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REVIEW

Animal Models of Parkinson's Disease: A Gateway to Therapeutics?

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Abstract Parkinson's disease (PD) is a progressive, neurodegenerative disorder of unknown etiology, although a complex interaction between environmental and genetic factors has been implicated as a pathogenic mechanism of selected neuronal loss. A better understanding of the etiology, pathogenesis, and molecular mechanisms underlying the disease process may be gained from research on animal models. While cell and tissue models are helpful in unraveling involved molecular pathways, animal models are much better suited to study the pathogenesis and potential treatment strategies. The animal models most relevant to PD include those generated by neurotoxic chemicals that selectively disrupt the catecholaminergic system such as 6-hydroxydopamine; 1-methyl-1,2,3,6-tetrahydropiridine; agricultural pesticide toxins, such as rotenone and paraquat; the ubiquitin proteasome system inhibitors; inflammatory modulators; and several genetically manipulated models, such as α-synuclein, DJ-1, PINK1, Parkin, and leucine-rich repeat kinase 2 transgenic or knock-out animals. Genetic and nongenetic animal models have their own unique advantages and limitations, which must be considered when they are employed in the study of pathogenesis or treatment approaches. This review provides a summary and a critical review of our current knowledge about various *in vivo* models of PD used to test novel therapeutic strategies.

Keywords Parkinson's disease · animal models · neurotoxins · transgenic · motor symptoms · non-motor symptoms · therapeutics · neuroprotection

Introduction

Parkinson's disease (PD), the second most common neurodegenerative disease after Alzheimer's disease, is characterized by the loss of dopamine (DA) neurons within the substantia nigra pars compacta (SNpc), striatal DA depletion, the presence of Lewy bodies (LB)—composed mainly of α-synuclein and ubiquitin—and gliosis. In addition to the involvement of the nigrostriatal pathway, neurodegeneration and LB are also found in the locus ceruleus, nucleus basalis, hypothalamus, cerebral cortex, cranial nerve motor nuclei, and central and peripheral components of the autonomic nervous system [1, 2]. Many pathogenic mechanisms such as oxidative stress, mitochondrial defects, proteolytic stress, neuroinflammation, and impaired ubiquitin proteasomal system (UPS) and autophagy have been suggested to play a role in PD [3–5]. About 10 % of PD cases have identifiable genetic defects, such as α-synuclein, Parkin, leucine-rich repeat kinase 2 (LRRK2), PINK1, DJ-1 ATP13A2, GIGYF2, HTRA2, PLA2G6, FBX07, VPS35, EIF4GI, and others, but the pathogenic mechanisms of neurodegeneration leading to these forms of genetic parkinsonism remain unclear [6–8] (Tables 1 and 2).

Motor symptoms of PD do not become clinically apparent until 60–80 % loss of DA from the striatum, but many non-motor symptoms, such as loss of smell, rapid eye movement (REM) sleep behavior disorder (RBD), and dysautonomia may precede the onset of motor symptoms by years or decades [2]. It has been suggested that as a result of deficiency in transcription factors required for the development and maintenance of the various neurotransmitter systems, prenatal

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Table 1 Rodent and primate animal models of Parkinson's disease (PD)

PD animal models	Animal behaviors	Neuropathology
6-OHDA unilateral or bilateral stereotaxic injection in MFB in rats or mice	Apormorphine or amphetamine induced rotations in unilateral lesioned model. Reduced locomotion, poor performance of pole test and rotarod in bilateral lesioned model	Severe DA neuron loss and DA deficiency in the nigro-striatal projection in the lesioned side. No inclusion bodies are present
MPTP in C57BL.6 mice by i.p or s.c. or in primates by carotid injection or s.c.	Reduced locomotion, poor performance of pole test and rotarod; decreased stride length and grid. Bradykinesia, rigidity, tremor, dyskinesia, and stereotypy can be seen in primate models	Acute use of MPTP causes reversible DA neuron injury and DA deficiency in the nigro-striatal projection. Chronic use of MPTP may cause long-lasting DA neuron injury and DA deficiency in the nigro-striatal projection. Inclusion bodies are occasionally seen in primate models
Rotenone in rats by i.v., i.p.or oral feeding	Reduced locomotion and poor rotarod performance. Decreased stride length	Wide spread neurodegeneration in midbrain and other regions; LB-like inclusions in nigral DA neurons
Paraquat + Maneb in rodents by i.p. or oral feeding	Reduced locomotion and poor pole test performance	Moderate DA neuron loss and DA deficiency in the nigro-striatal projection; neurons in other regions may be affected
Lactacystin in mice or in rats by stereotaxic injection in MFB	Reduced locomotion; poor performance of pole test and rotarod	Sustained nigral DA neuron degeneration, profound inhibition of proteasomal activity, apoptosis,, elevated ubiquitin conjugates and α-synuclein inclusion
Autophagy atg7 KO mice.	Reduced locomotion, tremulousness, weight loss, and a wide-based and ataxic gait	Wide spread age-related neurodegeneration in CNS with preferably in nigral DA neurons; accumulation of α-synuclein, and ubiquitinated protein aggregates
Wild-type, or A30P, A53T-Syn, Y39C Tg	Slightly increased locomotion. No effect on rotarod performance. Slightly decreased stride length	No obvious loss of nigral DA neurons and striatal DA contents; α-synuclein positive inclusion-like granules can be seen in old animals
Parkin KO, or Q311X Tg	No effect on locomotion, pole test and rotarod performance. No effect on stride length and grid test	No obvious loss of nigral DA neurons and striatal DA contents; no obvious α-synuclein positive inclusion-like granules
LRRK2 KO, or G2019,R1441G Tg	Reduced locomotion. Decreased rearing	No or mild loss of nigral DA neurons and striatal DA contents; no obvious α-synuclein positive inclusions
PINK1 KO	Reduced locomotion. No effect on rotarod performance	No or mild loss of nigral DA neurons and striatal DA contents; no obvious α-synuclein inclusions
DJ1 KO	Reduced locomotion. No effect on rotarod performance. Decreased stride length	No or mild loss of nigral DA neurons and striatal DA contents; no obvious α-synuclein inclusions
Nurr1 KO or condition KO	Reduced locomotion and poor performance of pole and rotarod tests. Increased foot faults in grid test. Decreased rearing	Agenesis of nigral DA neurons and striatal DA contents in general KO mice; progress loss of nigral DA neurons and strital DA contents in condition KO mice; no obvious α-synuclein inclusions
Pitx3-aphakia	Reduced locomotion. Poor performance of pole and rotarod	Progressive loss of nigral DA neurons and striatal DA contents; no obvious α-synuclein inclusions
Mitopark	Slowly decreased locomotion exploratory activity. Tremor and rigidity may present	Intraneuronal inclusions and moderate nigro-striatal DA neuron degeneration
VMAT2-deficient mice	Reduced locomotion. Decreased performance on challenging beam. Decreased stride length	Progressive loss of nigral DA neurons and striatal DA, and α-synuclein accumulation. Olfactory impairment. and depression
NFκB/c-Rel-deficient mice.	Age-dependent deficits in locomotor and gait, bradykinesia, and muscle rigidity	Fibrillary α-synuclein and increased iron deposition in both SN and striatum, reactive microglia, mild nigral DA neuron degeneration

