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Experimental Animal Models of Parkinson's Disease: A Neurotoxin Overview

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Abstract

Parkinson's disease is a neurodegenerative disorder occurs due to selective degeneration of dopaminergic neurons in substantia nigra pars compacta and nigrostriatal pathways. Neurotoxins causing selective striatal/nigral degeneration of dopaminergic neurons have led us to understand the pathological aspects of Parkinson's disease. Although the current understanding of PD pathology has significantly increased, however, the exact pathogenic mechanisms involved in PD remained elusive and so the treatments. The present review is aimed to critically discuss the neurotoxic models of PD and to provide an updated summary of the main characteristics of these model systems along with their advantages and limitations of what we believe to be the most popular PD animal models.

Keywords: Parkinson's disease; 6-hydroxydopamine; MPTP; neurotoxins; paraquat; rotenone.

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 1% of the population over the age of 55years. The greatest known risk factor for PD is advancing age and, with the aging population, it is expected that the number of individuals seeking treatment for PD will dramatically increase over the next several decades [1]. The main features of PD are tremor, rigidity, bradykinesia, and postural instability. Moreover, these motor manifestations can be accompanied by nonmotor symptoms such as olfactory deficits, sleep impairments, and neuropsychiatric abnormalities [2-4]. Pathologically loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) has been reported to occur in relatively early stages of the disease [5].

Although the disease pathology has not yet been completely understood, however, the experimental models of PD have led us to understand its etiology and the pathophysiological mechanisms involved in the development of PD [6]. The experimental animal models can be divided into those using environmental or synthetic neurotoxins [7]

and recently, the identification of different genetic mutations have led to develop genetic models of PD. It is important to remember that, at best, only ~10% of PD cases are due to genetic mutations [6], while the vast majority of PD cases arise as sporadic from unknown origins.Thus understanding of pathogenic mechanism experimental parkinsons diseases induced by environmental neurotoxins is considered to be important. Of the neurotoxic models, compounds that produce both reversible (reserpine) and irreversible {MPTP (1-methy-4-phenyl-1,2,3,6-tetrahydropyridine), 6-OHDA (6-hydroxy dopamine), paraquat, rotenone} effects have been used effectively; however recent studies have focused more on irreversible toxins to produce PD-related behavioral and biochemical changes [8-9]. A common feature of all toxin-induced models is their ability to produce selective degeneration of dopaminergic neuronal populations that reflect what is seen in PD. In this review, we have tried to critically discuss the neurotoxic animal models and their potential roles in revealing the mechanisms for PD pathogenesis.

2. Neurotoxic Models

2.1 6-Hydroxydopamine (6-OHDA):

Since its first description in 1959, 6-hydroxydopamine (6-OHDA) has played a fundamental role in preclinical research on Parkinson's disease (PD). 6-OHDA is a structural analogue of catecholamines, selective for monoaminergic neurons and exerts its toxic effects on catecholaminergic neurons [10]. Ungerstedt, 1968 first used this neurotoxin in the rats, since that time 6-OHDA has become one of the most widely used neurotoxins for modeling PD in experimental animals. Different 6-OHDA rodent models have been developed in order to obtain a degree of neurodegeneration which replicates the disease pathology to the same extent as seen in human PD. Mice, cats, dogs, and monkeys are all sensitive to 6-OHDA; however it is used much more frequently in rats [11-14]. The magnitude of the lesion depends on the amount of 6-OHDA injected, the site of injection, and the animal species used. When injected into the striatum of rats, 6-OHDA has been well documented to produce degeneration of nigrostriatal neurons over several weeks and leads to a stable and permanent depletion of tyrosine hydroxylase (TH) - positive nigral neurons [15]. Systemically administered 6-OHDA fails to cross the blood–brain barrier, so it has to be injected locally using stereotaxic procedures to obtain a unilateral lesion [16-17]. Usually, there are three sites where 6-OHDA injections was made; into the medial forebrain bundle, the Substantia nigra pars compacta(SNPC) or the striatum [15, 16]. One of the most attractive features of the unilateral 6-OHDA model is the fact that each animal can serve as its own control as there is a lesioned and an unlesioned hemisphere.

