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# Experimental Models of Parkinson's Disease: Strengths, Limitations, and Translational Perspectives

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## ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by the selective loss of dopaminergic neurons in the substantia nigra pars compacta and the accumulation of α-synuclein aggregates. Despite extensive research, the precise molecular triggers of PD remain unclear, and current treatments primarily address symptoms rather than halting disease progression. Experimental animal models have been indispensable for dissecting the pathophysiological mechanisms underlying PD and for testing novel therapeutic interventions. This review summarizes the principal animal models of PD, including rodents, non-human primates, and non-mammalian organisms such as C. elegans, Drosophila melanogaster, and zebrafish. Both genetic models—based on mutations in SNCA, LRRK2, PINK1, PARKIN, and DJ-1—and neurotoxin-induced models, such as MPTP, 6-OHDA, rotenone, paraquat, and drug-induced parkinsonism, are discussed in relation to their mechanistic fidelity and translational value. Understanding the strengths and limitations of these models is critical for bridging the gap between preclinical findings and clinical applications. Integrating insights across model systems may advance the development of disease-modifying therapies for PD-

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## 1. INTRODUCTION

Parkinson's disease (PD) ranks as the second most prevalent neurodegenerative disorder linked to aging, impacting up to 3% of individuals over the age of 65. It is characterized as a progressive, multifaceted, and diverse condition. Those afflicted with PD experience motor impairments, including resting tremors, stiffness, and slow movement. The primary cause of these symptoms is the deterioration of dopamine (DA) producing neurons in a region of the brain known as the substantia nigra pars compacta (SNpc) [1,2]. Beyond motor issues, PD is also associated with a range of non-motor symptoms such as sleep disturbances, autonomic dysfunction, cognitive and psychiatric issues, gastrointestinal problems, changes in weight and vision, and fatigue. The development of the disease correlates with the buildup of Lewy bodies, which are clumps of the protein α-synuclein (α-syn). The exact reason for the loss of DA neurons is still a mystery, though evidence suggests it may be related to problems with protein clearance by the proteasome, mitochondrial dysfunction, and inflammation in the brain [3-5]. Despite a thorough understanding of its characteristics, PD can only be definitively diagnosed through an autopsy after death, and the initial cause of the disease remains elusive.

In research, animal models have been developed to mimic aspects of PD pathology, but they only partially replicate the signs observed in humans. These models do not fully capture the onset, progression, and outcome of the disease as seen in patients. However, they are still vital for investigating the complex brain networks involved in the disease and for testing potential treatments [6,7]. The selection of an appropriate animal model is critical, and the results from

such studies need to be considered within the context of the model's specific limitations. This review covers a broad spectrum of animal models used in PD research, including rodents, non-human primates, and non-mammalian species like Drosophila (fruit flies) and C. elegans (nematodes) [8,9].

## 2. COMMON LABORATORY ANIMALS USED TO MODEL PD

Rodents

Rodents are highly favored as animal models in various research domains due to their ease of handling and minimal care requirements. They do not necessitate complex or difficult-to-maintain breeding and management conditions. These small-sized animals share a degree of anatomical similarity with humans, making them suitable for certain types of research. Rats and mice, in particular, are commonly utilized to simulate PD because of the observable link between motor impairments and the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc). PD in these animals can be triggered through pharmacological means or by specific genetic modifications, leading to what are known as transgenic rodents [10,11].

The use of pharmacological or toxin-based methods to induce PD often does not mirror the molecular characteristics of human parkinsonism but is valuable for studying the motor, non-motor, and behavioral symptoms of PD. These symptoms include bradykinesia (assessed through the pole test), locomotor activity (evaluated via the open field test), akinesia (measured with the stepping test), as well as strength, balance, and coordination (tested through the rotarod test). Additionally, the daily activities of the animals, such as drinking, sleeping, and eating, along with any compulsive behaviors or signs of apathy, are monitored [12,13].