6-OHDA=6-hydroxydopamine; MFB=medial forebrain bundle; MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine; i.p. = intraperitoneally; s.c. = subcutaneously; i.v. = intravenously; Maneb=manganese ethylene-1,2-bisdithiocarbamate; KO=knockout; VMAT2=vesicular monoamine transporter 2; NFκB=nuclear factor kappa b; DA=dopamine; LB=Lewy bodies; CNS=central nervous system; SN=substantia nigra

Table 2 Drugs tested in various animal models of Parkinson's disease (PD)

Drug tested	Administration	Animal model	Motor tests	LIDs	Results of the motor tests	Reference
Levodopa	Oral feed	6-OHDA-lesioned rats	Open field, horizontal grid, cylinder	None	Reduction in ipsilateral turning behavior in open field test	[123]
Levodopa Benserazide	Oral feed	6-OHDA-lesioned rats	Open field, horizontal, grid cylinder	None	Decrease in contralateral forelimb slips on horizontal grid test.	[123]
Levodopa Methyl ester Benserazide	Sustained release microspheres	6-OHDA-lesioned rats	APO-induced rotations, Forepaw stride	None	Reduction in APO-induced rotations and forepaw imbalance	[124]
Rasagiline mesylate	Polylactide coglycolide microspheres	Rotenone-treated Wistar rats	Swim test	CatalepsyAkinesia	Attenuated the catalepsy and akinesia and reversed the latency in swim test	[148]
Resveratrol	Oral feed	HtrA2 knockout PD mice	Modified inverted grid	None	Improved the performance on inverted grid test	[179]
Idebenone	Oral feed	HtrA2 knockout PD mice	Modified inverted grid	None	Delayed the deterioration of motor function on modified inverted grid test	[179]
Baicalein	Oral feed	6-OHDA-lesioned rats				
treated rats	None	Tremor	Ameliorated tremor		Significantly attenuated muscle tremor of PD rats	[153]
Adenosine antagonist: MSX3	Oral feed	L-DOPA-treated mice	Numerous motor activity tests	None	Attenuation in motor activity	[137]
Allosteric modulator of mGlu7 (AMN082)	Oral, feed	Haloperidol- or 6-OHDA-lesioned rats	APO-induced rotations	CatelepsyAkinesia	Reversal of catalepsy, reduction of APO-induced rotations, improved akinesia in bilateral 6-OHDA-lesioned rats	[183]
Allosteric modulator of mGlu4 VU0155041	Oral feed	Haloperidol- or reserpine-treated rats	None	CatalepsyAkinesia	Reduction in the haloperidol-induced catalepsy and reserpine-induced akinesia	[184]
mGlu3 agonists, l-SOP, l-AP4	Oral feed	Reserpine-treated rats	None	Akinesia	Reduction in akinesia	[185]
Meloxicam	Oral feed	MPTP mice	Pole	None	Improved performance on pole test	[177]
Quercetin	Oral feed	MPTP mice	Rota rod	None	Improved balance and coordination	[156]
Rotigotine	Transdermal patch	Several animal models	Various motor	None	Improved motor symptoms	[127]
Ropinirole	Osmotic pumps	MPTP marmoset model	Various motor	Dyskinesia	Decreased dyskinesias and reverse motor deficits	[128]
Monoclonal α-synuclein antibody (9E4)	Infusion	α-synuclein transgenic mice	Water maze	None	Promote α-synuclein clearance	[158]
LRKK2 kinase inhibitors GW5074, and sorafenib	Oral feed	*Caenorhabditis elegans* and *Drosophila*	Locomotion	None	Protect again DA neuron degeneration	[164]
Chaperon activator sodium 4-phenylbutyric acid (phenylbutyrate)	Oral feed	MPTP, α-synuclein mutant mice	Locomotion	None	Reduce DA neuron degeneration, ROS, and inflammation	[174, 175]

LRKK2=leucine-rich repeat kinase 2; 6-OHDA=6-hydroxydopamine; L-DOPA=L-dopamine; MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine; APO=apomorphine; DA=dopamine; ROS=reactive oxygen species

injury, or some other prenatal events may lead to loss of PD-related neurons before birth [9].

