An Overview of Animal Models and Symptomatic Treatment of Parkinson’s disease

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**A B S T R A C T**

The broad theory indicate that neurological ailment is caused by intricate interactions between environmental and genetic factors is supported using animal models to better understand the cause and pathogenesis of Parkinson’s disease (PD), as well as its cellular and molecular mechanisms. The more recent models use genetic manipulations that either introduce mutations similar to those found in familial cases of PD (a-synuclein, DJ-1, PINK1, Parkin, etc.) or selectively disrupt nigrostriatal neurons (MitoPark, Pitx3, Nurr1, etc.). “Classic” models are based on neurotoxins that specifically target catecholaminergic neurons. All of these together each model has its own benefits and drawbacks. The use of medication, deep brain stimulation, and physical therapy has been optimised for the symptomatic treatment of the motor symptoms of Parkinson disease (PD). L-dopa, several dopamine agonists, inhibitors of MAO-B and catechol-o-methyltransferase (COMT), and amantadine are among the pharmacotherapies available.

**Keywords:** Parkinson disease, Models, Toxicant, Genetic, Treatment.

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**INTRODUCTION**

Parkinson was first described by James Parkinson. (PD) in 1817. It is a chronically progressive neurodegenerative illness that affects at least 1 % of people over 55 years. Around the world, there are 10 million people with PD, and it affects 2 -3% of those over 65. More people are becoming disabled and dying due to Parkinson’s disease (PD) globally than any other neurological condition. In the last 25 years, PD prevalence has doubled. Parkinson’s disease affects men 1.5 times more frequently than it does women. The majority of Parkinson disease diagnoses are made in patients 65 years of age. Until the early 20th century, when the German pathologist Frederick Lewy observed neuronal cytoplasmic inclusions in several brain locations, the pathology of PD was not well known. The loss of neurons in the substantia nigra pars compacta (SNc) of the midbrain, according to Tretiakoff's observations in 1919, is the most significant anomaly in Parkinson's disease (PD). Dopamine’s significance and its depletion from the basal ganglia were found by researchers in the 1950s as the key to understanding the pathophysiology and pathologic biochemistry of Parkinson's disease.

Among the key neurochemical characteristics Dopaminergic nigrostriatal pathway degeneration causes parkinsonian diseases. Animal models are utilised for anything from basic research testing of novel treatments or vaccine resulting in closely watched advances in medical knowledge. Parkinson’s disease's clinical symptoms include problems with motor coordination such as muscle rigidity, tremor, postural instability, hypersalivation, bradykinesia, and slowness of movement (PD). Mood disorders, sleep issues, cognitive impairments, pain, anxiety, and depression are examples of non-motor symptoms. A Parkinson's illness Age, catalepsy, brain damage, exposure to chemicals, environmental and genetic influences, severe psychiatric problems are some risk factors.
Models used in Parkinson disease:

Three categories can be used to group animal models of Parkinson's disease: those based on neurotoxins or neuropharmacological substances that target catecholaminergic neurons; those based on genetic alterations related to the disease. This is primarily because each model is based on the production of one or a small number of PD pathological processes, which are either artificially induced in a way that is rarely relevant to the disease (such as toxin models) or that is relevant to the disease but only produces a small portion of the pathology (such as genetic models).[7,8]

Neurotoxin models: Animal models for PD have been created using a variety of poisons and pharmaceuticals. Typically, neurotoxins are known to cause severe nigrostriatal degeneration. Significant motor symptoms (however, notably in rodents, these symptoms are rarely equivalent to those found in PD patients). As a result, these models are ideal for researching the neurodegenerative processes that affect SNc DAergic neurons and testing symptomatic medications.[9,10]