2.1.1 Mechanism of 6-OHDA mediated neurotoxicity:

6-OHDA is toxic, both centrally and peripherally, since this neurotoxin is not capable of crossing BBB, It causes toxicity only when it is injected directly into brain by stereotaxic surgery. 6-OHDA exhibits a high affinity for catecholaminergic transporters such as the dopamine transporter (DAT) and norepinephrine transporter (NET), [18].Thus it is often used in conjunction with a selective noradrenaline reuptake inhibitor such as desipramine in order to spare the noradrenergic neurons from damage [19]. When 6-OHDA is infused into the brain, it produces cytotoxic species through both enzymatic and non-enzymatic mechanisms. These mechanisms are intensified by endocellular trace elements such as manganese and iron [20-22]. Once 6-OHDA is inside the neurons, it accumulates in cytosol and get oxidized by monoamine oxidase (MAO-A) enzyme and generates hydrogen peroxide (H2O2) which is highly cytotoxic and triggers the production of oxygen radicals [23]. Moreover, 6-OHDA undergoes strong auto-oxidation generating H2O2, reactive oxygen species (ROS) and catecholamine quinones which attack endocellular

nucleophilic groups [24-25]. Increase in the levels of ROS and other reactive species result in a rapid depletion of endocellular antioxidant enzymes, in turn leading to an increased metabolic abnormalities and structural damage to the neurons [15,26-27]. (Fig. 1).

2.2 1-Methyl 4-phenyl 1,2,3,6 - tetrahydropyridine (MPTP):

In 1979 and 1983, MPTP was identified as a strong neurotoxin when young drug addicts developed an idiopathic parkinsonian syndrome. After investigating the etiology of their condition, it was found that MPTP was the neurotoxic contaminant responsible for the parkinsonian effect [28]. The tragic results of MPTP poisoning in the heroin addicts led to the development of MPTP-induced rodent and nonhuman primate animal models of PD and proved to be extremely valuable [29-33]. Monkeys, humans and many other animal species including nonhuman primates, guinea pigs, mice, rats and cats are susceptible to this neurotoxin [34]. MPTP can be administered by a variety of regimens, but the most common and reproducible form is still systemic injection (subcutaneous, intravenous) [35]. The acute regimen consists of multiple systemic administration of MPTP (usually four doses at 2-h intervals per day). The subacute regimen consists of a single systemic administration per day for several consecutive days (usually 5 days) and the chronic regimen through several weeks [36]. The comparison of these different models indicated clearly that different schedules of administration of MPTP mimic distinct stages of the disease and might induce neuronal death by different mechanisms [15].

It has been repeatedly demonstrated that MPTP is indeed the gold standard for toxin-based animal model for replicating almost all of the hallmarks of PD. Unfortunately, lacking in this list is the definitive characteristic of PD, Lewy body formation [37-38]. Interestingly, some studies have demonstrated the production of Lewy body-like inclusions after MPTP administration [39-40] although these studies have been difficult to replicate. The studies suggest that, under the right circumstances, we may be able to reproduce majority of hallmarks found in PD. Increase in nigral extracellular glutamate levels and reduction in glutathione (GSH) levels as seen in PD have also been reported to occour following MPTP in mice [41-42]. Further neuroinflamatory events such as ractive microgliosis in substantia nigra and increase in proinflamatory cytokines has also been reported following MPTP in mice [43-44]. In addition MPTP in monkeys has been used to evaluate nonmotor symptoms and to identify the potential of deep brain stimulation which is currently the best surgical method to ameliorate symptoms in PD patients [45-51].

