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Review Article

PARKINSON'S DISEASE AND NEUROTOXIC ANIMAL MODELS: A MECHANISTIC VIEW

VIVEK SHARMA

Department of Pharmacology, Govt. College of Pharmacy, Rohru, Distt. Shimla 171207, Himachal Pradesh India.
Email: viveksharma_pharma@yahoo.co.in

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder whose etiology is not understood. This disease occurs both sporadically and through inheritance of single genes, although the familial types are rare. Over the past decade or so, experimental and clinical data suggest that PD could be a multifactorial, neurodegenerative disease that involves strong interactions between the environment and genetic predisposition. Our understanding of the pathophysiology and motor deficits of the disease relies heavily on fundamental research on animal models and the last few years have seen an explosion of toxin-, inflammation- induced and genetically manipulated models. The morbidity and mortality due to PD is continuously increasing worldwide and the therapeutic agents currently available are limited. During the past few decades, the use of animal models has provided new insights into understanding the complex pathogenesis of Alzheimer's disease. Important pathogenic mechanisms still remain active and unmodified by present therapeutic strategies. Identification of signaling culprits involved using various animal models may provide the lead in discovering novel therapeutic agents. The insight gained from the use of such models has strongly advanced our understanding of the progression and stages of the disease. The models have also aided the development of novel therapies to improve symptomatic management, and they are critical for the development of neuroprotective strategies. This review critically evaluates these *in vivo* models and the roles they play in mimicking the progression of PD.

Keywords: Parkinson's disease, Oxidative stress, OHDA, MPTP, Paraquat, Rotenone

INTRODUCTION

Ageing is a universal biological fact and a natural process. It begins from the day we are born, or perhaps even before. In India, as per Census 2001, the number of older persons in 2001 were 70.6 million (6.9%), 83.5 million in 2006 (7.5%). As per the projections, the percentage of older persons are 94.8 million in 2011 (8.3%), 118 million in 2016, (9.3%) 143.7 million in 2021(10.7%) and 173.1 million in 2026 (12.4%) [1]. Of the world's 580 million elderly (>60 yrs), 355 million (61%) live in developing countries and, of these, 77 million (22% of total) live in India.

In general, health is considered to be an essential part and determinant of quality of life and diseases are known to be more prevalent with advancing age. The increasing life expectancy of Indians, in the last decade, is likely to result in an increase in age-related diseases like Parkinson and Alzheimer's disease. Parkinson's disease is the second most common idiopathic disorder of the extra pyramidal system characterized by tremors, rigidity and bradykinesia. Though James Parkinson is credited for his very clear description of Parkinson's disease, evidence exists that the disease has affected mankind since 2500 BC.[2] Earlier than James Parkinson, many physicians have picked up some of the features of Parkinson's disease and described them in their writings, for example, Franciscus de le Boe (1614–1672) who described tremors and Francois Boissier de Sauvages de la Croix (1706–1767) who described patients with "running disturbances of the limbs".[3]

The Ayurvedic physician, Charaka, was possibly the first to describe Parkinson's disease in his treatise "Charaka Samhitha" where he called it 'Kampavata', literally meaning 'tremors of neurological origin'. Interestingly, the treatment recommended in Ayurveda for PD is the seeds of Mucuna Pruriens whose extract contains levodopa. All this was known much before James Parkinson described this disease in modern times.[4]

Little has been added to the clinical description since its first crisp description in the monograph "An essay on shaking palsy" by James Parkinson in 1817. However, the management strategies have been revolutionized over time and much is now known about the pathogenesis. As the disease progresses, the number of clinical complexities also rises proportionally and includes camptocormia, dystonia, cognitive deficits, siallorohea, sexual dysfunction, psychosis, dementia, hypomimia, speech disturbances (hypokinetic dysarthria), hypophonia, dysphagia and respiratory difficulties. Loss of associated movements, shuffling, short-step gait, festination, difficulty turning in bed, Slowness in activities of daily living, stooped posture, kyphosis, scoliosis, orofacial dyskinesia and decreased blink rate are also experienced by the patients depending on the status and progress of disease.[5-7]

