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# A review on recent pharmacological screening models to evaluate Parkinson's disease

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**Abstract**

This review aims to summarize the different Parkinson's disease models and their potential impact on their mechanism of induction. Parkinson's disease is the second most common neurodegenerative movement disorder. *In vitro* and *in vivo* models are indispensable tools to study the pathological mechanisms of Parkinson's disease. Currently, invertebrate and vertebrate animal models have been developed by using several pharmacological agents, neurotoxins, and pesticides. Aspects to be considered can be achieved by these models, which enable to study of parameters including motor defects, progressive loss of dopaminergic neurons in substantia nigra pars compacta, and the formation of lewy bodies. In this review, we will highlight the pathogenic mechanisms of those neurotoxins with the hope to help researchers choose among them accurately.

## 1. Introduction

Neurodegenerative disorders are characterized by progressive loss of neuronal cells due to chemical agents and genetic mutation. They can be clinically classified as disorders of extrapyramidal and pyramidal movements. Patients with behavioral or cognitive disorders have similar clinical features like bradykinesia, akinesia, postural instability, rigidity, tremors, memory loss, irritability, and aggression (Ghaffari *et al.,* 2018; Özdemir *et al.,* 2018). However, it is difficult to diagnose these disease conditions due to their convoluted features. Hence, attempts have been made to classify them as primary (*e.g.,* Parkinsonism, Dementia), anatomic distribution of neuro-degeneration (*e.g.,* Frontotemporal degenerations or spinocerebellar degenerations), and principal molecular abnormality (*e.g.,* Prion and Huntington's disease). The most common neurodegenerative disorders are Alzheimer's, Parkinson's, Amyotrophic lateral sclerosis, Huntington's, and Frontotemporal dementia, among which (Sumithra *et al.,* 2022; Gitler *et al.,* 2017; Paramita *et al.,* 2021), Parkinson's disease (PD) can be regarded as one of the most frequently occurring neurodegenerative disease.

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200 years ago, James Parkin diagnosed a condition called "shaking palsy" which is further recognized as PD. It is caused due to degeneration of dopaminergic neurons of the substantia nigra pars compacta (SNPC) and striatum. The loss of this neuronal population results in functional imbalances in the nigrostriatal cascade, leading to a reduced level of dopamine (DA) in the striatum. This leads to motor dysfunction and the development of the classical symptoms of PD such as bradykinesia, resting tremors, and rigidity (Shweta *et al.,* 2021).

The incidence of PD is in the geriatric population, affecting 1.5-2% above the age of 60 and 4% above the age of 80 years. The prevalence of PD is higher in males regardless of race than in females and it is expected that it can increase to 12 million cases by 2040 (GBD 2016 disease and injury incidence and prevalence collaborators 2017). Which made PD, a more important area of research to focus on, improved therapeutic efficacy, reduction in side effects, and increased life expectancy (Nazim *et al.,* 2019).

Diagnostic biomarkers and imaging studies are conducted along with the clinical features of PD. However, highly efficacious therapies have become available such as dopamine supplements accompanied by levodopa, catechol-o-methyl-transferase (COMT) inhibitors, anticholinergics, dopaminergic agonists, and monoamine oxidase-α (MAO-B) inhibitors to alleviate symptoms and enable enhanced motor functions and prolong the life expectancy of PD patients. (Li *et al.,* 2017; Xu *et al.,* 2013).

There are various etiological factors responsible to potentiate PD including age, environmental and genetic implications. However,

pathological changes in PD are unknown, although several studies suggest that neuronal degeneration is related to an increase in mitochondrial dysfunction, oxidative stress, neuroinflammation, apoptosis, and necrosis of the neurons at substantia nigra (SN) (Xie *et al.,* 2010).

In the pre-clinical phase, different approaches have opted for drug discovery such as *in vitro* and *in vivo* models which include cell culture, organ culture, pharmacological drugs, neurotoxins, pesticides, and herbicide-induced vertebrate or invertebrate animals. The following review discusses the several models used for the induction of PD associated with its mechanism of action, advantages, and disadvantages.

## 2. Experimental models used in Parkinson's disease

Drug discovery is a complex procedure here it starts with finding a lead molecule and structural elucidation of the same followed by the screening of these molecules by various methods available to establish preclinical data. As far as pre-clinical studies are concerned, different *in vitro* and *in vivo* methods are available from which the best suitable model or method is picked up to explore the efficacy of the study molecules. The criteria for the selection of any *in vitro* or *in vivo* method depends on the study requirement, idea, and outline of the study planned by the researchers. In these lines for PD also different methods are available *in vitro* and *in vivo*.