The most common motor symptoms associated with PD are resting tremor, rigidity, bradykinesia or slowness of voluntary movement, gait disturbance and postural instability. The non-motor symptoms include hyposmia/anosmia, pain and other sensory abnormalities, gastrointestinal motility disturbances, sleep abnormalities, cardiovascular abnormalities, urinary tract problems, ocular changes, disturbance of sexual activity, autonomic dysfunction, anxiety, depression, dementia, psychosis, and impaired cognition [2].

The most prevalent treatment modality of PD consists of a DA replacement using the DA precursor levodopa. Even though levodopa is considered the gold standard in the treatment of motor symptoms of PD, it is often associated with acute and chronic adverse events, particularly motor fluctuations and dyskinesia [10]. Many other therapeutic options have their own limitations. Therefore, there is a need to develop novel therapeutic strategies. Advances in experimental therapeutics, however, would not be possible without robust investment in preclinical studies, including the use of suitable animal models [11].

There are basically 2 broad categories of animal models used to study mechanisms and treatment of PD: the neurotoxic models and the genetic models that utilize the *in vivo* manipulation of PD-related genes [12–14]. Several other models have been also developed to explore the role of UPS and inflammatory or immune effects. However, there is no model that holistically represents the molecular mechanisms, pathophysiology, progressive nature of the disease, and the preclinical and clinical states of PD [13].

The neurotoxic models appear to be best suited for testing therapeutic interventions aimed at counteracting motor symptoms of PD. There are, however, many limitations to these models. For example, the pathological lesion in the toxic models is usually produced acutely and the resulting phenotype has features of late-stage PD. Furthermore, the neurotoxic animal models do not reproduce the progressive course of PD. However, transgenic or knockout genetic models may better simulate the pathogenic mechanisms of genetic forms of PD, but their pathological and behavioral phenotype is often quite different from the human condition [13]. Other models may be required to study the non-motor aspects of PD [14]. Therefore, the selection of a particular animal model largely depends on the specific objectives and goals of the experiments.

When evaluating the importance of animal models and their relevance to human disease it is essential to ask the following critical questions: 1) Does the DA neuron loss in the animal models adequately recapitulate that of the human disease counterpart?; 2) Are the PD models and control animals used in experiments properly randomized?; 3) Is the sample size adequate to test the hypothesis?; and 4) Are the investigators blinded when making the various behavioral, biochemical and pathological assessments? Unfortunately, answers to these critical questions are often not included in the published articles, which may account for the low replication rates of preclinical and clinical studies [15, 16].

Toxin Models

Animals with toxin-induced neuronal loss are the most widely used animal models of PD. There are 3 types of these toxin models: 1) neurotoxin models; 2) pesticide/herbicide models; and 3) UPS/autophagy inhibition models. In order to induce these toxin models to have clinical phenotypes, over 50 % of the DAergic neurons in the substantia nigra (SN) of the brain should be destroyed.

Neurotoxin Models

6-Hydroxydopamine-Lesioned Model

6-Hydroxydopamine (6-OHDA) is one of the most commonly used neurotoxins in animal models of PD. It is a selective catecholaminergic neurotoxin that was first used to generate lesions in the nigro-striatal DA neurons in rats [17]. 6-OHDA is structurally similar to DA and norepinephrine (NE) and has high affinity for their catecholaminergic transporters like DA transporter (DAT) and NE transporter. Administration of selective noradrenaline reuptake inhibitors, such as dismethylimipramine or imipramine, before 6-OHDA protects the noradrenergic neurons from damage in these animals [18]. DAT facilitates transport of 6-OHDA into DA neurons where it accumulates in cytoplasm and undergoes prompt autooxidation, producing hydrogen peroxide and paraquinone, both of which are highly toxic [12, 13, 19].

As 6-OHDA does not cross the blood–brain barrier (BBB), it is locally injected directly into the SNpc, medial forebrain bundle (MFB), which consists of efferent fibers from nigral neuronal cell bodies to the striatum, or the striatum, where it specifically kills DA and NE neurons [19]. The most common lesion produced by 6-OHDA is via unilateral injection into the rat MFB [17]. Usually a few weeks after 6-OHDA lesion, the rats show spontaneous rotation (turning) [12]. Application of DAergic agonist apomorphine or DA release stimulator amphetamine can induce animal rotation contralateral or ipsilateral to the side of the lesion, respectively [12]. The unilaterally lesioned rats can also display some parkinsonian features, such a shuffling and short-stride gait [12]. After injecting unilaterally into the MFB, 6-OHDA causes marked anterograde degeneration of the nigrostriatal pathway [19, 20]. The degeneration starts first in the tyrosine hydroxylase (TH)-positive (TH^+) SNpc neurons with subsequent loss of TH^+ striatal DAergic terminals, along with associated DA depletion [20]. However, 6-OHDA does not produce LB-like

inclusions in the nigrostriatal pathway, nor does it cause progressive DA neuron degeneration [13].