Conversely, genetic models may offer a closer representation of familial PD. Although genetic modifications can lead to various molecular abnormalities associated with PD, such as mitochondrial dysfunction, impaired mitophagy, ubiquitin-proteasome system issues, and altered reactive oxygen species (ROS) production, they often do not replicate key pathological features of PD, including the presence of Lewy bodies and the loss of DA neurons [14-16].

## 3. NON-HUMAN PRIMATES (NHPS)

Non-human primates share significant genetic and physiological similarities with humans, making them invaluable for advancing our understanding of disease mechanisms, including those underlying PD. Despite their importance, the use of NHPs in research is constrained by ethical considerations, high costs, and the extensive effort and resources needed for their care. Nevertheless, for pre-clinical therapeutic evaluations, research involving NHPs can be pursued when necessary. NHP species such as macaques, marmosets, squirrel monkeys, baboons, and African green monkeys are frequently employed to model PD [17-19].

PD in NHPs can be induced through the administration of neurotoxins like MPTP and 6-OHDA or through genetic manipulation. Genetic methods to model PD include the use of viral vectors to overexpress genes associated with PD, such as α-synuclein and LRRK2, or to create knockout or knockdown models for genes like PINK1, Parkin, and DJ-1. Notably, the introduction of mutated human α-synuclein gene via adeno-associated virus (AAV) vectors in monkeys and macaques has led to the observation of both motor and neuropathological features characteristic of PD [20,21].

NHP models of PD not only exhibit symptoms seen in human patients, such as chorea and dystonia, but also share similar sleep patterns, making them superior to rodent models for certain research purposes. Neuroimaging studies have further validated the reliability of NHP models in providing crucial insights into PD. Importantly, the presence of Lewy bodies, a key pathological marker of PD, can be observed in NHPs, a distinction not found in other animal models [22,23].

Despite their significant contributions to PD research, the use of NHPs is limited by the need for specialized skills, expertise, and considerable time and support. This underscores the complexity and challenges involved in utilizing NHPs for scientific investigation, even as they remain a critical resource for understanding and developing treatments for PD [24,25].

## 4. NON-MAMMALIAN SPECIES (NMSS)

This collection includes tiny creatures like C. (Caenorhabditis) elegans, zebrafish, and Drosophila melanogaster, among others. Their characteristics, including minimal upkeep expenses and brief lifecycles, make them perfect subjects for studies, particularly those focused on genetics and gene editing. Key attributes of these organisms are their distinct neuropathological traits and measurable behaviors. They are particularly valuable in conducting whole-genome sequencing studies and extensive drug discovery trials [26,27].

## 5. CAENORHABDITIS ELEGANS

The nematode C. elegans possesses a neural network comprising 302 neurons, including 8 dopaminergic neurons. It expresses counterparts of several human genes linked to familial Parkinson's disease (PD), such as LRRK2 (lrk-1), PINK1 (pink1), PARKIN (pdr-1), and DJ-1 (dnaj-1.1, dnaj-1.2), although it does not express the α-synuclein gene. This model organism was utilized by Sydney Brenner in the 1970s to explore the genetic foundations of neuromuscular functions. The precise count of eight 'anatomically defined' dopaminergic neurons in C. elegans enables accurate measurement of

neurodegeneration, which can be influenced by various stress factors [28,29].

## 6. DROSOPHILA MELANOGASTER

The fruit fly, Drosophila, possesses a clearly organized nervous system, with its adult brain containing a cluster of dopamine-producing neurons, approximately 200 in number. This makes it an excellent model for replicating and investigating the neurodegeneration associated with PD. Symptoms of PD, including loss of dopaminergic neurons, formation of inclusion bodies, oxidative stress, and impaired movement, have been observed in Drosophila when subjected to neurotoxins or when expressing wild-type or mutant forms of α-synuclein. The genetic model provided by Drosophila serves as a powerful tool for exploring the roles of genes linked to PD, a topic that will be explored in greater depth later in this review [30,31].

Zebrafish

Zebrafish have undergone thorough research in the development and progression of PD. When exposed to neurotoxins, these fish display changes in their movement patterns. They can replicate the essential biochemical, structural, neurochemical, and behavioral characteristics of PD. The genes in zebrafish that are equivalent to human genes associated with PD are highly conserved in both their function and sequence [32,33].