6-OHDA: A structural analogue of catecholamines is 6-OHDA. The traditional animal model of PD is 6-hydroxydopamine (6-OHDA). Since the late 1960s, PD has been studied using 6-OHDA, a structural homolog of catecholamines, primarily in rodents.[11,12] 6-OHDA causes the nigrostriatal system to slowly retrograde over the course of a week. This molecule, being hydrophilic, is unable to penetrate the blood-brain barrier (BBB), hence it must be stereotaxically injected directly into the target brain structure, which is typically the striatum, MFB (medial forebrain bundle), or SNc. It has also occasionally been administered intracerebrally. 6-OHDA's neurotoxicity is caused by a two-step mechanism that involves the DA metabolites. The DA accumulates in the chemical into catecholaminergic neurons, noradrenaline membrane transporters and its inhibition of mitochondrial complex I.[13] 6-OHDA creates an intracellular oxidative stress by using the DA transporter to enter the cytosol, where it can auto-oxidize. After 2-3 days of striatal dopamine depletion, 6-OHDA infusion into substantia nigra or nigrostriatal tracts dopaminergic neurons causes their degeneration within 24 hours. In the brain's striatum, 6-OHDA has a negative impact on GSH and SOD activity and an increase in malondialdehyde levels.[14,15] Because it is thought and proven that the TH-positive terminals in the striatum die before the TH-positive neurons in the SNpc, which is thought to be a replication of the PD picture, many researchers have directly injected this substance into the striatum to study retrograde degeneration of TH-positive DAergic neurons in the SNpc.[16] 6-OHDA creates an intracellular oxidative stress by using the DA transporter to enter the cytosol, where it can auto-oxidize.[17]

MPTP: MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) was first identified as having neurotoxic properties in the early 1980s when drug-dependent Californians accidentally injected "synthetic heroin" contaminated with MPTP (1-methyl-4-phenyl-4-propionoxypyridine, also known as MPPP or dimethylpyridine).[18] These individuals suddenly experienced parkinsonian symptoms. Once MPTP in the brain is taken up by the astrocytes, and is metabolized to MPP+, its active metabolite, by monoamine oxidase-B (MAO-B). Recent findings show that once released from the astrocytes enters the extracellular environment via the OCT-3 transporter.[19] MPP+ is taken up into the neuron by the dopamine transporter and can be stored in vesicles via uptake by the monoamine transporter vesicular. In order to create experimental PD models, MPTP, a highly lipophilic that readily crosses the BBB, can be administered systemically. MPTP is often taken systemically (subcutaneous, intraperitoneal, intramuscular, intravenous). Acute MPTP exposure causes the substantia nigra pars compacta to lose 50% to 93% of its cells and the striatum to lose more than 99% of its dopamine. This causes a particular degeneration of the nigrostriatal dopaminergic pathway.[20] Typically, MPTP-treated mice experience motor dysfunction that can be identified by behavioural tests that are alert to even the slightest variations in DA levels. Several low dose injections are typically used in protocols for monkeys. These injections usually result in persistent loss of DAergic neurons, as well as akinesia, "freezing," bradykinesia, muscle rigidity, aberrant posture, stereotypy, and occasionally tremor.[22] Application of MPTP having Pharmacological and genetic therapies intended to protect dopaminergic neuron are being tested in preclinical studies to help with symptoms. The MPTP model of Parkinson's disease has some drawbacks, such as being often acute, non-progressive, and reversible, with inclusion bodies being uncommon.[23]

