkinson's disease.[4] The precise etiology of Parkinson's disease remains largely unknown; however, research suggests that aging, environmental factors, and genetics may all have a role.[5] Current treatment regimens for neurodegenerative disorders, such as Parkinson's disease, often include medications like levodopa and various dopaminergic agonists. These drugs work by replenishing dopamine levels in the brain, effectively alleviating symptomatic motor difficulties such as tremors, stiffness, and bradykinesia (slowness of movement). While these interventions can significantly improve patients' quality of life, they frequently result in severe side effects, including dyskinesias (involuntary movements), hallucinations, and mood changes.

Additionally, long-term use of these medications can lead to fluctuating responses, often referred to as "on-off" phenomena, where patients experience periods of improved mobility followed by sudden loss of motor function. Unfortunately, despite advances in symptomatic treatment, there are currently no pharmacological options available that can halt the underlying neurodegenerative process, meaning the progression of the disease continues unabated in most patients.[6]

Identifying the most effective disease model and thoroughly investigating the underlying mechanisms of Parkinson's disease (PD) is critical due to the multifaceted nature of the disorder and its complex etiology, which involves genetic, environmental, and neurobiological factors. In recent decades, the utilization of various animal models, such as mice and non-human primates, along with advanced cellular models, including induced pluripotent stem cells (iPSCs), has led to significant advancements in our understanding of PD. These models have provided valuable insights into the pathophysiological processes that characterize the disease, including protein aggregation, mitochondrial dysfunction, and neuroinflammation.[7]

Significant progress has been made in developing models for Parkinson's disease; however, the search for an ideal model that accurately reflects the human condition and predicts therapeutic outcomes continues. Such a model could lead to critical breakthroughs in treatment strategies, including innovative pharmacological interventions and other novel therapeutic approaches. This review aims to examine the current experimental model systems for Parkinson's disease, highlighting their respective strengths and weaknesses, potential directions for future research, and the pressing unresolved issues facing the field.

Animal Model of PD

Parkinson's disease (PD) has several animal models, unlike many other neurodegenerative illnesses. A few of these classes—pharmacological, toxin, genetic, and α-synuclein[8] are briefly discussed here. Since we have focused on mammalian models here, readers who are interested in the various non-mammalian models, such as those in Drosophila melanogaster or Caenorhabditis elegans, are directed to the reviews that are currently available on mammalian models.

The pharmacological model

Reserpine

Reserpine and Haloperidol were among the first drugs used to develop in vivo models for Parkinson's disease, playing a foundational role in early research on the disorder.[9] In 1957, Carlsson and his colleagues developed one of the earliest animal models of Parkinson's disease by administering reserpine.[10] The vesicular monoamine transporter (VMAT) type 2 is inhibited by reserpine. Monoamine storage and release in nerve terminals are decreased when this transporter is blocked. Muscle rigidity and reduced mobility are the results of this monoamine deficiency.[11] Reserpine administration in rodents' mimics early Parkinson's disease (PD) symptoms, including motor issues like slowed movement and rigidity, along with cognitive and emotional deficits.[12] In male rats, it leads to temporary dopamine neuron loss in movement-related brain areas, while females show less damage. Levodopa (L-DOPA) can partially reverse these effects.[11] Reserpine also increases striatal oxidative stress by raising lipid peroxidation and the oxidized/reduced glutathione ratio (GSSG/GSH), causing cellular damage.[14,[15] However, it does not replicate advanced PD features like Lewy body formation or permanent neuron loss. Despite these limitations, reserpine induces non-motor symptoms such as sleep disturbances and anxiety, making it a valuable model for studying early PD and oxidative stress-related neurochemical changes.[16]