## 7. GENETIC ANIMAL MODELS

The exploration of genetic mutations in Parkinson's disease is grounded in the clinical similarities observed between its sporadic and inherited versions, both of which share a common mechanism that aids in pinpointing molecular and biochemical pathways involved in the development of the disease. Studies in animal models with gene defects have revealed various cellular and molecular abnormalities, including impaired mitophagy, malfunctioning of the ubiquitin-proteasome system, fragmented mitochondria, and altered ROS levels [34,35]. Nonetheless, the pathological and behavioral manifestations in genetic models of Parkinson's disease differ from those seen in humans, as some models do not exhibit significant loss of dopaminergic neurons, which is a critical characteristic of the disease. Genetic mutations offer a promising avenue for uncovering the mechanisms underlying Parkinson's disease and identifying new targets for therapeutic intervention [36-38]. In the following section, genetic models that encapsulate the mutations identified in familial cases of Parkinson's disease will be discussed.

α-Synuclein

The α-Syn gene is crucial for synaptic vesicle recycling. Mutations in the α-Syn gene, specifically PARK1 with A30P, A53T, and E46K mutations, are associated with autosomal dominant PD. α-Syn's role is underscored by its significant presence in Lewy bodies and its involvement in PD pathogenesis through gene duplication or triplication. Various PD models, including transgenic mice, intracerebral protein injections, grafting, and viral expression techniques, have been developed based on α-Syn mutations [39,40]. Despite some models showing reduced DA or tyrosine hydroxylase (TH) levels and behavioral changes, significant nigrostriatal degeneration is often absent. Behavioral changes were noted in A30P and A53T mouse models, but these did not lead to cell loss in the SNpc or locus coeruleus. Similar outcomes were seen with the hamster prion promoter. Mice with the platelet-derived growth factor subunit B (PDGF-β) promoter showed DA cell and terminal loss in the striatum without TH+ loss. Few studies using the Th promoter reported TH+ cell loss, but α-Syn pathology was effectively induced by the Thy-1 promoter, leading to reduced striatal DA levels and dopaminergic neurodegeneration in the SNpc [41,42]. Overexpression of α-Syn A53T in DA neurons via the Pitx3 promoter in tetracycline-regulated transgenic mice resulted in motor impairments and midbrain neurodegeneration, alongside decreased DA release and impaired autophagy. Additionally, new bacterial artificial chromosome (BAC) transgenic mice (SNCA-OVX) overexpressing wild-type human α-Syn exhibit age-dependent DA neuron loss in the SNpc, reduced terminal DA release in the striatum, and decreased SNpc DA neuron firing [43,44]. Lentivirus and AAV vectors have been utilized to introduce external α-Syn in rats, mice, and primates, showing similar α-Syn pathology and clear DA neurodegeneration. AAV-mediated introduction of the A53T α-Syn mutation leads to progressive, age-dependent DA neuron loss, motor function impairment, dopaminergic degeneration, and α-Syn positive inclusions, although variability in AAV models indicates a need for further refinement to assess neuroprotective approaches [45,46]. Interest is growing in models based on cell-to-cell α-Syn transmission, demonstrated by intrastriatal injections of α-Syn fibrils or purified α-Syn from PD brains into wild-type mice, leading to DA neuron degeneration in the SNpc, reduced striatal DA levels, and motor deficits. Similarly, intramuscular injections in transgenic mice can induce PD-like pathology. Current reviews suggest that preformed fibril models of α-Syn are valuable for studying its prion-like behavior and propagation, while viral overexpression models help in understanding α-Syn-induced toxicity pathways but not its prion-like properties. However, the challenge in replicating comparable phenotypes across α-Syn models highlights the complexity of accurately modeling PD, underscoring the need for a deep understanding of these models to address scientific questions related to Parkinson's disease [47-49].