2.2.1 Mechanism of MPTP- induced neurotoxicity:

The mechanism behind the neurotoxic action of MPTP has been the subject of intense investigation and is relatively well understood (Figure 1). MPTP is a lipophilic toxin that, following systemic injection (usually i.p or s.c), rapidly crosses the blood–brain barrier [52]. Once inside the brain, MPTP is converted by MAO-B (principally in glia) into the intermediary, 1-methyl-4-phenyl-2,3,dihydropyridinium (MPDP+) before its rapid and spontaneous oxidation to the toxic moiety, 1-methyl-4-phenylpyridinium (MPP+) [53]. Following its release into the extracellular space, MPP+ is taken up via dopamine transporter (DAT) into dopaminergic neurons where cytoplasmic MPP+ can trigger the production of ROS, which may contribute to its overall neurotoxicity [54]. However, the majority of MPP+ is eventually accumulated within mitochondria and impairs mitochondrial respiration via inhibition of complex I of the electron transport chain [55]. This action impairs the flow of electrons along the respiratory chain, leading to reduced ATP production and the generation of ROS, such as superoxide radicals. The combined effects of lowered cellular ATP

and elevated ROS production are most likely responsible for the initiation of cell death-related signalling pathways such as p38 mitogen-activated kinase [56], c-junN-terminal kinase (JNK) [57] and bax [58-59], all of which have been demonstrated in vivo following MPTP treatment and may contribute to apoptotic cell death [60-61]. MPTP stimulates glial cells and a neuroinflammatory pathway such as cyclooxygenase-2 (COX-2) expression which is a rate-limiting enzyme involved in the production of prostaglandins from arachidonic acid and also enhances the expression of various pro-inflammatory mediators causing the neuronal death [62-63]. Indeed,microglial activation and increased COX-2 expression in SNpc has also been demonstreated in postmortem studies in PD patients. Moreover, COX-2 deficient mice were resistant to MPTP toxicity, suggesting potential role of COX-2 enzyme in neurotoxic mechanism following MPTP [64]

2.3 Rotenone model:

The realization that MPTP produced nigro-striatal degeneration through inhibition of mitochondrial complex I led to the search for other mitochondrial toxins that might be used to model PD. Rotenone is used as an insecticide and fish poison it belongs to the family of natural cytotoxic compounds called rotenoids and extracted from tropical plants. [65].

2.3.1 Mechanism of rotenone-induced neurotoxicity:

Like MPTP, rotenone is highly lipophilic, readily crosses the blood–brain barrier and diffuses into neurons similar to MPTP.It accumulates within the mitochondria and inhibits complex I (Figure 1). The ensuing reductions in ATP are not, however, considered a cause of the toxicity; rather the production of ROS, subsequent to glutathione depletion, is thought to induce oxidative stress [66]. Oxidative damage, in the form of protein carbonyl formation, has certainly been found in the midbrain, olfactory bulb, striatum and cortex of rats treated with rotenone [67], similar oxidative damage has been reported in postmortem PD brain [68]. The extensive microglial activation seen in both SNpc and the striatum following rotenone infusion [69] and is consistent with the inflammatory features found in idiopathic PD [70-72].

2.3.2 Routes:

In animals, rotenone has been administered by different routes. Oral administration appears to cause little neurotoxicity [73-74]. Chronic systemic administration using osmotic pumps has been the most common delivery regimen, especially in the Lewis rat, which may be more sensitive to rotenone than other strains of rats [75]. Intraperitoneal injections have been reported to elicit behavioral and neurochemical deficits, although the mortality is very high [76]. Intravenous administration is able to cause damage to nigrostriatal DA neurons that is accompanied by α-synuclein aggregation, Lewy body formation, oxidative stress, and gastrointestinal problems [77]. The apparent beauty of this model is that, like paraquat, it seems to replicate almost all of the hallmarks of PD including causing α-synuclein aggregation and Lewy-like body formation [78-79].Unfortunately, in addition to its central toxicity, rotenone shows a high degree of systemic (primarily cardiovascular) toxicity that produces high mortality rates (~30% of animals) regardless of route of administration [75]. There also appears to be an intrinsic resistance of some rats to rotenone, with as few as 50% of treated animals displaying neurodegeneration [75]. All of these factors combined; result in the necessity for using a larger numbers of animals at the start of any study to ensure relevant numbers are available for biochemical and histological analysis.