Haloperidol

Haloperidol is a commonly used antipsychotic medication that serves as a valuable tool for simulating Parkinson's disease in rodent models. This drug reversibly inhibits dopamine D2 receptors, which are crucial in regulating movement and coordination.[9] The inhibition of these receptors leads to catalepsy, a condition characterized by a lack of response to external stimuli and prolonged muscle rigidity. This behavioral response is widely regarded as a primitive but useful model for studying the motor deficits associated with Parkinson's disease, allowing researchers to investigate potential treatments and the underlying mechanisms of this neurodegenerative disorder.[17] Furthermore, acute treatment with haloperidol, an antipsychotic medication, significantly reduces the concentration of neurotransmitters such as dopamine, noradrenaline, and serotonin within the striatum, a critical region of the brain involved in functions like motor control and reward processing. This decrease in neurotransmitter levels can affect various neurobiological pathways and may contribute to both the drug's therapeutic effects and its side effects.[18] Haloperidol may be less pertinent for investigating new neuroprotective or neurorepair strategies for Parkinson's disease.[10]

Neurotoxin-induced PD

6-Hydroxydopamine (6-OHDA)

More than 60 years have passed since 6-hydroxydopamine (6-OHDA) was identified as a neurotoxin that mainly damages neurons by causing severe oxidative stress. Because of its structural resemblance to dopamine, 6-ODHA is absorbed into dopaminergic neurons via the dopamine transporter. Auto-oxidation occurs after it enters the cell, producing reactive oxygen species, particularly hydrogen peroxide.[19,[20] This highly oxidizable dopamine analog directly inhibits mitochondrial complex I and produces reactive oxygen species (ROS). As a result, cytochrome c is released, which activates microglia and astrocytes. 6-

OHDA must be injected intracranially to produce its harmful effects since it cannot pass through the blood-brain barrier (BBB).[21] Damage to dopaminergic axon terminals brought on by 6-OHDA injection into the striatum sets off neurodegenerative processes that eventually result in the death of neurons in the substantia nigra, a crucial area of the brain for controlling movement. Deficits in dopamine signaling resulting from the death of these neurons mimic the deficits in motor control observed in diseases like Parkinson's disease.[22]

MPTP

MPTP is one of the most often employed neurotoxins in animal models of Parkinson's disease. MPTP readily penetrates the blood-brain barrier since it is a lipophilic molecule. Following systemic injection, MPTP is changed into the powerful dopaminergic neurotoxin 1-methyl-4-phenylpyridinium ion (MPP+) by astrocyte monoamine oxidase B. The dopamine transporter (DAT) allows dopaminergic neurons to easily absorb MPP+ because of its structural resemblance to dopamine.[5,[23 MPTP-induced toxicity is frequently characterized as being “specific” to dopamine neurons, primarily because it is known to cause significant damage to these cells, particularly in the context of Parkinson's disease. However, extensive research has demonstrated that MPTP induces a range of multisystemic lesions, affecting not only the dopaminergic pathways but also various other neurotransmitter systems and neural populations throughout the central and peripheral nervous systems, leading to broader neurodegenerative effects.[24 MPTP can be administered through a variety of methods, such as oral ingestion or intracerebral stereotaxic injections, which allow for precise targeting within the brain. However, the most reliable and reproducible techniques for inducing lesions involve systemic injections—whether subcutaneous, intravenous, intraperitoneal, or intramuscular—and intracarotid artery injections of a freshly prepared MPTP solution. These methods ensure consistent outcomes in experimental settings. Among the animal models, mice and monkeys are predominantly used for MPTP research due to their susceptibility to the compound, while rats exhibit a notable insensitivity to MPTP, limiting their utility in such studies.[25 The specificity of MPTP can help clarify the role of dopamine in the development of certain neurological movement syndromes.