### 2.1 *In vitro* Parkinson's disease model

As far as PD is concerned to study the pathogenesis, culture systems are developed such as immortalized cell lines, human induced pluripotent stem cell (iPSC) derived cell lines, and organ-like models. Immortalized cell lines like HEK293 cells (human embryonic kidney 293), PC12 (pheochromocytoma cells derived from rat adrenal medulla), or SHSY5Y (human neuroblastoma cell line) cell culture but it has some limitations like maintaining cultures a bit tedious and difficult task, which leads to the inconsistent experimental outcome even though SHSY5Y cell lines are used in PD (Buttiglione *et al.,* 2007; Encinas *et al.,* 2000).

As opposed to this, LUHMES cell lines were derived from human embryonic mesencephalic tissues of 8-week-old humans and are immortalized by inserting the v-myc transgene. These cells can be differentiated into dopaminergic neurons. Further, the 3D model of LUHMES is developed by the gyratory shaking technique (Zhang *et al.,* 2014). The advantage of this 3D model is it can acquire biochemically and morphologically similar to primary neurons within 25 days of they get mature, and they can be maintained for two months (Bolognin *et al.,* 2019; Kane *et al.,* 2019). To overcome the difficulties with the above-stated methods, the novel organoid culture has been established as the primary culture. However, culturing and isolation of post-mortem brains from elderly and adult patients is a difficult task. Hence, they are obtained from the embryonic murine brain tissue, which can be differentiated from cultures to form synapsis. The advantage of this culture is they are with glial cells because the target-specific cells are achieved, and the drug effect on the remaining part of the cell environment can be estimated (Cavaliere *et al.,* 2010).

The model discussed above consists of valid clues for a better understanding of PD mechanisms and drug targets. Apart from this, the advanced and innovative model system which is identified as the available *in vivo* models to study PD includes organoids, 3D cultures, and organotypic cultures. Unlike 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP) and 6-OHDA, this model has a mechanical method for the degeneration of neurons (Iwashita *et al.,* 2004). During slice preparation, mechanical damage led to progressive degeneration of the striatal pathway. The advantage of this method is the replication of physiological processes and controlled genetic study. Despite the merits of this model, it is quite tricky and difficult to produce this type of culture because it requires proficient and skilled expertise to perform the dissections accurately with final precision and it is not an easy task as it looks in humans. Preparation and isolation of primary cultures are highly expensive, laborious, and time-consuming it is not suitable for large-scale studies. To establish reproducible models related to human pathology, iPCS lines have emerged as one of the fastest-moving drug discovery topics as they are suitable for target validation, filling the gap between animal models and humans. (Reinhardt *et al.,* 2013; Slanzi *et al.,* 2020).

### 2.2 *In vivo* Parkinson's disease model

Owing to the heterogeneous nature of PD, numerous animal models are required to elucidate different aspects of PD. The motor, as well as non-motor symptoms, can be clinically detected; however, in humans, brain pathology can be confirmed only by analyzing post-mortem tissue (Lopes *et al.,* 2017). Therefore, experimental models are required to enhance our understanding of this complex disorder and to broaden the limited therapeutic approaches. The models must be such that they can replicate the various aspects of PD in disease models primates, non-human primates, and other models (Nimisha *et al.,* 2022).

Over many years, the destruction of dopaminergic neurons in the PD model relies on toxins that produce relevant PD symptoms. These toxins have provided researchers with information related to the molecular study of dopaminergic neurons, but no model is still showing the exact imitation of human PD. Hence, no single model can be suitable for the study of PD. Therefore, various models with different approaches can be useful like pharmacological, neurotoxins, pesticide, and genetical based on reversible and non-reversible parkinson's symptoms. The pharmacological model (reversible PD) will cause degeneration of all neurons not specific to dopamine but produce effects of Parkinson's disease. Dopaminergic neurodegene ration associated with environmental factors that have been implicated in PD can be emulated by neurotoxins. In the substantia nigra pars compacta (SNPC), they usually cause a rapid and robust loss of cells, incite motor symptoms and changes in behavior, but lack lewy body formation. Genetic variants, on the other hand, not only display variable cell loss and motor symptoms but can also, depending on the particular model, display α-synuclein pathology. Though transgenic organisms or viral transfection, genetic mutations or changes in gene expression may be modeled.