Paraquat and Maneb: cybersquat for potential application as a pesticide in the 1950s. Paraquat (N,N-dimethyl-1,4-4'-bipyridinium) is used frequently in agriculture. An herbicide, that is. According to epidemiological studies, using pesticides raises The risk of finding Parkinson's disease.[24] based on the active metabolite of MPTP, MPP+, and its structural similarities. Albeit slowly and to a small extent, paraquat does pass the blood–brain barrier.[25] A slow-moving degeneration of the DAergic neurons in the brain SNpc[26] and the VTA[27] has been observed following systemic (i.p or other means), chronic administration of paraquat (up to 24 weeks). This results in delayed deficits in DAergic transmission that mimic the early presymptomatic stages of PD.[28,29] Mice exposed systemically to this herbicide show decreased motor as well as an activity of dose dependent TH-positive cell loss striatal fibres and SNpc neurons. The capacity of the Paraquat (and/or Maneb) model to promote the development of LB-like inclusions harbouring a-synuclein is one of its benefits.[31] The only agricultural pesticide with a proven adverse effect on the dopamine system is paraquat. Maneb, which is utilised in an area where paraquat is also used, has been demonstrated to reduce locomotor activity and enhance the effects of MPTP.[32] increased levels of synuclein in specific DA neurons within the SNpc, as well as the appearance of Lewy bodies in those DA neurons. In light of this, paraquat has a role in PD research because, should the aforementioned observations be verified, it may enable us to explore how Lewy bodies develop in DA neurons as well as the function of synuclein in PD. The outcomes of this model, however, are inconsistent and vary in terms of DAergic cell death, striatal DA depletion, and behaviour.[33]
Rotenone: The rotenoid neurotoxic family includes rotenone, a herbicide, insecticide, and piscicide. It is found in nature tropical plants like the j'cama vine (Pachyrhizus erosus) and several Derris genus leguminous plants. The rotenone model demonstrates that systemic complex I inhibition can cause the symptoms of PD. Nearly all PD symptoms, including the loss of SNcDAergic neurons, nigrostriatal DAergic denervation, behavioural changes, inflammation, LB-like inclusions containing a-synuclein and ubiquitin, oxidative stress, and digestive issues, are replicated in the rotenone model. The Rotenone model demonstrates that PD symptoms can result in extreme rigidity, tremor, akinesia, and flexed posture. Rotenone, however, has a high mortality rate in experimental animals and generates variable, challenging-to-replicate DAergic harm. Rotenone has been used to test pharmacological and genetic therapy intended to protect dopamine cells. The challenge with using rotenone as a Parkinson's disease model is that, while increasing DA oxidation, there is little evidence that it depletes DA in the nigrostriatal pathway. Rotenone therapy produces motor and non-motor Parkinson's disease (PD)-like symptoms as well as central and peripheral neuropathological characteristics.

Genetic Model: Autosomal dominant or recessive inheritance genetic alterations account for 20% of PD cases. Nonetheless, these examples are extremely fascinating because the cause of disease is at least partially characterised, and these studies provide justification for creating animal models with comparable mutations. Synuclein is the first gene that has been conclusively related to familial Parkinson's disease. Many other family PD-related genes connected to autosomal dominant or recessive inheritance types of PD were further discovered after this finding in 1997. More than 25 genetic risk factors, including 15 causative genes, have been discovered so far.
and they are categorised as "PARK" and "non-PARK" (>20) loci/genes. A-synuclein, PARK1 and 4, PRKN (parkin RBR E3 ubiquitin protein ligase, PARK2), PINK1 (PTEN-induced putative kinase 1, PARK6), DJ-1 (PARK7), and LRRK2 (leucine rich repeat kinase 2, PARK8) are some of them that have been modelled in mice and rats, while others are still being developed. Among the different models of Parkinsonian neurodegeneration, protein aggregation, dysfunction of the mitochondria, dysfunction of the secretory pathway organelles, and oxidative stress are common variables. (Edward d). If the inheritance pattern of PD-linked genes in humans indicates a dominant transmission, these genes are typically produced as transgenes in heterologous organisms. These non-mammalian PD models' well-characterized genetics provide a special benefit for the human model over the mouse for the quick discovery of modifiers that could shed light on crucial disease pathogenesis pathways, insights into which could aid the subsequent development of novel treatments.