The prevalence of PD is of 0.3% in the whole population, affecting more than 1% of the humans over 60 years of age.[8] The disease has worldwide prevalence, with our part of world (South Asia), including India, not being excluded. The prevalence is however extremely variable, ranging from as low as 31/100,000 population in Libya to 300/100,000 and 328/100,000 population from Canada and India (Parsi community), respectively. The prevalence of PD in Indians is lower than people of European origin. Parsis who emigrated to India centuries ago from Persia have a much higher prevalence of PD than the Indians.[9]

PD symptoms first manifest when approximately 60% of the dopaminergic neurons have already died[10] and 70% of dopamine responsiveness disappears.[11] Increased oxidative stress,[12] mitochondrial dysfunction,[13] apoptosis[14], neuroinflammation and proteasomal dysfunction[15] are suggested to be initiators or mediators of neuronal cell death in PD. The symptoms of PD are mainly due to a progressive loss of dopaminergic neurons within the pars compacta of the substantia nigra (SNpc). This degeneration decreases the levels of the neurotransmitter dopamine in the nigrostriatal system. In the past 15 years, an increasing amount of evidence has emerged to suggest that oxidative stress may contribute to nigrostriatal pathway degeneration and accelerate the progression of pathology in PD patients.

PD is treated by administration of the dopaminergic precursor, L-3,4- dihydroxyphenylalanine(L-DOPA), which is transformed in residual dopaminergic neurons of the substantia nigra. Furthermore, L-DOPA is suspected to exert neurotoxic properties that accelerate the loss of dopaminergic neurons.[16] There have been additional anti-parkinsonian agents, such as dopamine receptor agonists and selective inhibitor of monoamine oxydase-B (MAO-B), but the available therapies do not protect against dopaminergic neuronal

cell death. PD patients begin not to respond well to treatment, and start to suffer disabilities which cannot be controlled with existing medical therapies. The prevalence of PD is likely to increase in the coming decades, as the number of elderly people increases. Therefore, it is of utmost importance to develop new drugs or targets that show or halt the rate of progression of PD patients in the world.[17] The major problem concerning a better therapeutic approach to the treatment and prevention of the disease is the enigma of its underlying cause.

Animal models of neurological disorders are critical for determining underlying disease mechanisms and developing new therapeutic modalities. In general, the utility of an animal model for a particular disease is often dependent on how closely the model replicates all or part of the human condition. In PD and related disorders there exists a variety of animal models, each of which makes a unique contribution to our understanding of the human condition.

Much of our knowledge about dopaminergic neurodegeneration has come from studies with two neurotoxins that produce animal models for oxidative stress and Parkinsonism syndrome in rodents, primates and other species. Both neurotoxins, namely 6-hydroxydopamine (6-OHDA) [18] and MPTP (N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine)[19] cause the degeneration of nigro-striatal dopamine neurons with the subsequent loss of striatal dopamine. Beside them, there are other models too which have contributed to our understanding of molecular pathogenesis of PD and in the development of newer and better therapeutic breakthroughs. Current work is an effort to elucidate the molecular mechanisms involved with these models and rationale of their uses.

OLDER MODELS

RESERPINE & ALPHA-METHYL-PARA-TYROSINE

The first animal model for PD was demonstrated by Carlsson in the 1950s using rabbits treated with reserpine. Reserpine is a catecholamine-depleting agent that blocks vesicular storage of monoamines. The akinetic state, resulting from reserpine-induced dopamine depletion in the caudate and putamen, led Carlsson to speculate that PD was due to striatal dopamine depletion. This speculation was supported by the discovery of striatal dopamine depletion in postmortem brain tissue of PD patients and led to the subsequent use of levodopa (in conjunction with a peripheral dopadecarboxylaseinhibitor) for symptomatic treatment of PD. [20,21] Thus, the initial observations derived from an animal model led to an important clinical therapy that remains a gold standard.

Although less commonly used, alpha-methyl-para-tyrosine (AMPT), like reserpine, serves as an effective catecholamine-depleting agent. By directly inhibiting tyrosine hydroxylase (the rate-limiting enzyme in dopamine biosynthesis), the nascent synthesis of dopamine in neurons of the substantia nigra pars compacta and ventral tegmental area is prevented.

Both reserpine and AMPT have been used to discover new dopaminomimetics for the treatment of PD, but since their effects are transient (hours to days), these models are primarily useful for acute studies. In addition, neither agent can duplicate the extensive biochemical and pathological changes seen in PD. Consequently, other models with long lasting behavioral alterations have been sought using site-specific neurotoxicant injury.