#### 2.2.1 Pharmacological Parkinson's disease model

##### 2.2.1.1 Reserpine model

The first therapeutic efficacy of L-DOPA in the treatment of PD was done on rodents treated with reserpine, and it is said that it is the earliest PD model in the research of PD. The reserpine had a tranquilizing effect when pretreated in the mice in the 1950s. L-DOPA had successfully reversed the effect of reserpine. Then in the 1960s, the same effect was seen in humans, hence, the reserpine

model is established as a research tool for the PD as an asymptomatic screening model to check new drug efficacy. The reserpine model has contributed to the link between parkinson's symptoms and monoamine depletion.

Reserpine is an extract from *Rauwolfia serpentina* it works by reducing monoamines in the brain's peripheral region as it irreversibly inhibits vesicular monoamine transporter 1 and 2 (Cristina *et al.,* 2018; Leão *et al.,* 2017), which includes noradrenaline, 5-HT, and dopamine; therefore, it leads to loss of storage capacity of monoamines (Cristina *et al.,* 2018), which results in the depletion of catecholamine in nerve terminals (Santos *et al.,* 2013).

As reserpine selectivity is heterogeneous, it leads to controversy for the failure of this model but subsequently, the realization of serotonergic and noradrenergic systems also affects the PD, which made it to successful PD model. 4-5 mg/kg s.c. of reserpine can produce >95% of dopamine depletion within 2 h in the striatum, but after 24 h, it will reduce to nearly 30% by replacement of striatal dopamine (Table 1). For this reason, they used AMPT, *i.e*., a-methyl-p-tyrosine combined with reserpine can be administered to inhibit the synthesis of noradrenaline and dopamine (Ortiz-Padilla *et al.,* 2020; Yuan *et al.,* 2002). The disadvantage of this model is that it fails to study the efficacy of repeated-dose administration treatment protocol. Even though, it mimics the major biochemical components such as rigidity and akinesia that show clinical features in PD these behavioral changes occurred due to striatum and globus pallidus (Cristina *et al.,* 2018), this model is restricted to symptomatic treatment as there is no nigral dopaminergic depletion.

In this context, the reserpine treated rat has shown to be quite resourceful in predicting the effectiveness of dopaminergic and non-dopaminergic drugs, which are then examined in more complex models the currently used treatment in PD has shown efficacy in this model, which has justified its position as one of the critical models in the preclinical stage of drug discovery.

#### 2.2.1.2 Haloperidol model

The drug-induced Parkinson's is also one of the fundamental etiology in elderly patient's haloperidol is a first-generation antipsychotic drug that produces extrapyramidal symptoms of Parkinson's disease (Beam *et al.,* 2006; Kabra *et al.,* 2020). The exact pathophysiology of haloperidol is not yet confirmed, but it is said that it acts by antagonizing the D2 and D1 receptors and overexpression of gamma amino butyric acid (GABA) and encephalin-containing neurons at the striatum which is responsible for the motor dysfunction. This blocking of dopamine transmission leads to the production of increased reactive oxygen species (ROS) and a reduction in antioxidants due to oxidative stress (Adedeji *et al.,* 2014; Ward *et al.,* 2018). Haloperidol induces PD symptoms like rigidity and catalepsy within 60 min of intraperitoneal administration of dose 0.5-5 mg/kg (Beam *et al.*, 2006) (Table 1). These two symptoms can not define Parkinson's disease. Still, biochemical parameters with haloperidol mimic the PD, and Kulkarni *et al.* (2009) demonstrated the acute administration of haloperidol could reduce monoamine contents in the striatum, including dopamine, and elevate glutamate levels. The clinically used antiparkinsons drug has shown the efficacy of the haloperidol model by facilitating behavioral tests like bar tests and catalepsy. Haloperidol fails to display characteristic pathological mechanisms related to Parkinson's disease, hence the use of this model is limited.