When injected directly into the striatum to test the retrograde degeneration, the TH^+ striatum terminals die prior to TH^+ neurons in the SNpc, replicating the pathological process of PD in humans [20]. Indeed, there is some evidence suggesting that the initial site of pathology in PD may start from the striatum and that "dying-back" axonopathy results in retrograde degeneration and neuronal loss in SN [21]. The 6-OHDA model results in DA depletion, nigral DA neuron loss, and behavioral deficits, but it does not affect other brain regions, such as olfactory structures, lower brain stem areas, or locus coeruleus [22]. The extent of SNpc damage with striatal injection is less when compared with the MFB injection, and it evolves over a period of 4–6 weeks [22]. Despite its limitations, the 6-OHDA lesion is highly reproducible and has been, therefore, used commonly to study new therapeutic strategies in PD.

1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropiridine-Lesioned Model

Another commonly used neurotoxic model utilizes 1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine (MPTP). In the early 1980s, a group of young drug abusers from northern California developed a parkinsonian syndrome after an inadvertent intravenous injection of a narcotic meperidine analogue [23]. The substance, later identified as MPTP, can rapidly cross BBB and enter the brain, where it is converted by monoamine oxidase B (MAO-B) to its active metabolite, 1-methyl-4-phenylpyridinium ion (MPP^+) [23]. MPP^+ is taken up by DAT into the DA neurons of SNpc, where it inhibits the mitochondrial electron transport chain complex 1 activity, resulting in the release of reactive oxygen species (ROS), as well as reduced adenosine triphosphate production [23, 24]. DA neurons in putamen with a higher DAT/vesicular monoamine transporter 2 (VMAT2) ratio than caudate neurons are more severely affected [25]. MPTP is less toxic to norepinephrinec and serotonergic neurons [24, 25]. The MTPT-induced DAergic neurotoxicity can be blocked by the pretreatment with MAO-B inhibitors (e.g., selegiline or rasagiline) or DAT inhibitor (e.g., difluoropine) [24, 25]. MPTP administration in non-human primates can cause changes in locomotor activity, and in some cases the MPTP-treated primates may show some features of bradykinesia, rigidity, abnormal posture, tremor, motor "freezing", dyskinesia, and stereotypy [25, 26]. These symptoms appear less characteristic in mice [13]. Acute toxic effects of MPTP include sedation and hypothermia [13, 26].

MPTP-induced selective DA neuron toxicity is species-specific and therefore it is usually used to model PD mainly in primates and mice [26–28]. Age and gender may influence the susceptibility of the animals to MPTP [29]. Although MPTP is more often used in mice models than in primates, largely because of lower cost, primate models are preferred when testing drug treatment protocols before human studies since they are more reproducible and better resemble human PD [27–30]. MPTP is mainly administered via systemic route through subcutaneous, intravenous, or intracarotid injections. The major limitation of MPTP models is that they do not reproduce the progressive nature of neurodegeneration and LB pathology, although under certain circumstances, for instance, MPTP application in aging monkeys or slower intoxication in mice may produce LB-like structures in the brain [13, 26].

MPTP is also used to study certain non-motor features of PD [14]. For example, in a marmoset monkey model, MPTP administration manifests conspicuous sleep changes resembling RBD [29]. Chronic low-dose MPTP treatment in macaque monkeys results in poor performance of spatial delayed responses, delayed matching-to-sample, and delayed alternation, object retrieval, and discrimination reversal tasks, as well as a variety of specific impairments of attention and executive functions [30].

One example of the use of the MPTP primate model in predicting the response to therapeutic intervention is the clinical pharmacologic study of safinamide [31]. Although this drug has not yet been approved by regulatory agencies for clinical use, there is growing interest in this drug because of its dual pharmacological action and some encouraging results from early clinical trials. An inhibitor of MAO-B and of glutamate release, safinamide pre-treatment of MPTP-lesioned dyskinetic macaque monkeys has been found to prolong response to levodopa and reduce levodopa-induced dyskinesias (LIDs) in a dose-dependent manner [32]. These effects have been largely reproduced in clinical trials of safinamide in PD [33, 34].

Another example of a primate model used in a study of a novel treatment of PD includes the study of neurturin [35]. Adeno-associated virus 2 (AAV2)-mediated human neurturin (NTN) (AAV2–NTN; also called CERE-120) has been tested in the unilateral MPTP-lesioned rhesus monkeys by injecting it into the striatum and SN [35]. This treatment showed a 80–90 % improvement in motor deficit starting at approximately 4 months after treatment and lasting until the end of the experiment (month 10) [35]. AAV2–NTN significantly preserved nigral neurons and striatal DAergic innervation, and activated phospho-extracellular signal-regulated kinase, involving a trophic factor-initiated molecular cascade [35, 36]. However, in a multicenter, double-blind, sham-surgery controlled trial of AAV2–NTN injected bilaterally into the putamen or putamen plus SN showed no statistically significant change in the primary endpoint (change in motor Unified Parkison's Disease Rating Scale after 12 months) (http://www.ceregene.com/press_052113.asp) [37–39]. This experience underscores the unfortunately common situation when clear benefits

demonstrated in a suitable animal model cannot be reproduced in human clinical trials. Another example is glial cell-derived neurotrophic factor (GDNF), an analogue of NTN. Despite its reported benefits in some clinical trials, GDNF has failed to protect nigral DA neurons against α-synuclein-induced neurodegeneration in animal models [40]. In these *in vivo* studies α-synuclein has been found to block intracellular response to GDNF in DA neurons, accompanied by reduced expression of the transcription factor Nurr1, which normally plays an important role in the cellular defense against α-synuclein toxicity [40].