Leucine-Rich Repeat Kinase-2 (LRRK2)

Mutations in LRRK2 are known to cause a late-onset, autosomal dominant form of PD. The most common mutations in LRRK2 are G2019S, found in the kinase domain, and R1441C, located in the guanosine triphosphatase domain. Mouse models overexpressing LRRK2 have shown either mild or no disruption in the DA neurons of the SNpc. Specifically, overexpression of the G2019S LRRK2 mutation leads to progressive and selective neurodegeneration of DA neurons in the SNpc, though no changes in DA levels in the striatum or in locomotor activity were observed in adult mice with this mutation [50,51]. Conditional overexpression of the R1441C LRRK2 mutation results in nuclear abnormalities without causing neurodegeneration. BAC transgenic mouse models of LRRK2 have shown an age-dependent progressive motor deficit and mildly reduced striatal DA release. In these models, neurogenesis was impaired in adult mice, but no neurodegeneration was observed at 9-10 months of age. LRRK2 knockout (KO) mice did not show neurodegeneration or altered neuronal structure, but they did exhibit aggregation of α-Synuclein in the brain [52,53]. Overexpression of G2019S LRRK2 induced through a herpes simplex virus amplicon led to DA neurotoxicity, with a 50% loss of neurons and reduced DA fiber density following injection. Similarly, unilateral injection of a human serotype 5 adenoviral vector expressing G2019S LRRK2, driven by a neuronal-specific human synapsin-1 promoter, caused progressive DA neuronal loss in the ipsilateral SNpc [54,55].

LRRK2 models of PD have provided valuable insights into the mechanisms of LRRK2-mediated neurodegeneration, including the regulation of protein translation, autophagy, and vesicle trafficking. However, these models have limitations, such as not exhibiting all features of Parkinson's disease, lacking alpha-synuclein pathology associated with Lewy bodies seen in human LRRK2 mutations, and the need for validation of mechanisms identified in LRRK2 models in human PD [56,57]. Additionally, rodents seem to exhibit resistance to LRRK2 toxicity, suggesting there might be additional mechanisms protecting against DA neuronal loss. These aspects of LRRK2 animal models should be carefully considered in Parkinson's disease research [58].

Pten-Induced Kinase 1 (PINK1)

Mice lacking PINK1 showed a decrease in DA levels in the striatum as they aged, accompanied by reduced motor activity, yet no significant changes were observed in the striatal DA levels and DA neurons. Up to 18 months of age, these mice did not exhibit Lewy body formation or neurodegeneration. However, when α-Syn was overexpressed in PINK1-deficient mice, it led to dopamine neuron degeneration and an increase in α-Syn phosphorylation at serine 129 within four weeks of the injection [59,60]. A gradual reduction in striatal DA was observed in PINK1 mutant mice with deletions in exons 4-5, but there was no degeneration in the SNpc. The pathogenesis of PD also involves PINK1/Parkin-mediated mitophagy, calcium signaling, and contacts between the endoplasmic reticulum and mitochondria. Nonetheless, the view of heterozygous mutations in PINK1 as a significant risk factor for Parkinson's Disease has been reconsidered [61,62].

## 8. PARKIN

Alterations in the PARKIN gene lead to early-onset PD, responsible for about 50% of PD cases in individuals under 30 years old. These genetic changes result in defective mitophagy, protein accumulation, and mitochondrial dysfunction. Additionally, the PARKIN gene is crucial for the ubiquitin-proteasome system (UPS). Creating PARKIN KO mice by deleting exon 3, exon 7, or exon 2 in the PRKN gene has led to the absence of DA-related abnormalities in these animals [63,64]. However, some KO mice have shown reduced DA release and lower norepinephrine levels, alongside abnormalities in the nigrostriatal region, but without loss of neurons in the SNpc. The PARKIN-Q311X-DAT-BAC mice exhibit progressive motor impairments, degeneration of DA neurons in the SNpc, decreased levels of striatal DA, and reduced striatal dopaminergic terminals. Furthermore, prolonged overexpression of both wild-type human parkin and the T240R-parkin variant in rats triggers dose-dependent neurodegeneration [65,66].