#### 2.2.1.3 Chlorpromazine

Chlorpromazine is one of the essential antipsychotic drugs listed by world health organization (WHO) in 2003. It is a widely accepted catalepsy model for PD. It produces symptoms of PD by catecholamine storage disturbance at synapses and nerve terminals; therefore, resulting in the reduction of DA, 5HT, and noradrenaline at the nerve ending. However, chlorpromazine is also responsible to produce extrapyramidal symptoms due to the depletion of dopamine at the striatum (Bais *et al.,* 2015; Sandhua *et al.,* 2013). Chlorpromazine increases the DA receptor binding site in the nigrostriatal and mesolimbic region which results in DA hypersensitivity; therefore, induces dyskinesia, which interferes with the storage of catecholamine and causes depletion of monoamines (DA, 5HT, and noradrenaline) and at the end produce motor deficit such as hypo locomotion and muscle rigidity (Naeem *et al.,* 2019; Sandhua *et al.,* 2013). As pharmacological models have shown useful effects on behavioral and biochemical aspects, which made them useful models for the symptomatic screening of novel drugs.

### 2.2.2 Neurotoxins and pesticides

Neurotoxins administered by local or systemic routes lead to the degeneration of dopaminergic neurons which forms the basis of numerous PD models. 6-hydroxydopamine was amongst the first few toxicants to be discovered. It was previously employed peripherally for the degeneration of sympathetic nerves and thereafter it was used in the brain for modeling PD. The neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine was discovered as a result of chemically induced PD following unsuccessful synthesis of the opioid drug 1-methyl-4-phenyl-4-propionpiperidine (MPPP). Several reports have hinted that exposure to agricultural pesticides leads to an enhanced risk of PD.

#### 2.2.2.1 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

Mitochondrial dysfunction is one of the important causes of PD including deficiency in energy supply, the free radical generation which disrupts the mitochondrial-dependent redox signaling pathway which ultimately leads to cell degeneration. One such potent toxicant is MPTP which is used frequently for modeling PD (Xu *et al.,* 2013), along with probenecid which induces PD symptoms (Choi *et al.,* 2021). Acute or chronic administration of MPTP can be carried out by various routes like intraperitoneal, intramuscular, and direct brain inoculation by stereotaxic surgery. However, it is the best preclinical model for PD as it shows the same clinical features within humans, monkeys, and mice whereas some animals like rats, gerbils, and guinea pigs show resistance to produce symptoms of PD and higher doses will increase mortality rate (Jackson-Lewis *et al.*, 2007). Some research attempts have suggested that the amount of neuromelanin present in substantia nigra will play a vital role in the accumulation of neuromelanin to cause PD. However, rats and other immune animals do not accumulate neuromelanin and hence, the preferred model used in PD might be the mice model (Blesa *et al.*, 2014).

The MPTP model has a multistep process from systemic administration to induction of PD. Due to its lipophilicity, it crosses the blood-brain barrier (BBB) with ease. Systemic administration of MPTP crosses BBB which is taken up by glial cells and by the action of enzyme MAO-B it forms intermediate 1-methyl-4phenyl-,3-dihydropyridinium ($MPDP^+$) which produces toxic molecule $MPP^+$ by oxidation. The organic cation transporter 3 releases MPP+ into

the parenchyma which is then selectively transported with the help of dopamine transporter (DAT). This $MPP^+$ starts accumulating in the cytoplasm as well as in vesicles of the vesicular monoamine transporter (VMAT). It further inhibits mitochondrial complex I which leads to a cascade of events namely a reduction in adenosine triphosphate production, increased caspase-3 and caspase-7 activity, and increased oxidative stress by producing ROS (Zhang *et al.,* 2014), ultimately leading to cell death and neuroinflammation. ROS is produced by several mechanisms some of which are increased metabolism of dopamine at SN, low glutathione (GSH) and high levels of iron and calcium, reduced nicotinamide adenine dinucleotide phosphate oxidase, and flavoenzymes.

Exposure of MPTP to produce PD has been carried out in mice and non-human primates (NHP). Amongst these two models, the mouse MPTP model is more popular because of its easy access and reliability of results. The important reasons for MPTP to be used firstly in the induction are it is the only known dopaminergic neurotoxin capable of causing a clinical picture in both humans and animals, secondly, it produces reliable and reproducible lesions of the striatal pathway, and it is not technically challenged nor it requires specificity as in rotenone (Betarbet *et al.,* 2000), 6-OHDA and lipopolysaccharide (Przedborski *et al.,* 2001). Based on the dose, route of administration, and strain used, the extent of the lesion will vary (Jackson-Lewis *et al.*, 2007). The most frequently used method involves the administration of an acute dose of MPTP intraperitoneal to mice, this results in the degeneration of dopaminergic neurons in SNPC within hours but the stabilization occurs within a week. Four injections of an acute dose (up to 20 mg/kg) with 2 h intervals cause 90% of striatal dopamine depletion and 70% loss of dopaminergic neurons in the SNPC but no α-synuclein aggregate is produced, hence different doses of MPTP can be administered as given in (Table 1) for better understanding of dose fixation. Apart from the similarity of MPTP models in rodents and humans, some safety measures have to be followed such as personal protection, a negative pressure procedure room and proper handling of toxicants, detoxification, and disposal of contaminated materials and samples.