TOXIN-BASED MODELS

Among the neurotoxins used to induce dopaminergic neurodegeneration, 6-hydroxydopamine (6-OHDA), MPTP, and more recently paraquate and rotenone have received the most attention. Presumably, all of these toxins provoke the formation of reactive oxygen species (ROS).

Rotenone and MPTP are similar in their ability to potently inhibit complex I, though they display significant differences, including, importantly, their ease of use in animals. Only MPTP is clearly linked to a form of human Parkinsonism, and it is thus the most widely studied model.

THE MPTP-MOUSE MODEL OF PARKINSON'S DISEASE

An interesting study reported the occurrence of an akinetic rigid syndrome responsive to L-DOPA resembling the clinical features of PD in seven individuals after intravenous administration of an illicit synthetic heroin analog (meperidine) that contained high amounts of by-product MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine).[22] Subsequent studies demonstrated that systemic administration of MPTP into non-human primates[23] and mice[24] caused an irreversible and selective loss of dopaminergic neurons in the substantia nigra. MPTP is a highly lipophilic molecule and crosses rapidly the blood-brain barrier in a matter of seconds of systematic injection.[25]

MPTP is a synthetic substance and to date no such toxin has been identified in the environment or in the brain. MPTP, similar to 6-OHDA is thought to initiate its dopaminergic neurotoxicity via metabolism by monoamine oxidase (MAO), giving rise to its reactive metabolite MPP^+. This is thought to begin the neurodegeneration process via generation of reactive oxygen species (ROS) and inhibition of mitochondrial complex I,[26] as it produces sustained dopamine oxidation, hydroxyl radical formation and membrane lipid peroxidation.

MPTP can produce an irreversible and severe parkinsonian syndrome that replicates almost all of the features of PD, including tremor, rigidity, slowness of movement, postural instability, and even freezing.[27] In non-human primates, a resting tremor characteristic of PD has only been demonstrated convincingly in the African green monkey.[28]

Within a minute after MPTP injection, levels of the toxin are detectable in the brain. Once in the brain, MPTP is metabolized to 1-methyl-4-phenyl-2, 3-dihydropyridinium ($MPDP^+$) by the enzyme monoamineoxidase B (MAO-B) in non-dopaminergic cells. Then $MPDP^+$ is oxidized to the active MPTP metabolite, MPP+, which is then released into the extracellular space, where it is taken up by the dopamine transporter and is concentrated within dopaminergic neurons, where it exerts its toxic effects.[29]

MPP+ is selectively accumulated by high affinity dopamine transporters (DAT) and taken up into the mitochondria of dopaminergic neurons, where it disrupts oxidative phosphorylation by inhibiting complex I (NADH-ubiquinone oxidoreductase) of the mitochondrial electron transport chain.[30] This leads to impairment of ATP production, elevated intracellular calcium levels and free radical generation, thereby exhibiting dopaminergic neurotoxicity. Therefore, MPTP treatment is known to cause a marked depletion of dopamine and nigrostriatal neuronal cell death in a wide variety of animal species, including mice, dogs and non-human primates.[31-33] Although MPTP-treated monkey model remains the best, most studies have been performed in MPTP treated mice as a good model of PD.[31]

The several mechanisms that play a major role in the neurotoxic processes of MPTP include, production of reactive oxygen species (ROS), reactive nitrogen species (RNS), the over expression of iNOS, the modulation of eNOS and the involvement of inflammatory response.[34] The increased expression of iNOS correlated with NO overproduction in the substantia nigra of PD patients could contribute to the formation of free radicals that could be involved in the damage of dopaminergic neurons, leading to the development of PD symptoms.[17]

Furthermore, Poly (ADP-ribose) polymerase (PARP) is an abundant nuclear enzyme that uses nicotinamide adenine dinucleotide (NAD^+) as a substrate. PARP is also known to be involved in DNA plasticity such as repair of DNA damage, gene expression, and carcinogenesis. However, extensive PARP activation can promote cell death through processes involving energy depletion. Several studies have reported

that ROS-induced damage of DNA activates PARP, culminating in cell death or necrosis.[35] On the other hand, PARP plays a key role in a caspase-independent apoptosis pathway mediated by apoptosis-inducing factor (AIF) and translocation of AIF from mitochondria to the nucleus is dependent on PARP activation in neurons after various DNA-damaging stimuli.[36] The cellular suicide mechanisms of both apoptosis and necrosis by PARP activation have been implicated in the pathogenesis of neurodegenerative disorders such as PD.[17] Researches have indicated that toxic effect of MPTP is mediated through an excessive production of PARP.[37,38]