Pesticide/Herbicide Models

1,1'-Dimethyl-4-4'-Bypiridinium Dichloride-Lesioned Model

1,1'-Dimethyl-4-4'-bypiridinium dichloride (Paraquat; PQ), a nonselective herbicide, with a close structural resemblance to MPP^+ has been suggested as a possible PD-inducing agent [41]. PQ cannot cross the BBB, but it enters the brain through an amino acid transporter called systemic l-amino acid transporter [42]. Chronic administration of PQ in C57BL/6 mice caused significant decrease of locomotor activity [43], and in rats it also caused anxiety-like behavior and a deficit in the sense of smell [44]. The toxicity of PQ is mediated through oxidative stress by redox cycling, with a diaphorase such as nitric oxide synthase, generating ROS [43, 44]. PQ also exerts its deleterious effects by impairing recycling of oxidized glutathione (GSH) to its reduced form, which curtails the efficacy of intracellular antioxidant mechanisms [44]. PQ-induced neurotoxicity does not involve mitochondrial complex 1 blockade because this toxin has low affinity for mitochondrial complex I [45]. The mechanism of PQ on the nigrostriatal DA system and its subsequent effects is somewhat unknown. Several studies demonstrate that systemic administration of PQ to mice may produce impaired motor activity and a dose-dependent degeneration of nigrostriatal DA neurons and loss of striatal TH^+ fibers without a substantial decrease in striatal DA release [45, 46]. PQ in higher doses is transported by DAT and accumulates in DA neurons; it is also transported by organic cationic transporter-3 found in non-DA neurons of SN [47]. One of the advantages using PQ in PD research is its ability to induce the expression and aggregation of α-synuclein and possibly LB-like structures in SNpc DA neurons, which are primarily affected in human PD [48].

Manganese ethylene-1,2-bisdithiocarbamate (Maneb) is a fungicide that inhibits glutamate transport and disrupts DA uptake and release [49]. Chronic systematic use of Maneb alone in rodents causes a mild deficit in open field locomotor activity and coordination performance [50]. However, when co-administered with PQ in mice, it exerts a synergistic effect in motor activity reduction, SNpc DA neuron damage, DAT immunoreactivity reduction, and reactive gliosis [50]. In older mice, concomitant use of Maneb with PQ produced similar results with a greater percentage loss [50].

Rotenone-Lesioned Model

Rotenone is a pesticide that belongs to the rotenoid family of neurotoxins [51]. Highly lipophilic, it easily crosses the BBB and does not depend on DAT to enter DA neurons [51]. After entering the neurons, rotenone blocks the mitochondrial complex I activity, increases ROS, and inhibits proteasome activity generating proteolytic stress [51]. Rotenone decreases the DA and GSH levels, and increases lipid peroxidation in DA neurons, resulting in oxidative damage. Rotenone has been shown to produce cell apoptosis and endoplasmic reticulum stress *in vitro* [52]. *In vivo*, chronic systemic (intravenous) exposure rotenone in rat models induces nigrostriatal DAergic neurodegeneration, LB-like cytoplasmic inclusions in the DA neurons, and parkinsonian features, such as bradykinesia, rigidity, postural instability, unsteady gait, and tremor [51, 52]. Rotenone-treated rats also display an increase in oxidative damage, enhanced iron deposits, and microgliosis [51]. However, systematic administration of rotenone in rats causes high mortality and, somehow, is difficult to replicate. Bilateral stereotaxic injection of rotenone into the MFB of rats causes a depletion of DA in the nigrostriatal system with associated rigidity and decreased motor activity, which can be reversed by levodopa therapy [53]. Rotenone has also been tested in mice through chronic intragastric administration, which is able to induce α-synuclein accumulation in the enteric nervous system, the dorsal motor nucleus of the vagus, the intermediolateral nucleus of the spinal cord, and the SN [54, 55]. The progressive α-synuclein accumulation in this model suggests the possibility of transynaptic transmission of synunclein pathology in the central nervous system [56].

UPS/Autophagy Inhibition Model

UPS is an intracellular mechanism designed to clear aberrant and misfolded proteins from cells [57, 58]. Dysfunction of the UPS in neuronal cells has been proposed as a pathogenic mechanism underlying several neurodegenerative diseases characterized by intra- or extraneuronal protein deposits [57]. UPS inhibitors, such as lactacystin, epoxomicin, MG-132, and and N-[(Phenylmethoxy)carbonyl]-L-isoleucyl-L-α-glutamyl-tert-butyl ester-N-[(1S)-1-formyl-3-methylbutyl]-L-alaninamide (PSI), are naturally occurring substances [58]. Systematic administration of these substances in rodents produces variable DA neuron degeneration, which is difficult to replicate by different laboratories [58]. Inhibition of 26/20S proteasomal degradation by lactacystin, PSI, and MG-132 via microinjection in the nigro-striatal pathway of rodents can lead to the accumulation of α-synuclein in the SN

neurons, and the rodent models display a progressive course and pathological changes reminiscent of PD [57, 58]. In a lactacystin-injected mouse model, DA neurons degenerate preferentially in the SN, accompanied by apoptosis and ubiquitin, and/or α-synuclein-positive aggregates, and focal inflammation [59, 60]. Thus, this model recapitulates several features of PD, rendering it suitable for the study of nigral DA neuron degeneration and for the investigation of potential anti-PD medications [59, 60].