#### 2.2.2.2 6-hydroxydopamine

In animal models of PD, 6-OHDA/hemi-parkinsonism is the classic and more widely used neurotoxin (Cristina *et al.,* 2018). Many species, including monkeys, cats, dogs, and rodents, are susceptible to 6-OHDA intoxication. The structure of 6-OHDA resembles that of dopamine and noradrenalin; however, an additional OH group renders it toxic to the DA neurons. Besides, poor BBB permeability this compound is widely used, Hence, needs to be directly injected into the brain, specifically in the SNPC, medium forebrain bundle, or striatum. Generally, the administration of 6-OHDA is done unilaterally with effective results because the intact side serves as a control. On the other hand, the bilateral administration causes severe adipsia, aphagia, and even high mortality. Upon nigrostriatal administration, a progressive loss of neurons is observed in SNPC and ventral tegmental area (VTA). Typical PD patterns have been observed in animals with >90% lesions with higher neuronal loss in SNPC as opposed to VTA. Though 6 OHDA interacts with α synuclein, it does not form LB inclusions, and 6-OHDA will interact with other neurotransmitter transport hence, for target specificity along with pargyline (5 mg/kg) and desipramine (10 mg/kg) is given to inhibit the uptake of 6-OHDA by noradrenergic neurons (MD Imad Uddin *et al.,* 2020). This model is good as it replicates features of PD such as depletion of DA, nigral DA cell loss, and behavior.

#### 2.2.2.3 Rotenone

Rotenone is both an insecticide as well an herbicide obtained from tropical plants *Derris eliptica*, *Lonchocarpus,* and *Tephosia* spp. (Fabaceae), which is known as general mitochondrial poison (Bolam *et al.,* 2012; Siima *et al.,* 2020). It has a half-life of 3-5 days and undergoes quick degradation in soil and water. Owing to its high lipophilic nature, it can easily penetrate the BBB and cause toxicity. Rotenone has proven to be effective in rats but has failed to express a greater effect on mice or monkeys. The ability of rotenone to degenerate dopamine neurons, α-synuclein aggregation, and motor dysfunction makes it a great candidate as a pesticide model of PD. Daily intraperitoneal 3 mg/kg injection of rotenone for 6-10 days can induce a 45% degradation of DA neurons in the SNPC, depletion of striatal dopamine (Table 1), and several motor symptoms such as bradykinesia, postural instability, and rigidity. It can also trigger non-motor symptoms such as sleep disturbances in rats and can be administered by numerous routes, out of which the oral route has been considered the least effective one. The intraperitoneal route has been effective in inducing behavioral and neurochemical dysfunction, however, it leads to a high mortality rate. IV administration of rotenone may cause a loss of nigrostriatal DA neurons. It is also capable of inducing aggregation of α synuclein and formation of a lewy body. Rotenone's last aspect makes it an attractive model for PD. Not many documents are available that would suggest rotenone intoxication as a cause for PD in patients. Hence, rotenone is not preferred as much as other toxicants such as 6-OHDA and MPTP models.

#### 2.2.2.4 Paraquat

The year 2018 first meta-analysis on paraquat-induced PD has been carried out by (Wimonchat *et al.,* 2018), which concluded that paraquat has been linked to inducing oxidative stress and subsequently causing dopaminergic degeneration. paraquat is an herbicide that exhibits a similar structure to $MPP^+$ and hence has been suggested to have the potential inducer of a parkinsonian effect. However, paraquat produces toxicity through redox cycling of the cells.

Despite having high polarity ($PQ^{+2}$), paraquat can cross the BBB. The exact mechanism is unknown, however, it is said that the penetration is slow and ineffective as positron emission tomography scans of macaques depict that the BBB hinders paraquat from entering the brain. Systemic administration of paraquat also confirms this fact. Hence, this model is rarely used in the induction of PD but this herbicide can increase the susceptibility in humans for producing PD.