MPTP has also been shown to release massive amounts of striatal dopamine (Rollema et al., 1986), which in turn may generate more ROS contributing to dopamine neuron death. This supports the hypothesis that intracellular dopamine-mediated oxidative stress is a contributing factor in the death of dopamine neurons.

Although the monkey MPTP model remains the best, most studies have been performed in mice. In these studies, several MPTP dosing regimens have been used. The so-called acute regimen consists of multiple systemic administration of MPTP (usually 4 doses at 2-h intervals) per day, and the sub-acute regimen consists of a single systemic administration per day for several consecutive days (usually 5 days) or even weeks for the chronic case.[39] According to Jackson-Lewis and Przedborski, tissue striatal dopamine (DA) depletion can range from 40% (when MPTP is given at 14 mg/kg per dose × 4) to approximately 90% (20 mg/kg per dose × 4) 7 days after the last MPTP dose. With this acute regimen, death of nigral neurons occurs in a non-apoptotic form with tissue striatal DA depleted by at least 40-50% in young adult C57bl/6 mice by day 7 after MPTP administration. However, the extent of functional impairment of striatal fibres remains unknown.[40]

However, two typical neuropathologic features of PD have, until now, been lacking in the MPTP model. First, except for SNpc, pigmented nuclei such as locus coeruleus have been spared, according to most published reports. Second, the eosinophilic intraneuronal inclusions, called Lewy bodies, so characteristic of PD, thus far, have not been convincingly observed in MPTP-induced parkinsonism,[41] although, in MPTP-injected monkeys, intraneuronal inclusions reminiscent of Lewy bodies have been described.[42]

6-HYDROXYDOPAMINE (6-OHDA) MODEL OF PARKINSON DISEASE

6-hydroxydopamine, the first animal model of PD associated with SNpc dopaminergic neuronal death, was introduced more than 30 years ago.[42] 6-OHDA-induced toxicity is relatively selective for monoaminergic neurons, resulting from preferential uptake by DA and noradrenergic transporters.[43]

The neurotoxin, 6-OHDA, is structurally similar to dopamine and norepinephrine (NE) and has a high affinity for the plasma membrane transporters of these catecholamines.[44] Once inside the neurons, it is readily oxidized and produces hydrogen peroxide and paraquinone, both of which are highly toxic.[45] This toxin does not readily cross the blood-brain-barrier, but when administered directly in the brain, it specifically kills DA and NE neurons and their terminals.[46]

6-OHDA, is a neurotoxin widely used to selectively destroy catecholaminergic systems in either in vivo[47] or in vitro studies. Different cell types have been described as susceptible to 6-OHDA treatment, including primary rat striatal neurons,[48] chick sympathetic neurons, [49] human neuroblastomacells[50] and rat pheochromocytoma (PC12) cells.[51]

Inside neurons, 6-OHDA accumulates in the cytosol, generating ROS and inactivating biological macromolecules by generating quinones that attack nucleophilic groups.[52] The consequence of OS is the initiation of ROS generation followed by brain membrane lipid peroxidation. Because 6-OHDA cannot cross the blood-brain barrier, it must be administered by local stereotaxic injection into the substantia nigra, median forebrain bundle (MFB; which carries ascending dopaminergic and serouotonergic projections to the forebrain), or striatum to target the nigrostriatal dopaminergic pathway.[46] After 6-OHDA injections into substantia nigra or the MFB, dopaminergic neurons start degenerating within 24 hr and die without apoptotic morphology.[53] When injected into the striatum, however, 6-OHDA produces a more protracted retrograde degeneration of nigrostriatal neurons, which lasts for 1–3 weeks.[54]

The unilateral lesion can be quantitatively assayed; thus, a notable advantage of this model is the ability to assess the anti-PD properties of new drugs and the benefit of trans plantation or gene therapy to repair the damaged path ways.[55] However, it is not clear whether the mechanism by which 6-OHDA kills dopaminergic neurons shares key molecular features with PD.[56]