Administration of rotenone using intermittent ip dosing schedules has proven more effective to date. When low doses (1.5–2.5 mg•kg-1 ip) were administered daily for up to 2 months, a dose-dependent reduction in striatal TH+ neurons and dopamine levels were found [79], Behaviorally the animals exhibit reduced locomotor activity in the open-field test with marked [80].

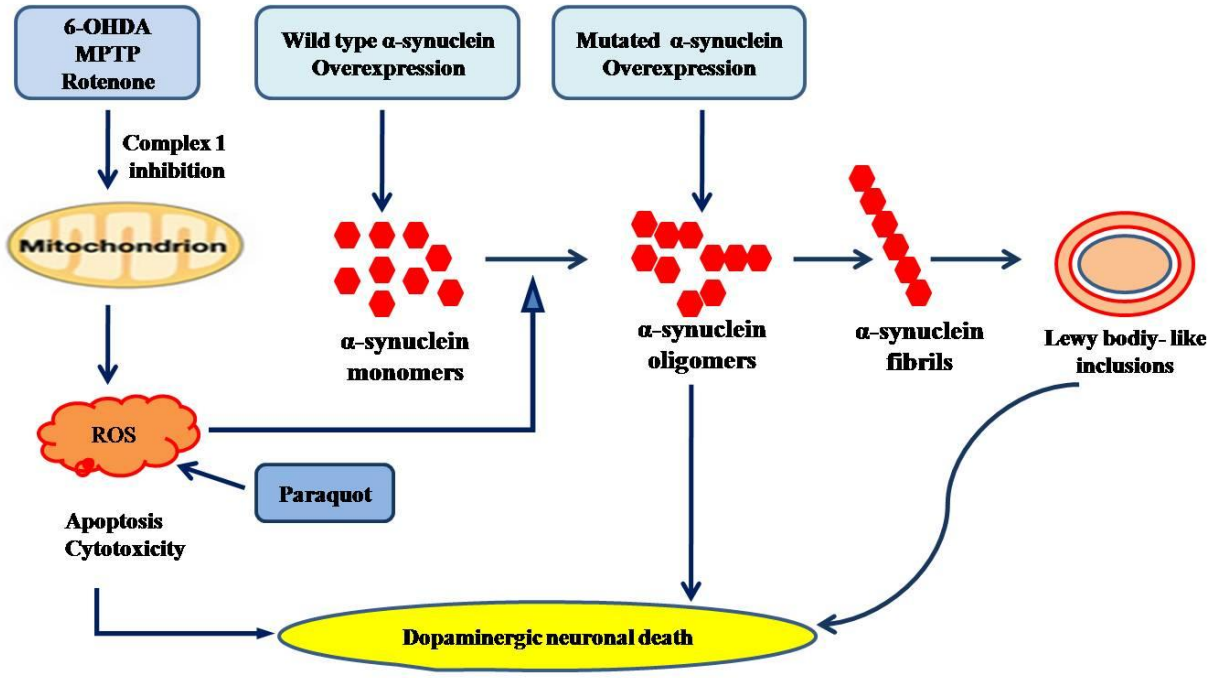

Fig 1: Mechanisms of neuronal death induced various neurotoxins used in experimental Parkinson's disease.