There are few studies concerning the autophagy defect in PD model. Using conditional knockout of autophagy gene *Atg7* in the nigral DA neurons produce the age-related nigrostriatal DA neuron degeneration along with the presence of aggregation of α-synuclein and ubiquitinated proteins, which recapitulate many pathologic features of PD [61].

Genetic Models

Although the majority of PD is sporadic, approximately 20 % of PD cases are familial, and 5 % are caused by autosomal dominant or recessive genetic mutations. At least 18 PD-associated genes or loci have been identified [6], and *SNCA* (α-synuclein), *LRRK2*, *PRKN*, *PINK-1*, *and DJ-1* genetic manipulation models (transgenic mutant or wild-type genes, or knockout endogenous genes) have been generated in mice or in rats [62]. A few more genetic models of PD, such as *GIGYF2*, *HTRA2*, *PLA2G6*, *FBX07*, *VPS35* and *EIF4GI* mutant mice, are under development.

Models of Autosomal Dominant PD

Among the 18 PD-associated genes or loci identified in PD, more than half of them are inherited in an autosomal dominant pattern [6–8]. So far, many genetic manipulations on *SNCA* and *LRRK2* genes have been tried to produce animal models of PD, and almost all of the animal models do not develop obvious clinical and pathological phenotypes [62].

SNCA Gene Model

Isolated point mutations or gene multiplication (duplication and triplication) of the *SNCA* gene are known to cause a rare form of autosomal dominant PD [63]. α-Synuclein is an integral component of LB and glial cytoplasmic inclusions in PD, dementia with LB, and multiple system atrophy—all of which are classified as α-synucleinopathies [64]. α-synuclein can form a complex with the presynaptic human DAT (hDAT) through direct binding to the carboxyl-terminal tail of the hDAT [65]. The α-synuclein–hDAT complex formation facilitates membrane clustering of the DAT, thereby accelerating cellular DA uptake and DA-induced cellular apoptosis [65]. Masliah et al. [66] generated transgenic mice expressing wild-type α-synuclein, and demonstrated α-synuclein and ubiquitin inclusions in the SN, with moderate loss of DA neurons and subsequent motor deficits. Another study reported that A53T mutant α-synuclein transgenic mice may have motor dysfunction and filamentous inclusions that initiate neurodegeneration [67]. Numerous α-synuclein transgenic mice are being used as animal models for PD, although none of them show robust nigrostriatal degeneration [62]. Even with the use of a prion promoter, such α-synuclein transgenic mice show some motor dysfunctions that are responsive to DA, but do not display the characteristic DAergic neurodegeneration of PD [68]. Thy-1 promoter-driven wild-type and mutant α-synuclein transgenic mice, however, can achieve broad neuronal expression in SNpc, cortical and subcortical neurons, olfactory bulb, and locus coeruleus [62, 69]. A moderate but progressive reduction of striatal DA content, decreased number of TH immonoreactive cells in the striatum, bradykinesia, motor dysfunction, and increased susceptibility to MPTP toxicity have been noted in this model [69]. Transgenic mice with truncated form of α-synuclein show some loss of nigral DA neurons, decrease in striatal DA, and reduced motor activity that can be reversed with levodopa. Unfortunately, this model does not show age-related progressive neurodegeneration [68, 70].

Several studies have demonstrated that α-synuclein may be transmissible in a prion-like fashion [71]. Young α-synuclein transgenic mice when inoculated intracerebrally with either the brain tissue derived from older transgenic mice with α-synuclein pathology or aggregated recombinant human α-synuclein display LB-like inclusions, and spread of pathological α-synuclein to areas distant from the site of inoculation [55]. This model may help understand the progression of PD from the periphery (via the olfactory bulb or the medula) and its caudal-rostral evolution of neurodegeneration [56]. More recent studies have shown that small fibrils of certain strains of α-synuclein initially seed and then gradually aggregate in distal fibers before they propagate into the soma of neurons and transynaptically to other neurons. These "seeded" mice provide the best models of progressive sporadic pathology seen in human PD (Lee, personal communication).

LRRK2 Gene Model

Mutations in *LRRK2* are known to cause a late-onset autosomal dominant inherited form of PD [72]. The toxicity of mutant *LRRK2* may be related to its kinase activity and guanosine triphosphate binding activity [73, 74]. Many point mutations of the *LRRK2* gene associated with PD have been identified [6]. Among these, G2019S, a point mutation in the kinase domain, is the most common one, whereas R1441C; the second most common one is a mutation in the guanosine triphosphatase domain [75]. Several lines of evidence indicate that *LRRK2* and *α-synuclein* may interact. Thus, overexpression of *LRRK2* can increase the neuropathologic abnormalities

and α-synuclein accumulation in A53T α-synuclein transgenic mice, whereas knockout of *LRRK2* decreases these abnormalities [76].

Overexpression of wild-type *LRRK2* in transgenic mice causes an enhancement of DA release from the striatum and motor hyperactivity owing to this excess DA. On the contrary, overexpression of mutant $LRRK2^{G2019S}$ mice decreases the release and uptake of DA, thereby suggesting a role for *LRRK2* in DA transmission [77]. Transgenic mice overexpressing mutant $LRRK2^{R1441G}$ show progressive, age-dependent motor deficits that progress to immobility that can be reversed by levodopa or apomorphine, similar to akinesia of PD [78]. However, bacterial artificial chromosome transgenic mice overexpressing the wild-type or mutated *LRRK2* (R1441G, G2019S) have minimal evidence of neurodegeneration and fail to induce neuronal death [77, 78]. *LRRK2* knockout mice do not exhibit any significant neuropathological abnormalities or increased susceptibility to MPTP [79].