Rotenone

Rotenone is a broad-spectrum insecticide and pesticide derived from natural plant extracts. It can easily cross the blood-brain barrier because of its hydrophobic properties[26 Rotenone is a potent inhibitor of mitochondrial complex I, an essential component of the electron transport chain involved in cellular respiration. This compound selectively targets and damages dopaminergic neurons, which are crucial in regulating movement and coordination. As a result of this neurotoxic action, exposure to rotenone induces behavioral dysfunctions that closely resemble the symptoms of Parkinson's disease, including tremors, rigidity, and bradykinesia.[27 Rotenone is a lipophilic compound that easily crosses cell membranes and penetrates the blood-brain barrier. At doses of 2 to 3 mg/kg per day, it results in the loss of dopamine terminals in the striatum, which is followed by the gradual degeneration of dopamine neurons in the substantia nigra.[28 The toxin inhibits mitochondrial complex I, leading to an increase in reactive oxygen species (ROS), a reduction in proteasome activity, and lower levels of dopamine (DA) and glutathione (GSH). This sequence of events results in oxidative damage. In studies, this toxin has been administered daily to rats and mice through various methods, including intraperitoneal (i.p.) injections, intravenous and subcutaneous routes, intragastric administration, and stereotaxic injections into the brain.[29,[32 Rotenone, a potent inhibitor of mitochondrial respiration, achieves its maximum concentration in the central nervous system (CNS) in approximately 15 minutes following administration. After reaching this peak level, the concentration of rotenone reduces significantly, declining to roughly half of its maximal value within less than 2 hours. This rapid turnover may influence its overall efficacy and potential side effects in neurological studies and treatments.[31

Paraquat

Paraquat is a widely used herbicide recognized for its neurotoxic properties, which are attributed to its structural resemblance to MPP+. The extensive use of paraquat as a pesticide has raised public concern, as it may be linked to environmental factors contributing to Parkinson's disease (PD).[5 Paraquat is unable to penetrate the blood-brain barrier, leaving its precise mechanism of action in the context of Parkinson's disease (PD) largely unexplained. While paraquat itself is not directly transported by the dopamine transporter (DAT), it is converted into the active metabolite PQ2+. This compound is believed to infiltrate dopamine neurons through the DAT, potentially contributing to the neurodegenerative processes observed in PD.[10,32] Paraquat enters the brain through the neutral amino acid transporter, facilitating its passage across the blood-brain barrier.[33] Following this initial transport, paraquat is taken up into cells via sodium-dependent mechanisms. Once inside the cells, paraquat induces indirect mitochondrial toxicity through a process called redox cycling. This process produces reactive oxygen species, which causes oxidative stress and damage cellular components. Furthermore, at higher concentrations, paraquat directly inhibits complex I of the mitochondrial electron transport chain. This inhibition disrupts the production of adenosine triphosphate (ATP), further contributing to mitochondrial dysfunction and cellular injury[36 Paraquat disrupts the redox cycling of glutathione and thioredoxin, which impairs their protective functions against oxidative stress in cells.[5]