PARAQUAT INDUCED PARKINSON'S DISEASE

Paraquat (1, 1-dimethyl-4, 4'-bipyridinium dichloride) is a quaternary nitrogen herbicide widely used for broadleaf weed control. It is a fast-acting, non-selective compound which destroys tissues of green plants on contact and by translocation with the plant. The strong affinity for adsorption to soil particles and organic matter is one of the major advantages in introducing paraquat as an herbicide because it limits its bioavailability to plants and microorganisms. However, paraquat has been demonstrated to be a highly toxic compound for humans and animals and many cases of acute poisoning and death have been reported over the past few decades.

The interest in its potential neurotoxicity began after the observation that paraquat exhibits a striking structural similarity to MPP^+, the active metabolite of MPTP a neurotoxin that induces PD-like features in rodents, non-human primates and humans. Ironically, in the 1960s, MPP^+ itself had been tested as a herbicide under the commercial name of cyperquat. In keeping with this, significant damage to the brain was seen in individuals who died from paraquat intoxication.[57]

The cellular toxicity of paraquat is essentially due to its redox cycle including a well-known cascade of reactions leading to NADPH consumption and to generation of ROS mainly hydrogen peroxide (H_2O2) and hydroxyl radical (HO^-) with consequent cellular deleterious effects. Indeed, lipid peroxidation has been suggested as a potential mechanism of toxicity during exposure to paraquat *in vitro* and *in vivo.*[58]

Furthermore, apoptosis contributes to neuronal cell death in parkinsonian patients. In line with this, studies planned for a more thorough understanding of gene-toxicant interactions found that paraquat acts by regulating apoptosis-related genes belonging to BCL_2 family, tumor necrosis factor $(TNF)^-$ receptor and ligand family, the cell death-inducing DFF45-like effector (CIDE) and caspase family.[59]

In particular, paraquat triggers apoptosis through the intrinsic cell death pathway which includes Bak-dependent-mitochondrial outer membrane permeabilization, cytochrome c release, caspase-3 and c-*Jun*-N-terminal kinase (JNK) activation, and ultimately apoptotic cell death.[60,61] Researchers have concluded that paraquat neurotoxicity is not specific for the nigro-striatal dopaminergic system.[62] whose degeneration is responsible for most of the clinical Parkinsonian symptoms, since potent neurotoxic effects were reported following injection of this herbicide in brain areas such as locus coeruleus or raphe nuclei in which noradrenergic and serotoninergic neurons are located. Following this line, also PD pathology is not restricted to the DA system, but progressively involves noradrenergic and serotonergic neurons within the locus coeruleus and raphe nuclei.[63]

Exposure to paraquat may confer an increased risk for PD.[64] However, paraquat does not easily penetrate the blood brain barrier,[65] and its CNS distribution does not parallel any known enzymatic or neuroanatomic distribution.[66] Administration of

paraquat to mice leads to SNpc dopaminergic neuron degeneration accompanied by α-synuclein containing inclusions, as well as increases α-synuclein immunostaining in frontal cortex.[67]

Since paraquat is structurally similar to MPP^+, it has been hypothesized that the mechanism of paraquat-mediated neurotoxicityis also similar. However, recently, it has been found that paraquat is neither a complex I inhibitor nor a substrate for DAT,[68] indicating that the molecular mechanism of neuronal cell death induced by paraqaut may be different from MPP^+.

JNK, which is also known as stress-activated protein kinase has been shown to be involved in both survival and cell death depending on the cell type and stimulus.[69] JNK activation was shown to be closely associated with the dopaminergic cell death observed in PD.[60,70] Paraquat induces Jun Nterminal MAPK-mediated caspase-3–dependent cell death, unlike MPP^+ or rotenone-induced cell death. Paraquat has been shown to induce oxidative stress followed by Jun N-terminal MAPK-mediated caspase-3 dependent cell death in several model systems.[60, 71]