## DJ-1 (PARK7)

Mutations in the DJ-1 gene have been linked to autosomal recessive PD. Researchers created DJ-1 KO mice either by deleting exon 2 or by inserting a premature stop codon in exon 1. These mice exhibited reduced DA levels in the striatum and impaired motor function, yet they did not show DA neuron loss in the SNpc. Another strain of DJ-1 KO mice demonstrated DA neuron loss in the ventral tegmental area (VTA) [67,68]. Backcrossing DJ-1 KO mice onto a C-57/BL6 genetic background resulted in DA neuron loss in the SNpc and progressive deterioration of the nigrostriatal pathway. These mice also exhibited age-related motor deficits and progressive bilateral degeneration. PARK7 is crucial for antioxidative defense, safeguarding cells against oxidative stress. DJ-1 KO rats may serve as a valuable model for investigating the early stages of PD. However, further studies are necessary to validate the effectiveness of this animal model for PD research [69,70].

Neurotoxin-induced PD animal models

Research has shown that exposure to certain pharmaceuticals contaminated with the chemical 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can lead to a range of neurodegenerative symptoms in humans, ultimately resulting in PD.

MPTP serves as a neurotoxin, specifically harming dopamine-producing neurons and causing a condition similar to PD. This has made the PD model, induced by such neurotoxins, a focal point for scientific investigation [71,72]. Furthermore, agricultural chemicals, particularly pesticides, have been identified as significant risk factors for PD among those working in farming due to their frequent exposure. Historical research has demonstrated that neurotoxins like 6-hydroxydopamine (6-OHDA), rotenone, and paraquat (PQ) are effective in creating PD animal models. These models are widely used in scientific studies because they are cost-effective, methodologically mature, and replicate the disease's characteristics accurately [73,74].

### MPTP-induced PD animal model

MPTP, a chemical compound with pain-relieving properties, is safe, dissolves in fats, and easily crosses the blood-brain barrier (BBB). Once inside the brain, it specifically affects astrocytes. The enzyme monoamine oxidase B, found in the outer membrane of mitochondria, transforms MPTP into an intermediate, the 1-methyl-4-phenyl-2,3-dihydropyridinium ion. This intermediate then oxidizes into the 1-methyl-4-phenylpyridinium ion (MPP+), a neurotoxin structurally similar to dopamine [75,76]. This similarity allows MPP+ to be recognized and transported to DA neurons by the dopamine transporter. Inside neurons, MPP+ blocks the function of the mitochondrial complex enzyme I, leading to a drastic reduction in adenosine triphosphate levels and an increase in ROS production. The resulting oxidative stress causes the destruction and loss of DA neurons, leading to PD. MPTP's specific impact on mitochondrial function makes it an important tool for studying mitochondrial dysfunction in PD [77].

The MPTP model is the most widely used in PD research today. It not only mimics the behavioral symptoms of PD but also accurately represents the gradual loss of DA neurons in the SNpc and central nervous system (CS). The model takes advantage of MPTP's ability to cross the BBB easily, using various methods of administration including intraperitoneal, subcutaneous, intramuscular injections, and intravenous infusions. By adjusting the intensity and frequency of these injections, researchers can create different PD mouse models [78,79]. A single, low-dose injection of MPTP can create a model that precedes PD, while multiple injections within 24 hours can lead to acute PD models. Models that represent subacute and chronic stages of PD are developed through daily injections of MPTP, either continuously or intermittently, for days to weeks. Acute models, however, tend to have a brief disease progression with a high mortality rate and rapid onset, and animals might recover quickly, not truly reflecting the persistent progression seen in human PD [80]. In contrast, subacute models show longer neurological damage and a more extended pathogenic phase. Chronic models, created with low-dose MPTP over time, show a steady decrease in DA neurons and behaviors indicative of PD, such as reduced activity, slow movement, and the presence of α-synuclein aggregates. Non-motor symptoms have also been observed, with some mouse and rat models showing olfactory deficits through intranasal MPTP administration, and non-human primate models exhibiting signs of apathy and depression [81,82]. Recent research indicates that low-dose, long-term MPTP exposure produces models that more closely resemble the symptoms of human PD [83].