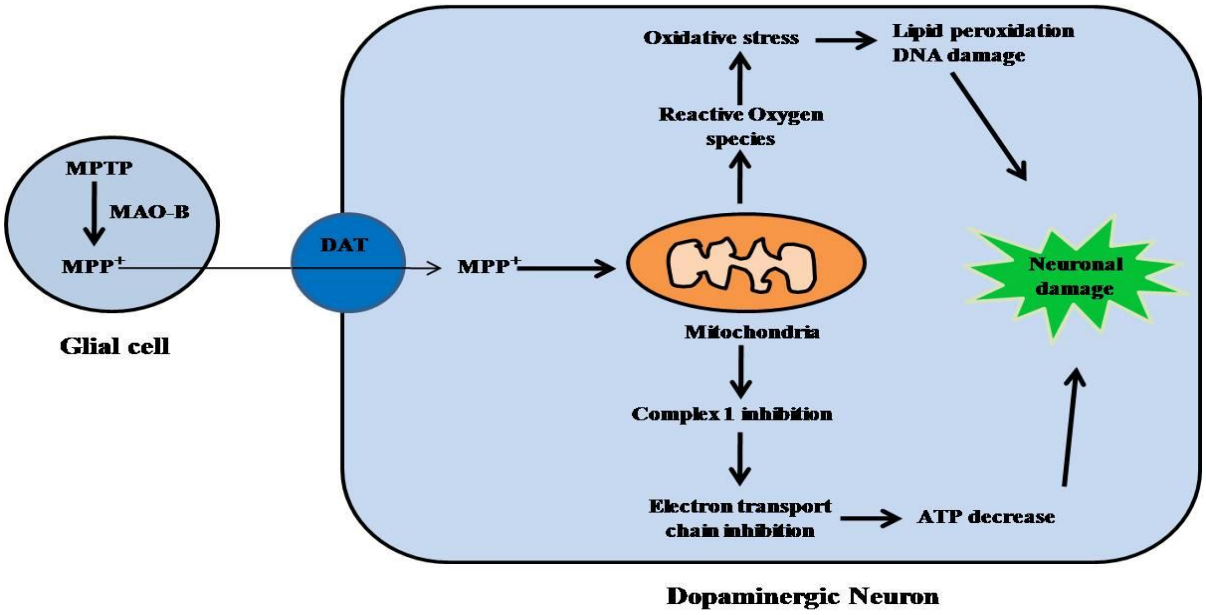

Fig 2: Mechanism of dopaminergic toxicity by MPTP.

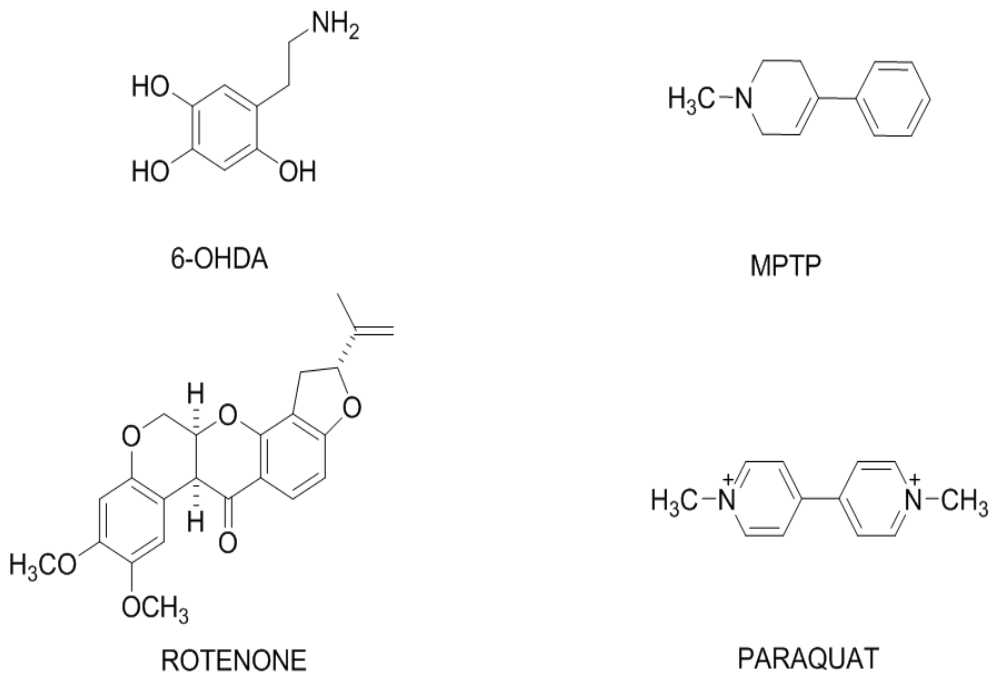

Fig 3:Structure of neurotoxic molecules used in animal models of PD to induce nigrostriatal damage