Drosophila expressing the $LRRK2^{G2019S}$ mutation has been found to have visual loss associated with degeneration of the retina [80]. As fly photoreceptors are histaminergic, rather than DAergic, the transgene is expressed in DAergic neurons, which suggests that the loss of function and neuronal degeneration require cell–cell transmission, suggesting a spread of degenerative process similar to what has been suggested for α-synuclein, although this protein is not expressed in *Drosophila* [56, 71].

Overall, *LRRK2* mice models depict mild functional disruption of the nigrostriatal DA neurons involved in PD [62]. It is therefore unlikely that the various *LRRK2* models will be valuable in testing the therapeutic neuroprotective agents applicable to PD.

Models of Autosomal Recessive PD

Mutations in the *PRKN* gene account for more than 50 % of early-onset familial PD cases and at least 20 % of early onset sporadic PD, also referred to as PARK2 PD [81]. Mutations in *DJ-1*, *PINK1*, *FBX07*, *ATP13A2*, *and PLA2G6* are less common forms of autosomal recessive PD [6]. So far, only *PRKN*, *DJ-1*, and *PINK1* genetic mice models are available for the study of PD.

PRKN Gene Model

Mutations in the *PRKN* gene are linked to autosomal recessive early-onset PD [82]. Patients with *PRKN* gene mutations usually have resting tremor, particularly involving the legs; bradykinesia and many other motor abnormalities that usually respond to levodopa therapy; and pathological neurodegeneration of nigrostriatal DA neurons without classic LB pathology [83]. Parkin is a 465-amino acid protein that functions as an E3 ubiquitin ligase as a part of ubiquitin proteasome system [84]. *PARK2* knockout mice are typically produced by deletion at exon 3, exon 7,or exon 2 in the *PRKN* gene [85–87]. *PRKN* exon 3 deleted knockout mice exhibit subtle nigrostriatal deficits in the absence of any evident nigrostriatal DA neuron loss. They may have increased extracellular striatal DA, reduced synaptic excitability in striatal medium-sized spiny neurons, and typical progressive sensorimotor and behavioral impairments that are typically seen in disorders with demonstrated pathologies in the nigrostriatal pathway[85]. This mouse model also has increased glutamate levels in the striatum and mild mitochondrial dysfunction, reduced antioxidant capacity, and increased oxidative damage in the absence of nigral degeneration [88]. Exon 7-annulled *PRKN* mice display subtle loss of catacholaminergic neurons in the locus coeruleus, and reduced norepinephrine levels in the olfactory bulb and spinal cord, without loss of nigral DA neurons [86]. Exon 2-disrupted *PRKN*-null mice show no loss of DA neurons in the SN or in the locus coeruleus, and no detectable motor or cognitive deficits [87].

DJ-1 Gene Model

DJ-1 mutations are linked to another autosomal recessive early onset PD [89]. DJ-1 is a multifunctional protein, which is localized to the cytoplasm, mitochondria, and the intermembrane space [90]. Down-regulation of *DJ-1* has been shown to increase the susceptibility to oxidative stress and proteasome inhibition [91, 92].DJ-1 also acts as a redox-dependent chaperone molecule and inhibits α-synuclein aggregation [93]. Over-expression of *DJ-1* protects against MPTP-induced neurodegeneration, indicating that the augmented expression of DJ-1 in response to the toxins is probably a helpful mechanism in fighting against the increased oxidative stress [94, 95]. Knockout models of *DJ-1* mice with a targeted deletion of exon 2 or insertion of a premature stop codon in exon 1 are more sensitive to toxins and oxidative stress. There is no loss of nigral DA neurons and no change of the DA level in *DJ-1* KO mice. However, there is a reduction in the release of evoked DA in the striatum, decreased responsiveness to D2 autoreceptor stimulation by nigral neurons, decreased locomotor activity, and increased vulnerability to PQ intoxication [96]. Another *DJ-1* knockout mouse model produced by insertion of a premature stop codon in exon 1 shows normal nigral DA neurons and DA levels [97]. However, these mice display hypoactivity upon amphetamine challenge and nigral DA loss upon MPTP challenge, and the cortical neurons in the mice have increased susceptibility to oxidative stress [97].

PINK1 Gene Model

Mutations in *PINK1* cause another autosomal recessive form of PD [6]. *PINK1* knockout mice do not exhibit major abnormalities in the DA neurons or striatal DA levels; only mild

mitochondrial and nigrostriatal neurotransmission deficits may be present, associated with increased susceptibility to oxidative stress and ROS production [62, 98]. *PINK1*^{G309D} transgenic mice have an age-dependent moderate reduction of DA levels accompanied by low locomotor activity [62, 98].

Other Genetic Models

Nurr1- and Pitx3-Deficient Model

Nurr1 and Pitx3 are transcription factors important for the development and maintenance of the nigro-striatal system [9, 99, 100]. *Nurr1* conditional knockout mice show progressive loss of DA neurons without LB formation [101]. Pitx3 is highly restricted and constitutively expressed in the SNc and ventral tegmental area. *Pitx3* gene mutation in Aphakia mice causes complete loss of SNc DA neurons and absence of projection to caudate putamen [100]. Aged Aphakia mice also display DA neurons loss in ventral tegmental area and altered locomotor activity [100].