Rodents are favored in research for their cost-effectiveness and established handling and care protocols. However, rats have a relatively resistant immune system to MPTP, leading to a less evident PD phenotype that develops quickly. Mice, therefore, have become the preferred choice for PD research, with the C57BL/6 strain being particularly susceptible to MPTP and widely used in studying the disease's pathogenic mechanisms and in developing diagnostic and therapeutic approaches [84,85].

6-OHDA-induced PD animal model

6-OHDA is a neurotoxin that closely resembles DA in its chemical structure and specifically targets and destroys DA neurons in the SNpc. When it enters the brain, 6-OHDA attaches to the DA transporter, which helps it enter the mitochondria of DA neurons. This leads to a decrease in the production of mitochondrial complex enzyme I. Inside the neuron, 6-OHDA boosts the generation of ROS and blocks the creation of antioxidant enzymes through its autoxidation and metabolic activities [86,87]. The failure of antioxidant enzymes to counteract ROS in DA neurons results in the oxidation of lipids, proteins, and DNA, causing oxidative stress and mitochondrial damage. Furthermore, 6-OHDA lowers the mitochondrial membrane potential by inhibiting mitochondrial complex enzyme IV, disrupting the mitochondrial respiratory chain and causing mitochondrial dysfunction. This depletion of intracellular adenosine triphosphate ultimately causes the degeneration and death of DA neurons [88,89].

6-OHDA specifically harms DA neurons in the SNpc. Since it cannot easily cross the BBB, it is delivered directly into the brain through stereotactic injection. PD models that feature either unilateral or bilateral lesions are usually created with single or double injections, targeting primarily the SNpc, CS, and medial forebrain bundle (MFB). Rodent models show both motor and non-motor impairments, varying with the method of administration [90,91]. The unilateral injection method is most commonly used to establish the 6-OHDA model, causing movement disorders on the side of the body opposite to the injection site. This method is preferred for studying the effects of clinical interventions due to its minimal unrelated side effects and high survival rate. Bilateral injections, however, lead to severe eating and drinking disorders and a higher mortality rate, making unilateral injections more favorable. In rodent models induced with 6-OHDA, increased depressive behavior was observed in forced swimming tests, along with gastrointestinal dysfunction evidenced by delayed gastric

emptying and impaired olfactory function [92,93]. Injecting 6-OHDA into the SNpc or MFB of mice results in a 90% loss of DA neurons within 12 hours, causing death from eating and drinking disorders without proper care. Direct injections into the CS result in a sustained loss of DA neurons in the SNpc. Compared to injections directly into the SNpc and MFB, injections at the CS site led to a slower and milder disease process, more closely mirroring the gradual onset and progression of human PD [94,95].

The 6-OHDA model offers a significant advantage by causing neurodegeneration in one hemisphere of the brain in test animals. This results in PD-like behavioral symptoms on the side of the body opposite to the affected brain hemisphere, allowing for a more precise assessment of movement disorders and the impact of potential treatments [96-98]. Nonetheless, the model has its drawbacks. The main motor dysfunction it replicates is lateral rotation, which does not fully represent the diverse and complex symptoms seen in human PD. Furthermore, the model typically shows a rapid onset and brief course of symptoms, which is in stark contrast to the slow and progressive nature of PD in humans. Another limitation is its failure to produce Lewy bodies (LB), a crucial pathological hallmark of PD [99,100].

Rats are commonly used as the experimental subjects in the 6-OHDA PD model, although mice, cats, dogs, and monkeys also show significant responses to 6-OHDA. The choice of experimental animals should be guided by the specific aims of the research and the practicalities involved [101,102].