Genetic model

Alpha-synuclein

Alpha-synuclein is a small yet important protein made up of 140 amino acids, primarily located in the neuronal cells of the brain, where it is especially abundant at the presynaptic terminals.[35] The exact physiological role of α-synuclein is still not fully understood. However, many studies suggest that it plays a crucial regulatory role in membrane and vesicular dynamics, which are essential for neurotransmitter release and effective synaptic communication. Additionally, extensive research has shown that specific mutations in the α-synuclein gene, such as the A53T, A30P, and E46K substitutions, as well as gene duplications or triplications, are responsible for dominantly inherited forms of Parkinson's disease (PD). This highlights the significant impact of α-synuclein on neural health and disease.[36] In pathological conditions, α-synuclein (α-syn) undergoes misfolding and aggregation, forming higher-order structures such as fibrils, oligomers, and protofibrils. These misfolded proteins can accumulate and coalesce into toxic, insoluble aggregates, which disrupt cellular function and contribute to neurodegeneration. The presence of these aggregates is particularly detrimental to neurons, as they interfere with cellular processes, lead to oxidative stress, and induce inflammation, ultimately resulting in neuronal death and the progression of neurodegenerative diseases like Parkinson's disease.[37] The injection of wild-type or mutant α-synuclein protein has been demonstrated to cause the loss of dopamine (DA) neurons and lead to motor impairments in both mice and rats. Several mutant mouse lines have been created that show reduced levels of striatal DA, exhibit inclusion bodies, and display motor deficits; however, many of these lines do not exhibit significant degeneration of nigrostriatal neurons associated with Parkinson's disease.[38] The main component of Lewy Bodies (LBs) is a protein called α-synuclein. Due to significant discoveries in this area, scientists have started modeling Parkinson's disease (PD) by overexpressing either wild-type or mutant forms of synuclein in animal models. Masliah et al. created the first-ever transgenic mouse model to study this condition.[39] Researcher indicates a progressive formation of neuronal inclusion in the hippocampus, substantia nigra (SN), and neocortex, which tested positive for alpha-synuclein antibodies. Notably, these inclusions do not exhibit the fibrillar structure characteristic of Lewy bodies (LBs). Furthermore, no significant degeneration of dopaminergic neurons was observed in the mice.[5, 39] Similar to mouse models, there are controversies surrounding the Drosophila α-synuclein model. Feany and Bender reported a near-complete loss of dopamine neurons in the DMCs of 30-day-old transgenic flies.[40]

Leucine-Rich Repeat Kinase 2(LRRK2)

LRRK2, or Leucine-Rich Repeat Kinase 2, is a large protein consisting of 2527 amino acids with multiple independent domains. One key domain is its kinase domain, which exhibits GTP-dependent phosphorylation activity, allowing it to add phosphate groups to specific substrates in the presence of guanosine triphosphate (GTP). This process is essential for regulating various cellular functions, including signal transduction and protein interactions.[36] The LRRK2 mutation was initially discovered in a Japanese family with autosomal-dominant parkinsonism in 2002.[41] LRRK2 mutation causes autosomal dominant inheritance in familial Parkinson's disease, with varied penetrance between populations. The two most prevalent LRRK2 mutations are G20195 and R1441C/G.[42] Worldwide, approximately 1% to 5% of individuals diagnosed with sporadic Parkinson's disease (PD) carry an LRRK2 mutation. In contrast, this genetic mutation is found in around 5% to 20% of patients with hereditary forms of the disease. These statistics highlight the significant role that the LRRK2 gene plays in the development of Parkinson's disease, particularly among those with a family history of the condition.[43] Individuals with the LRRK2 G2019S mutation have an increased risk of developing Parkinson's disease (PD) as they age. Research shows that by age 59, the risk reaches 28%; by age 69, it increases to 51%; and by age 79, it rises to 74%.[44] LRRK2 mutations increase kinase activity, contributing to neurodegeneration and Parkinson's disease (PD) pathology. This protein is involved in autophagy, vesicular trafficking, and inflammation, and its dysfunction can lead to the aggregation of toxic proteins like alpha-synuclein, a hallmark of PD.[44]

PARKIN

In 1997, the gene locus associated with autosomal recessive juvenile parkinsonism (AR-JP), known as PARK2, was mapped to chromosome 6q25.2–27. The gene was identified shortly thereafter, and the protein it encodes is called Parkin.[46] Parkin mutations are the leading cause of autosomal recessive early-onset Parkinsonism, including its juvenile forms. Within families affected by this condition, the mutation frequency is approximately 50%.[47] Parkin contains a homology to ubiquitin at its N-terminus, with two RING finger motifs that are separated by an intermediate RING finger (IBR) domain near the C-terminus.[48] Parkin, encoded by the PRKN gene (also known as PARK2), functions as a ubiquitin E3 ligase. The loss of its enzymatic activity is thought to contribute to both familial and sporadic forms of Parkinson's Disease (PD).[44] Mutations in the PRKN gene were initially discovered in Japanese patients with Parkinson's disease (PD) and are associated with cases of autosomal recessive and early-onset PD. These mutations often involve deletions in exons 2, 3, and 8, duplications in exons 2 to 4 and 9, as well as substitutions in specific regions.[49] The age range for the onset of Parkinson's disease (PD) has been broadened to include individuals older than 70, in addition to those with juvenile and early-onset forms. While Parkin mutations were previously thought to be recessive, recent evidence indicates that heterozygous mutations may also be

pathogenic or increase susceptibility to typical late-onset Parkinson's disease.