Toxic model	Dose	Route of administration	Advantages	Disadvantages
6-OHDA	4 or 8 µg/µl [92]	Stereotactic injection to SN, MFB, striatum [15-16][92]	• Show action after 24 hours of administration. [89-91] • It cause stable and permanent damage to tyrosine hydroxylase positive nigral neurons. [15] • Can be infused unilaterally and contralateral side can act as its control	•Can cause damage to non-adrenergic neurons [19]. •Do not cross BBB [16-17] •No lewis body formation for easy detection of PD. •Trained professional is required due to chances of mechanical damage of other areas of brain during surgry •Bilateral lesions result in marked adispsia and aphagia which interfere with the survival of animal.

				• Do not produce entire neuropathology of PD [15].
MPTP	Single injection of 30 mg/kg cause 20-30% loss of neurons [92]	Nonhuman primates i.p, i.m, intracarotid infusion Mouse Acute, subacute (i.p.) Chronic (osmotic minipumps)[92]	• Easily cross BBB [52]. • systemic injection also produces a bilateral degeneration of the nigrostriatal tract and reflect clinical PD. • No more skillful trained personal is required to inject MPTP systemically.	• Do not recapitulate the whole pathology of PD. • Rats are resistant to MPTP.If administered systemically • Inability to produce behavioural deficits apparent on standard motor mouse test [52].
Rotenone	2 to 3 mg/kg/day or 1.5–2.5 mg/kg/day for 60 days,[92]	Rat Infusion via osmotic minipumps i.p. injection [92]	• Readily crosses BBB [66]. • Cause selective degeneration of dopaminergic neurons [69].	• No inclusion body formation. • High mortality rate. • Results are inconsistent [66]. • Rats show intrinsic resistance to rotenone.
Paraquat and Maneb	30 mg/kg of maneb +10mg/kg paraquat (1-2 injection) in 3 weeks [92]	Mouse i.p.[92]	• Crosses BBB by amino acid transporter. • Capable of producing sufficient dopaminergic neuronal loss[93].	• It causes severe systemic toxicity [93].

Table 1: A critical overview on advantages and limitations on Key features of common neurotoxic models of PD

2.4 Paraquat and Maneb model:

It has been reported that exposure to the herbicide paraquat (1,1′-dimethyl-4,4′-bipyridinium) or the fungicide Maneb (manganese ethylene-bis-dithiocarbamate) have been associated with an increased incidence of PD [81-82]. So, it is not surprising that attempts have been made to model PD using these agents. Paraquat enters the brain via the neutral amino acid transporter [83] before Na+-dependent uptake into cells occur (Figure 1). Once inside the cells, paraquat lead to both indirect mitochondrial toxicity via redox cycling and also direct inhibition of complex I (at higher doses) [84]. Maneb, on the other hand, preferentially inhibits complex III of the mitochondrial respiratory chain following entry into the brain [85]. Paraquat and maneb have been shown to produce enhanced toxicity when combined [86], possibly as a result of maneb increasing the brain concentration and reducing clearance of paraquat [87]. Coupled with the fact that human exposure to one of these pesticides alone is unlikely as they are used in the same geographical regions, this provides a clear rationale for combining their administration in order to produce an animal model of PD. The combined administration of paraquat (10 mg/kg i.p) and maneb (30 mg/kg i.p) twice weekly for up to 6weeks in either C57bl/6 mice or Wistar rats produces only a modest but fairly consistent level of nigro-striatal degeneration (20–35%), with relative sparing of the VTA [86,88]. Further investigations using these models are needed to determine

the involvement of environmental exposures in the etiology of PD.

2. Conclusion

A number of animal models have been developed to understand the pathological aspects of PD.

The animal model systems are the important tool and provide a best way to study the human diseases and disorders due to somewhat resemblance with the humans. Neurotoxins such as paraquet, rotenone, 6-OHDA or MPTP have been used extensively & are reported simulate human PD in one or the other way by causing dopamenergic neuronal loss. Based on available reports, although none of these neurotoxins produces exact pathological features of clinical PD, however, among the available model systems MPTP stands to be a gold standard.

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