### Rotenone-induced PD animal model

Rotenone is a lipid-soluble organic pesticide found in the root bark of certain plants. It can cross the BBB efficiently, making it suitable for delivery through intravenous, intraperitoneal, subcutaneous injections, or orally to create chronic PD models. Once in the brain, rotenone blocks mitochondrial complex enzyme I, lowers glutathione levels, leads to the production of significant amounts of ROS, disrupts DA metabolism, causes oxidative stress in the SNpc, and damages mitochondrial function. This results in the degeneration and death of DA neurons and cells, ultimately causing PD symptoms to appear [103,104]. The absorption rate of rotenone can vary among different animals and body parts, necessitating precise dosing for long-term use in animal studies. A stable chronic model typically emerges after 30 days of continuous treatment. Research indicates that rats with chronic exposure to rotenone display motor symptoms akin to those seen in human PD, including slow movement, stiffness, and limb tremors. Rats receiving subcutaneous rotenone injections for over 30 days show decreased motor activity and lethargy, and exhibit depressive behaviors in forced swimming and sucrose preference tests, as well as gastrointestinal (GI) dysfunction. Moreover, these models show SNpc DA neuron degeneration and the formation of LB aggregates or α-synuclein in the cytoplasm of remaining neurons [105,106].

However, rotenone's high toxicity and unstable chemical nature pose challenges for its continuous use in animal studies, as prolonged and frequent doses increase mortality rates among experimental subjects. Therefore, although this model might not perfectly mimic the long-term progression of human PD, it does replicate symptoms similar to the disease's early stages, thereby aiding in the study of the peripheral nervous system's pathology at the onset of PD. The rotenone-induced PD model is primarily used in rats but can also be applied to mice, fruit flies, and zebrafish [107,108].

### PQ-induced PD animal model

PQ is a lipid-soluble organic herbicide with a structure similar to MPP+ and toxicity levels akin to MPTP. Unlike MPTP, PQ struggles to cross the BBB and is primarily utilized to create PD models in animals through various administration methods including intracerebral, intraperitoneal, subcutaneous injections, as well as oral and nasal routes. PQ targets the SNpc, selectively damaging DA neurons and inducing PD-like symptoms. The exact process by which PQ causes neurotoxicity is not fully understood. PQ is highly toxic to humans, causing significant organ damage [109,110]. It is thought to cause mitochondrial dysfunction and interfere with the redox reactions of glutathione and related proteins, reducing the cell's antioxidant capabilities. Long-term exposure to PQ has been shown to gradually reduce DA neurons, reflecting the characteristic decrease in activity seen in PD. This method of modeling effectively replicates the DA neuron degeneration seen with prolonged exposure to environmental toxins, aiding in the study of chronic PD symptoms in a preclinical setting. Research on rodent models has indicated that PQ can also induce non-motor symptoms such as depression and anxiety [111-113]. However, this method requires a longer experimental period and the onset of PQ toxicity is slow. Unlike acute PD models that use high doses over a short period, leading to rapid symptom onset but failing to accurately mimic environmentally induced human PD, PQ models are beneficial for studying α-synuclein production and Lewy body formation in SNpc DA neurons. Mice and rats are commonly used to establish these PD animal models with PQ [114,115].

### Drug-induced parkinsonism

Drug-induced parkinsonism (DIP) represents the predominant type of secondary parkinsonism, exhibiting symptoms in patients that closely mimic those associated with PD. Common manifestations of DIP encompass a diminished sense of smell, challenges in initiating and regulating movement, reduced or impaired movement, and tremors at rest. DIP ranks as the second leading cause of parkinsonism, following idiopathic PD. In the subsequent sections, an overview of current

drug-induced models that mimic various motor deficits observed in animals will be provided. Yet this still won't capture most of the neuropathological features characteristic of PD [116].