PINK1 (Pten-Induced Kinase 1)

Mutations in the PINK1 gene, much like those observed in the Parkin gene, are linked to autosomal recessive forms of Parkinson's disease.[36] PINK1 (PTEN-induced putative kinase 1) is an essential neuroprotective kinase predominantly found in the mitochondria and cytosolic compartments of neurons. It plays a crucial role in the process of neuronal differentiation.[51] Enhanced expression of PINK1 has been shown to stimulate neurite outgrowth in SH-Sy5y cells, a model for neuronal development. Furthermore, this increase in PINK1 levels significantly contributes to the elongation of dendrites in dopaminergic neurons, highlighting its importance in developing and maintaining neuronal structure and function.[52] The PINK1 gene has eight exons and encodes a 581-amino-acid protein with a predicted mass of 62.8 kilodaltons. It is highly expressed in the brain, particularly in the substantia nigra, hippocampus, and cerebellar Purkinje cells.[53] PINK1 is a key indicator of damaged mitochondria, accumulating specifically on those that need to be removed from the cell. Normally, healthy mitochondria keep PINK1 levels low by breaking it down quickly. When a mitochondrion becomes damaged, due to factors like oxidative stress or loss of membrane potential, this breakdown process stops. As a result, PINK1 builds up on the outer membrane of the damaged mitochondria. This signals the cell to remove the faulty organelle and helps keep the cell healthy and functioning properly.[54] Research utilizing Drosophila and mammalian models with PINK1 deficiency has revealed notable mitochondrial abnormalities. These abnormalities manifest as disrupted fission-fusion dynamics, which are crucial for maintaining mitochondrial function and morphology. Additionally, there is a marked loss of cristae, the inner membrane structures vital for energy production, resulting in decreased ATP synthesis. Furthermore, these models exhibit mitochondrial swelling, indicating a compromise in mitochondrial integrity and potential onset of cell death pathways. These findings underscore the critical role of PINK1 in mitochondrial health and cellular homeostasis.[55]

Protein Deglycase (DJ-1)

Mutations in the DJ-1 gene are linked to recessive forms of familial Parkinsonism, a group of inherited disorders marked by progressive movement difficulties. Research shows that DJ-1 serves a crucial role as an antioxidant protein, protecting dopamine neurons from oxidative stress, which can lead to cellular damage. This protective function is particularly significant in neurodegenerative diseases, where an imbalance in oxidative processes can contribute to the degeneration of these vital brain cells.[56,5] The exact function of DJ-1 remains unclear. Several studies suggest that DJ-1 acts as an antioxidant protein. It has been identified as a redox-regulated protein that serves as a sensor for oxidative stress. However, inherited mutations in DJ-1 can lead to early-onset Parkinson's disease, which is associated with α-synucleinopathies and the formation of Lewy body aggregates.[57] Mutations associated with Parkinson's disease (PD) can result in a loss of function of DJ-1 due to its instability, which affects dimer formation or reduces expression. In cellular models, DJ-1 regulates redox-dependent kinase signaling pathways and serves as a key regulator of antioxidant gene expression. In vivo, DJ-1 functions as an atypical peroxiredoxin-like peroxidase, protecting mitochondria from oxidative stress.[58] DJ-1 plays a vital role in signaling pathways associated with mitochondrial quality and the oxidative stress response. Cells with elevated levels of DJ-1 are more resistant to oxidative stress and neurotoxins like 6-OHDA, while those with lower levels are more susceptible.[59]

Table 1: Commonly Used Experimental Animal Models for Inducing Parkinson's Disease.