#### 2.2.2.5 Lipopolysaccharide

Lipopolysaccharides are a formidable bacterial endotoxin derived from gram-negative bacterial cell walls which generates a heterogeneous pathological condition in human beings. Neuroinflammation is one of the mechanisms which is responsible for PD. In the year 1998 the first intra nigral injection has been established, which induced microglial cell activation within two days, and a reduction in dopamine level and tyrosine hydroxylase activity for 21 days. Later studies suggested that single administration of lipopolysaccharide can produce PD symptoms for one year. (Batista *et al.,* 2019). Various *in vitro* and *in vivo* studies have reported that glial cells get activated by lipopolysaccharide, which leads to neuronal degeneration *via* neuroinflammation which is responsible for synaptic and memory

dysfunction. Hence, different lipopolysaccharide-induced rats and mice models have been validated and used for PD (Khan *et al.,* 2018). Reported that microglia and astrocyte respond immediately to stress, infection, and injuries which made it an important neuro-inflammatory response glial fibrillary acidic protein and allograft inflammatory factor 1 are specific markers for activated astrocytes and microglia. The expression of these inflammatory mediators along with tumor necrosis factor-2 and interleukin-6-in the brain increases after lipopolysaccharide injection at the striatum as well as substantia nigra therefore further it causes oxidative stress and apoptosis/ necrosis of the neuronal cells which leads to degeneration of neurons. (Singh *et al.,* 2018). Lipopolysaccharides can cause both acute and chronic state of PD, therefor can be used as the neurodegenerative model for PD *via* neuro-inflammatory mechanistic pathway.

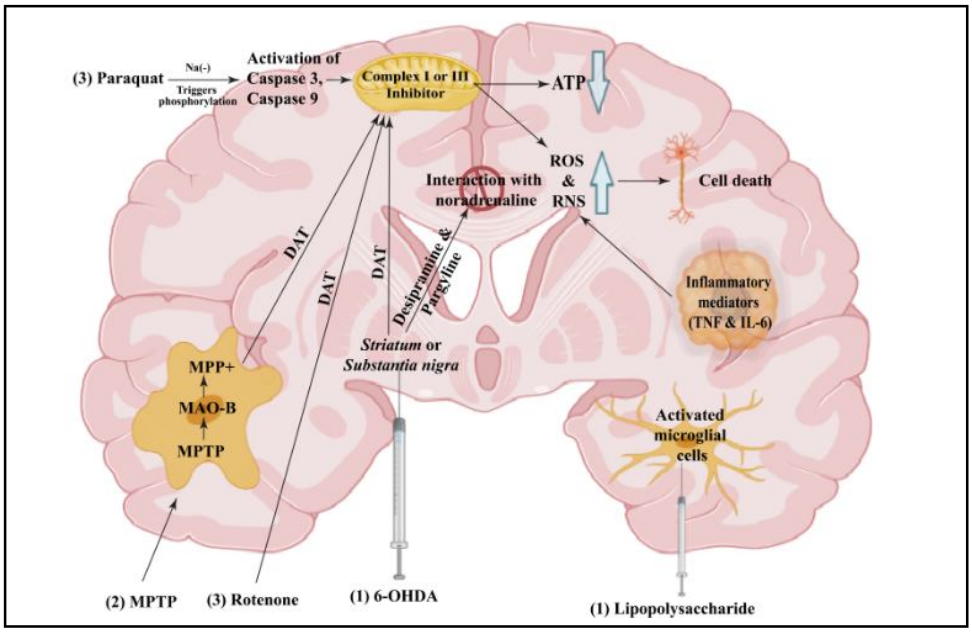


**Figure 1: Parkinson's disease inducing agents and their rout of administration.**

(1) 6-OHDA and lipolysaccharide must be delivered *via* i.c.v. into SNPC or striatum, which is transported into neurons by DAT. (2) MPTP can be administered both *via* i.c.v as well as systemic route it metabolizes monoamine in the glial cell into $MPP^+$ which is transported by DAT into dopaminergic neurons. (3) Rotenone and Paraquat will be administered *via* systemic route as they can cross BBB directly, Rotenone inhibits complex I of mitochondria and degenerate dopaminergic neurons. Paraquat is sodium-dependent which impairs redox cycling, increases oxidative stress, and causes neuronal death.