### Reserpine

In 1957, Carlsson and his team pioneered one of the initial animal models for PD through the administration of reserpine. This compound acts as an inhibitor of the vesicular monoamine transporter (VMAT) type 2, leading to a depletion of monoamines in nerve terminals by hindering their storage and release in vesicles. The resulting decrease in monoamines causes reduced movement and muscle stiffness. Initially, reserpine was employed as an antihypertensive medication due to its ability to lower cellular monoamine levels, but its use clinically led to side effects in patients such as lethargy, depression, and motor dyskinesia [117,118]. In rodent studies, reserpine has been shown to cause motor impairments as well as deficits in memory, cognition, and emotional well-being. The injection of reserpine in these animals induces symptoms akin to the pathogenesis of PD, including akinesia and rigidity, which are characteristic of the disease. Moreover, Carlsson's work demonstrated that the effects of reserpine could be partially reversed by Levodopa (L-DOPA). In rats, reserpine treatment results in sex-specific differences in motor abilities, mirroring those seen in PD. Within a few weeks, there is observable loss of DA neurons in the SNpc and their fibers in the dorsal striatum, although this effect is temporary [119,120]. Notably, female rats do not show significant loss of DA axonal innervation in the dorsal striatum, which may account for the observed differences in motor impairment. Reserpine has been found to induce PD symptoms in humans and parkinsonian-like symptoms in rodents. Its dosage and administration can be easily adjusted, facilitating various levels of PD symptomatology research. However, the reserpine model is less favored for studying late-stage PD pathology markers, such as Lewy body-like inclusions and permanent DA neuron loss [121]. While reserpine treatment in rodents has been linked to oxidative stress in the striatum, there's no evidence of mitochondrial or lysosomal dysfunction or inflammation. Beyond memory impairments, reserpine also induces non-motor symptoms relevant to PD's preclinical phase, including sleep disturbances, anxiety, depressive-like behavior, and gastrointestinal issues. Thus, reserpine serves as a useful model for exploring the progression and neurochemical aspects of PD [122].

### Haloperidol

Haloperidol, a conventional antipsychotic medication, acts by attaching to D2 dopamine receptors on postsynaptic neurons. This action inhibits dopamine transmission in the striatum, leading to altered activity in the basal ganglia circuits, which can cause muscle stiffness and catalepsy. When administered acutely, haloperidol decreases the levels of dopamine, noradrenaline, and serotonin in the striatum [123]. Long-term use in mice has been shown to lead to a deficiency in mitochondrial complex I (MCI) in several brain regions, including the frontal cortex, hippocampus, striatum, and midbrain. Researchers utilize the haloperidol model to study muscle stiffness, dyskinesia, or catalepsy and to explore new treatments for Parkinson's disease in both rodents and non-human primates [124]. Chronic haloperidol treatment in rodents also significantly elevates the levels of pro-inflammatory cytokines TNF-α and IL-1β in the cortex and striatum when compared to untreated animals. Nevertheless, haloperidol has not been associated with degeneration of dopamine neurons in the midbrain, suggesting it may not be the best option for researching new neuroprotective or neurorepair methods for Parkinson's disease [125].

## 9. CONCLUSION

Animal models remain fundamental to advancing our understanding of Parkinson's disease, offering valuable tools to explore the molecular, cellular, and behavioral consequences of dopaminergic neurodegeneration. Each model—ranging from invertebrates like *C. elegans* and *Drosophila* to vertebrates such as rodents, zebrafish, and non-human primates—contributes distinct insights into PD pathogenesis. Genetic models replicate familial PD mutations and reveal pathways related to mitochondrial dysfunction, protein aggregation, and impaired autophagy. In contrast, neurotoxin-based models provide rapid and reproducible systems that mimic dopaminergic neuron loss and motor deficits characteristic of idiopathic PD. Non-human primate models, while limited by ethical and logistical constraints, most closely reflect the neuropathological and behavioral spectrum observed in humans.

However, no single model fully reproduces the complex, multifactorial nature of PD. The integration of genetic susceptibility, environmental exposures, and aging-related factors represents the next frontier in model refinement. Advances in gene editing, viral vector technology, and multi-omics approaches promise to enhance model precision and translatability. Ultimately, the judicious use of complementary models—each tailored to specific research questions—will remain indispensable for elucidating disease mechanisms and identifying effective neuroprotective and restorative treatments for Parkinson's disease. Bridging these preclinical findings with human data will be essential for translating basic research into meaningful clinical advances..

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