Sr no	Animal model	Animal species	Dose	Route of administration	References
1	Reserpine	Rat: Wistar Rat, Sprague Dawley rat Mice: Swiss Albino Mice	1mg/kg, 5mg/kg 4mg/kg	Intraperitoneal Intraperitoneal Subcutaneous	[60,61] [62] [63]
2	Haloperidol	Rat: Wistar Rat Sprague-Dawley rats Mice: Swiss Albino mice	1mg/kg 2.5mg/kg 1mg/kg	Intraperitoneal subcutaneously Intraperitoneal	[64] [65] [66]
3	6-Hydroxydopamine (6-OHDA)	Rat: Male Wistar rats Sprague Dawley rat Mice: C57 BL/6 mice	5 µg/2 µL 2 /µl (0.5mL/min)	stereotaxic frame	[67] [68] [69]
4	MPTP	Mice: Swiss-albino mice C57BL/6 J mice Rat: Lewis strain rat	25 mg/kg 20mg/kg 20mg/kg	Intraperitoneal	[70] [71] [72]
5	Rotenone	Rat: Wistar rat Sprague Dawley rat	1.5mg/kg,2mg/kg 2.5mg/kg 2mg/kg	Subcutaneously Intraperitoneal Orally	[73] [74] [75]

		Mice: C57BL/6J mice Drosophila melanogaster	30mg/kg 500 µM 250 µM	Diet	[76] [77] [78]
6	Paraquat	Mice: Swiss albino mice Rat: Sprague –Dawley rats Male Wistar rats	10mg/kg 1–5 µg	Intraperitoneal Stereotaxic operation	[79,80] [81] [82]

Table 2: In-Vivo and In-Vitro Assessments of Common Experimental Animal Models for Parkinson's Disease.

Sr no	Animal model	In-vivo Assessment	In-vitro Assessment	References
1	Reserpine	Rota-rod test Pole-climbing test Open-field test Forced swimming test Tail suspension test Sucrose solution preference test Burying food pellet test Mechanical pain threshold Defecation test	Determination of lipid peroxidation Determination of reduced glutathione (GSH) Determination of nitric oxide (NO) level Determination of acetylcholinesterase activity Determination of TNF-α Determination of nuclear factor-kappa (NF-κ) Determination of monoamine concentrations	[83,84]
2	Haloperidol	Catalepsy test Akinesia test Swim-test Wire Hanging Test Grip Strength Test Vertical Pole Test Hole board test	Estimation of MDA Estimation of reduced GSH Determination of dopamine level Determination of acetylcholine Determination of lipid peroxidation Estimation of TNF-α and IL-6	[85,86]
3	6-Hydroxydopamine (6-OHDA)	Rota rod performance test Passive avoidance test Y-maze task Pole test Catalepsy test Beam walking test Open-field test Apomorphine-induced rotation Head position Curling Sensory test	Cell viability assay Hoechst staining of nuclear DNA (detection of apoptotic nuclei) Lipid peroxidation Reduced glutathione Verification of cannula placements Measurement of GDNF and BDNF levels in the striatum	[87,88,89,90]
4	MPTP	Narrow beam test Hang test Open field test	Measurement of cell viability Assessment of apoptosis Determination of striatal dopamine level Estimation of TBARS Assay of SOD Determination of activity of catalase Quantification of the Levels of TNF-α, IFN-β, IL-1β, and IL-6 mRNAs	[91,92,93]
5	Rotenone	Rotarod test Pole test Open field Grip strength Beam-crossing task Y-maze test Hole and board test	Nitrite estimation Analysis of dopamine, DOPAC, and HVA Estimation of endoplasmic reticulum stress markers (CHOP and GRP78) mRNA expression levels by real-time PCR:	[94,95,96]