**Alpha-synuclein**: The protein -synuclein, which is 140 length of an amino acid and is widely distributed throughout neurons, is notably enriched in pre-synaptic terminals. Since point mutations in the -synuclein gene were discovered to be the cause of rare forms of familial PD, genetic locus multiplication and genetic locus duplication of -synuclein has been PD genetic's primary area of concern research. addition, it was found that ubiquitinated aggregates of -synuclein. The idea that -synuclein aggregation is a key factor in sporadic PD has been strengthened by the discovery that are a substantial one of the Lewy bodies in postmortem PD brains. The original transgenic mouse version that overexpresses human -synuclein in its wild type was created by Masliah et al. In the neocortex, hippocampus, and SN of these mice, neuronal inclusions accumulated over time and stained positively with antibodies to -synuclein and ubiquitin. These inclusions don't, however, have the fibrillar makeup that often distinguishes LBs. Furthermore, these mice don't appear to have lost any DA neurons. The degeneration pattern is different from the severe DA cell loss reported in Parkinson's disease (PD), despite the highest-expressing line showing considerable degeneration of THpositive nerve terminals inside the striatum and accompanied with motor impairment on a rotarod. Using viral vectors to over-express PD-linked genes is a valid alternative and crucial method of modelling PD in rodents. So, it appears that for -synuclein to exhibit its toxicity in DA neurons, at least in rodents, a threshold expression level (achieved by viral administration) or some alterations (achieved by truncation or double mutation) are required. Interestingly, an RNAi genome-wide screening indicated suppressor roles for a number of age-related genes in synuclein-mediated inclusion development, including sir-2.1/SIRT1 and lagr-1/LASS2.

**Parkin**: Parkinson's disease has an autosomal recessive variant that is brought on by the parkin gene. In 1998, the gene was identified. The PARK2 gene, found on the 6q chromosome, encodes the Parkin (Parkinson juvenile disease protein 2) is a 52 kDa (426 amino acid) enzyme protein. It is a crucial component of the ubiquitin-proteasome system that controls the breakdown of proteins. Parkin is initially found in the cytoplast, but when a prolonged depolarization takes place, it is translocated to the mitochondrial surface and causes the degradation of a number of membrane proteins that are potential mitophagies candidates. The integrity of the cellular mitochondria depends on parkin. Proteins that are misfolded and aggregated as a result of the parkin mutation build up and degrade mitochondria. These alterations play a well-known part in the patho mechanism of neurodegenerative disorders. For a long time, it was widely believed that Parkinson's disease has no cure. Sporadic disease with a hereditary component. Shortly after the identification of the -synuclein gene as a familial PD-linked gene, it was found that parkin gene mutations cause autosomal recessive juvenile parkinsonism. Parkin is a ubiquitin E3 ligase, and it is considered that both familial and sporadic Parkinson's

**Figure 3**: Parkinsonism’s genetic origins and disease-related genetic pathways.
**Disease (PD)** are influenced by the loss of its enzymatic activity. At least some of the parkin-related Parkinson's disease cases may have parkin as a relevant pathogenic factor.[47]

**PINK1:** It has been demonstrated that the mitochondrially focused serine/threonine kinase PINK1 guards cells against oxidative stress-induced apoptosis.[48] The PINK1 protein has mutations related with PD throughout, however the majority are concentrated in the kinase domain. Italian families with autosomal recessive and early-onset PD cases were where mutations (missense or nonsense in the PINK1 gene were first discovered.[49] In addition to having mildly lower levels of brain DA as they age, PINK1/mice have moderate mitochondrial impairments, greater susceptibility to oxidative stress, and a progressive decline in weight and locomotor activity. In general, neither LB-like aggregates nor striatonigral DAergic system alterations are visible in PINK1/mice. Overall, PINK1 models do not result in other PD-related abnormalities or functional disruption of the nigrostriatal DAergic neurons.[50]