ROTENONE INDUCED PARKINSONISM

Rotenone, a naturally occurring insecticide extracted from Leguminosae plants, commonly used in small-scale organic food farming. It is also used as an insecticide and to kill fish perceived as pests in lakes and reservoirs. One of the major benefits of rotenone as a pesticide is that it biodegrades in several days, even if spread over extensive agricultural land. Based on its limited environmental use, short half-life, and limited bioavailability, it is unlikely that rotenone exposure has a significant impact on PD. The most common way that rotenone exposure to humans would take place is through ingestion. However, absorption in the stomach and intestines is slow and incomplete, and the liver breaks down the compound effectively. For this, chronic rotenone inhalation or ingestion fails to confer parkinsonian symptoms.[62]

Highly lipophilic, it easily crosses the BBB, and unlike many other toxic agents bypasses the dopamine transporter (DAT) for cellular entry. Once in the cell, it accumulates in subcellular organelles including the mitochondria,[72] where it binds specifically to complex I, disrupting mitochondrial respiration and increasing reactive oxygen species (ROS) production and oxidative stress.[73] For these reasons, rotenone has been used extensively as a classic mitochondrial poison on *in vitro* and *in vivo* models. Rotenone binds (at the same site as MPP-) to and inhibit mitochondrial complex I.[56]

Administration of low-dose intravenous rotenone to rats produces selective degeneration of nigrostriatal dopaminergic neurons accompanied by α synuclein-posttive LB-like inclusion.[73] Rotenone may freely enter all cells, this study suggested that dopaminergic neurons are preferentially sensitive to complex I inhibition. Rotenone-intoxicated animals developed abnormal postures and slowness of movement, but it is unknown whether these features improved with levodopa administration. Nevertheless, this model was the first to link an environmental toxin of possible relevance to PD to the pathologic hallmark of α synuclein aggregation, an association also seen in cell culture studies.[74]

Furthermore, a subsequent study of rats chronically infused with rotenone demonstrated significant reductions in striatal, cholinergic, and NADPH dopaminergic -positive neurons.[75] These results suggest that rotenone exerts a more widespread neurotoxicity than originally proposed, challenging the concept that dopaminergic neurons display preferential sensitivity to complex I inhibition.[73]

After a single intravenous injection, rotenone reaches maximal concentration in the CNS within 15 min and halves within 2 hours.[72] Its brain distribution parallels local differences in oxidative metabolism. Indeed, rotenone-treated rodents show behavior consistent with PD, including decreased locomotion, flexed posture, and rigidity.[76] Interestingly, continuous infusion of rats with rotenone is accompanied by nigro-striatal dopaminergic loss and cytoplasmic inclusions containing α-synuclein, resembling Lewy bodies found in humans with PD.

This toxin applied in a micromolar range interferes with mitochondrial function therefore it determines an energetic failure by causing mitochondrial membrane depolarization by inducing formation of ROS mitochondrial dysfunction contributes to hyperpolarize the plasmlemma membrane of dopamine through opening of K ATP channels.[77] Researchers have also reported an inhibition/hyper polarization of DA neurons induced by rotenone. The opening of KATP channels could be interpreted as an early defensive response of the cells. In fact, the hyperpolarization could spare the metabolic demand (oxygen consumption) sustained by the spontaneous neuronal activity. However, experimental evidence has emerged that KATP channels promote neuronal degeneration.[62]

Regarding these models, mechanism of action of the herbicide paraquat is fundamentally different from that of MPP+ and rotenone. MPP+ and rotenone being mitochondrial complex inhibitors primarily target mitochondria and induce oxidative stress, whereas paraquat induced cytosolic oxidative stress followed by caspase-3–mediated cell death. The distinct molecular mechanism of toxicity of these Parkinsonism inducing compounds should be taken into consideration when designing experiments aimed at understanding the pathogenesis of PD (Ramachandira et al., 2007).

CONCLUSION

Parkinson's disease is characterized by persistent, coordinated, nuclear-encoded cellular energy defects to which nigral dopamine neurons are intrinsically more susceptible than others cells. Complex I dysfunction in PD may be a biochemically detectable "tip of the iceberg" of a deeper molecular defect comprising the entire nuclear-encoded electron transfer chain. Overall, PD lack effective treatment options for patients. PD receives the most attention through extensive funding and research, yet PD have only palliative therapies available and none that significantly target the underlying pathology of the disease. The animal models discussed in the present review have helped a lot to understand the molecular pathogenesis of PD yet every success seems incomplete and every effort futile till we found a cure for PD which not only provide symptomatic relief but stop the progression of this devastating disease.

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