			Measurement of Striatal Caspase-3 Activity Assessment of striatal Interleukin-1β Protein carbonyl content (PCC) assay Estimation of GABA and Glutamate	
6	Paraquat	Hanging Test Narrow Beam Walking Test Foot Printing Test	Determination of ATP Glutathione peroxidase (GPx) assay Superoxide dismutase (SOD) assay Catalase (CAT) assay Qualitative DNA fragmentation assay Detection of the inflammatory cytokine levels in the striatum Determination of nuclear factor kappa B (NF-κB) gene expression Estimation of Nitrite	[80,97]

Author perspective

The motivation behind this review stems from the critical need to deepen our understanding of Parkinson's disease (PD). This complex and progressive neurodegenerative disorder continues to challenge the scientific and medical communities. As a researcher in pharmacology with a focus on neurodegenerative diseases, I recognized a significant gap in the comprehensive, comparative literature that critically examines and contextualizes the vast array of experimental models available for studying Parkinson's disease (PD).

This review was developed with the intention of not only summarizing the currently available models, ranging from neurotoxin-induced to genetic and pharmacological models, but also highlighting their strengths, limitations, and translational relevance. Each model, whether based on MPTP, 6-OHDA, rotenone, paraquat, reserpine, or α-synuclein overexpression, offers distinct insights into particular aspects of PD pathophysiology, such as dopaminergic neuron loss, mitochondrial dysfunction, oxidative stress, or protein aggregation. However, none of them fully replicate the entire clinical and pathological spectrum of human PD. This realization reinforces the idea that a combination or sequential use of multiple models may be necessary to more accurately simulate disease progression and therapeutic response.

In writing this review, I aimed to offer a resource that can assist fellow researchers, especially those entering the field, in selecting the most appropriate experimental model based on the specific objectives of their studies, whether they are investigating molecular pathways, testing novel therapeutic agents, or developing diagnostic biomarkers. I have also sought to critically analyse how closely these models mimic the human condition, and what this means for the interpretation of preclinical data in the context of clinical translation.

Additionally, I wanted to draw attention to recent advances and ongoing challenges in the field. While significant progress has been made, particularly with genetic and viral-vector-based models, there remains an urgent need to refine these systems to incorporate the multifactorial nature of PD, including aging, neuroinflammation, and non-motor symptoms, which are often overlooked. The review emphasizes the necessity of developing models that better reflect these underrepresented aspects to enhance the predictive validity of preclinical studies.

Ultimately, my goal was to contribute to the collective effort of the scientific community in building a more nuanced, integrative approach to PD research. I believe that through collaboration and the thoughtful application of experimental models, we can accelerate the discovery of disease-modifying treatments and move closer to improving the quality of life for individuals living with Parkinson's disease.

CONCLUSION

Parkinson's disease continues to be a major public health issue with serious individual and social consequences. Although significant advancements have been made in understanding its pathophysiology, there is still plenty to learn about its etiology and possible disease-modifying therapies. The current management approaches prioritize symptom control over disease reversal, highlighting the critical necessity for ongoing investigation into new therapeutic options.

Improvements in patients' quality of life may result from early diagnosis, individualized treatment regimens, and a comprehensive strategy that combines pharmacological and non-pharmacological therapies. The creation of more potent therapies is encouraged by developments in molecular biology, genetics, and neuroprotective strategies. In addition, improving preclinical PD models

to more accurately reflect human disease mechanisms is crucial for speeding up the conversion of potential treatments into clinical trials.

The scientific community has an urgent demand for better, more accurate, and representative animal models that reflect the progressive and varied characteristics of PD. Improved models that integrate environmental and genetic risk variables will be crucial for finding disease-modifying treatments and enhancing translational success. Future studies should focus on refining preclinical methods to bridge the gap between laboratory results and clinical outcomes. In the end, collaborative research initiatives and technological advancements will be essential for revealing fresh perspectives on Parkinson's disease and facilitating the development of more potent treatments in the days to come.

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