**DJ1:** Numerous roles are performed by the protein encoded by the DJ-1 gene (PARK7), including mitochondrial control, protease activity, and transcriptional regulation. Missense DJ-1 mutations are related to early-onset and autosomal recessive PD.[51] Mutations of DJ-1 associated with familial parkinsonism generally occur in a recessive fashion.[52] No SNc DAergic neurons are lost in DJ-1/mice, but they do exhibit altered corticostriatal synaptic plasticity, decreased striatal DA release, and a reduced sensitivity to D2 auto receptor activation. In a different model, mice with DJ-1 loss were obtained using the “gene trap” technique. These mice displayed changes in object recognition along with upregulated mitochondrial respiratory activity, fewer DAergic neurons in the VTA, but no decreased DAergic terminals in the striatum, suggesting the involvement of this protein in the early phase non-motor symptoms of Parkinson's disease and the existence of compensatory mechanisms.[53]

![Image](image_url)

**Figure 4:** Targeting DJ-1 as therapeutic approach for PD

**Table:** Symptomatic Treatment of Parkinson Disease:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Indication (Motor and Non-Motor Symptoms)</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td>Benzatropine, trihexyphenidyl are drugs that block and inhibit the activity of the neurotransmitter acetylcholine (ACh) at both central and peripheral nervous system synapses.</td>
<td>Tremor</td>
<td>Hallucinations, nausea, dry mouth, blurred vision, urinary retention, and constipation</td>
</tr>
<tr>
<td>Carbidopa/levodopa</td>
<td>The blood-brain barrier can be crossed by levodopa. (BBB). Both the CNS and the peripheral areas of the body convert levodopa to dopamine. Levodopa is frequently used along to boost its absorption and lessen its adverse effects. (such as carbidopa). Levodopa can can more readily cross the BBB cross to dopamine-decarboxylase inhibitors because they stop levodopa from being converted to dopamine in the peripheral area. It produces dopamine when converted, which then stimulates postsynaptic dopaminergic receptors to make up for the loss of endogenous dopamine.</td>
<td>The most successful drug for treating Parkinson's disease symptoms is levodopa, which is still used; Most effective at controlling disability.</td>
<td>Orthostatic hypotension, sedation, disorientation, dystonia, and psychosis symptoms.</td>
</tr>
<tr>
<td>COMT inhibitors</td>
<td>Entacapone, Tolcapone Levodopa is prevented from degrading in the by preventing the enzyme, the peripheral nervous system catechol-O-methyl-transferase (COMT), which enables a larger quantity to cross the blood-brain barrier.</td>
<td>Early modest signs, only motor signs frequently an additional drug medication</td>
<td>Dark-coloured urine, a worsening of levodopa's side effects, diarrhoea, and hepatotoxicity</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>Bromocriptine, Pergolide Pramipexole Ropinirole Dopamine agonists bypass the need for metabolic conversion, storage, and release by acting directly on postsynaptic dopamine receptors. Dopamine agonists increase the impact of dopamine by acting on dopamine receptors.</td>
<td>Motor symptoms Useful for the initial treatment of parkinsonism and as adjunct therapy in</td>
<td>Hallucinations, nausea edema, fibrosis of cardiac valves, lung, and retroperitoneum;</td>
</tr>
</tbody>
</table>
MAO-B inhibitors
Selegiline
Rasagiline

Dopamine is metabolised by the enzyme monoamine oxidase B (MAO-B), which produces 3,4-dihydroxyphenylacetic acid (DOPAC), which is then converted into Homovanillic acid by the enzyme catechol-O-Methyltransferase (COMT). To reduce dopamine metabolism and consequently boost levels of dopamine in the brain, MAO-B inhibitors have been added to the therapy regimen for PD treatment, which reduces motor symptoms. Selegiline and rasagiline, both irreversible MAO-B inhibitors.

NMDA receptor inhibitor
Amanadine

Amantadine's indirect dopamine-releasing activity and direct activation of dopamine receptors are most likely to play significant roles in the relief of Parkinson's symptoms.

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