Na (-): sodium depletion; ATP: Adenosine triphosphate; ROS: reactive oxygen species; RNS: reactive nitrogen species; DAT: dopamine transferase; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model; 6-OHDA: 6 hydroxydopamine; TNF: tumor necrotic factor; IL: Interleukin.

**Table 1: Toxicant or inducing agent used in various rout of administration for rodents**

| Sl.No. | Inducing agent | Animal | Route | Dose | Level of induction |
|---|---|---|---|---|---|
| 1. | Reserpine | SD rats- 200-225 g | i.p. | 5 mg/kg: single administration | Acute (Yuan *et al.,* 2002) |
| | | Wistar rats | s.c. | 0.1 mg/kg: fifteen injection | Progressive model (Cristina *et al.,* 2018; Santos *et al.,* 2013) |
| 2. | Haloperidol | Albino rats 2-3 months | i.p. | 5 mg/kg: four weeks | Develop extrapyramidal side effects (Amin *et al.,* 2017) |
| | | Wistar rats 230-250 g | i.p. | 1 mg/kg: one week | Extrapyramidal symptoms (Kabra *et al.,* 2020) |
| | | Swiss albino mice 25-30 g | i.p. | 1 mg/kg | Nigrostriatal behavior (Adedeji *et al.,* 2014; Beam *et al.,* 2006) |
| 3. | Chlorpromazine | Wistar rats 150-200 g | i.p. | 3 mg/kg: 21 days | Behavioral (Bais *et al.,* 2015; Naeem *et al.,* 2019; Sandhua *et al.,* 2013) |
| 4. | MPTP | Wistar rat 280-320 g | i.c.v. | 1 µmol in 2 µl of saline | Early phase PD (Xu *et al.,* 2013) |
| | | Male C57BL/6 mice; 25-30 g | i.p. | 10 mg/kg 3 doses at 2 h intervals each | Acute (Fujita *et al.,* 2020; Sun *et al.,* 2018) |
| | | Male C57BL/6 mice; 20-22 g | i.p. | 30 mg/kg5 days dose administration | Chronic (Feng *et al.,* 2014) |

| | | | | | |
|---|---|---|---|---|---|
| 5. | 6-OHDA | Wistar rats | i.c.v. | 2 µg/µlSingle-dose | Acute (Zhou *et al.,* 2010) |
| | | Sprague Dawley | i.c.v. | 10 µg/2 µlSingle dose | Acute (Jin *et al.,* 2008; Khan *et al.,* 2018; Sadan *et al.,* 2009) |
| | | Mice C57/BL6 | Intra striatal | 3 µg/µl | Acute (Lundblad *et al.,* 2004; Stott *et al.,* 2014) |
| 6. | Rotenone | Sprague–Dawley 250 g | i.c.v. | 8 µg/8 µl single dose 1µl/min | Behavioral (Khatri *et al.,* 2015) |
| | | Swiss albino mice : 25-27 g | s.c. | 1.5 mg/kg/48 h 6 dose | Adenosine A2a receptor target (Motawi *et al.,* 2020) |
| | | C57BL/6 : 8-9 weeks old | p.o. | 30 mg/kg 4 weeks | Neuronal degeneration and alpha -synuclein aggregation (Yang *et al.,* 2018) |
| 7. | Paraquat and Maneb | C57BL/6J : 3 week old | i.p. | 10 mg/kg 6 weeks | Anti-inflammatory (Che *et al.,* 2018) |
| 8. | Lipopolysaccharide | C57BL/6N : 8 week | i.p. | 0.25 mg/kg 1 week | Neuroinflammation (Khan *et al.,* 2018) |
| | | Wistar rats : 180-250 g | i.c.v. | 10 µg/ 2µl 1 day | Neuroinflammation (Singh *et al.,* 2018) |

## 3. Conclusion

As we are aware the importance of research in Parkinson's disease is multifactorial and multidimensional and has limited knowledge of the etiological aspects and even the mechanism. It is important to have clearer information on the existing models available to rule out the research queries in the process of designing the project in this area which can brush up the methodology with emphasis on model selection and executing the same in line with the disease mechanism. Our idea is to gather the scattered information regarding the disease mechanism, model systems, toxicants, various animal models, and cell lines available to obtain the productive outcome of the area of parkinson's research. We trust this article helps the budding researchers as a preliminary informative guide in constructing the systematic methodology to carry out their research and can add more relevant and valued data to help the community.

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## Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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