MitoPark Mouse

Conditional disruption of the gene for mitochondrial transcription factor A in DA neurons named *MitoPark* results in a parkinsonism phenotype in mice with adult-onset of slowly progressive impairment of motor function, and intraneuronal inclusions and DA neuron degeneration [102]. This genetic model may represent a valuable tool for the development and screening of new therapeutic strategies in PD [12, 102].

VMAT2-Deficient Model

VMAT2 is essential for monoamine, particularly DA storage, and plays a role in glutamate release in presynaptic neurons. *VMAT2*-deficient mice display progressive loss of nigral DA cells and striatal DA, levodopa-responsive motor deficits, and α-synuclein accumulation [103]. This mouse model also has deficits in olfactory discrimination, delayed gastric emptying, altered sleep latency, anxiety-like behavior, and age-dependent depressive behavior [103].

NFκB/c-Rel-Deficient Mice

Mice deficient of the c-Rel factor exhibits a marked immunoreactivity for fibrillary α-synuclein in the SNpc, as well as increased expression of divalent metal transporter 1 and iron staining in both SNpc and striatum [104]. Aged c-rel($^{-/-}$) mouse brain is characterized by increased microglial reactivity in the basal ganglia. In addition, c-rel($^{-/-}$) mice show age-dependent deficits in locomotor and total activity, and various gait-related deficits during a catwalk analysis that is reminiscent of bradykinesia and muscle rigidity [104].

Testing Anti-Parkinsonian Strategies in Animal Models

Although both the toxic and genetic models are widely used to study the pathogenesis of PD. The toxic models are mostly used to test drugs for the treatment of various PD-related motor, non-motor symptoms, and neurodegeneration, as well as side effects, such as LIDs.

Tests of Motor Symptoms

Animal models have been used to test novel modalities designed to primarily improve the motor dysfunction in PD. In rodents, motor function is usually assessed by measuring the following.

General Activity

1) Open field test for locomotion and 2) swim test in a water basin to observe the locomotive activity in the water [105].

Co-ordination

1) Rotarod test to observe motor co-ordination, in which a rat or mouse is placed on a rotating rod, and the time for which the animal can hold before falling down is measured [105]. 2) Cylinder test to analyze the loss of voluntary forelimb movement. This is especially useful in evaluating unilateral 6-OHDA-injected rats or mice, and also in some genetic models. It is also used to rate the LIDs in DA-depleted mice [105, 106]. 3) Pole test to observe the time taken by the rodent models placed on the top of a vertical pole to reach the floor is used to assess the motor activity [106]. 4) Challenging beam traversal test to detect subtle deficits in motor skills, motor coordination, and balance [106].

Gait Performance

1) Forepaw stride length test is used to analyze the gait abnormalities in rodents as they walk in a straight line on a white paper with their feet covered with black ink [106]. 2) A grid test is used to assess the coordination in rodents by measuring the number of footslips of a given limb during free exploration of the grid [106].

Tests of Non-motor Symptoms

Sleep Disturbances

Various sleep disturbances such as RBD, insomnia, hypersomnia, and excessive daytime sleep are evident in patients with PD, even appear before the onset of any motor symptom [107]. The various REM-related sleep problems have been replicated in MPTP-treated marmosets, providing support for

the notion that they are caused by disturbances in DA transmission [29]. Hypersomnolent behavior with an increase in the duration and the number of spells of REM sleep and non-REM sleep suggest that an inability to maintain wakefulness have been reproduced in cycad-fed rats [108]. This excessive daytime sleepiness has been attributed to dysregulation of orexin neurons as the cycad-fed rats demonstrate loss of orexin cells in the hypothalamus.

Gastrointestinal Dysfunction

Disturbances in the gastrointestinal (GI) tract are among the common non-motor symptoms observed in patients with in pre-motor stages [109]. Upper GI tract symptoms usually include drooling, dysphagia, delayed gastric emptying, and gastric retention [110]. Lower GI tract symptoms include constipation and defecator dysfunction [109]. Several animal models including MPTP-treated mice, and 6-OHDA-lesioned and rotenone-treated rats, display a low propulsive motility and constipation [111, 112]. In a rabbit model using anticholinergic drug biperidine to resembles lowness of gastrointestinal motility in PD [113]. Simultaneous use of fiber therapy with plantago ovata husk in this rabbit model increases the stool frequency, improves the levodopa pharmacokinetics, and also delays the onset of LIDs [113].

Urinary Tract Dysfunction

The exact mechanism of neuro-urological dysfunction in PD is not known, but it is well recognized that α-synuclein aggregates in the sacral spinal cord, pelvic plexus, and genitourinary tract, and may contribute to symptoms in PD [114]. Urinary tract dysfunction can be tested in animal models by demonstrating evidence of parasympathetic and somatic dysfunction, manifested by reduced bladder capacity, external sphincter relaxation, detrusor weakness, and urethral obstruction [115]. In a study of cats, it is found that stimulation of subthalamic nucleus can manifest inhibitory effects on the micturition reflex [116]. In another study, conducted on MPTP-treated mini-pigs, deep brain stimulation improves the urinary storage and voiding function [117].

Neuropsychological Dysfunction

Depression, one of the most common neurological non-motor symptoms in PD, is tested in rodent models by using forced swim test, tail suspension test, and learned helplessness [107]. Data from animal models and human studies have provided convincing evidence that D2/D3 agonists have antidepressant effect [118, 119]. Non-ergot DA agonist ropinirole demonstrates antidepressant effects when evaluated in acute and chronic behavioral PD models of depression in rats [119]. Chronic use of selective serotonin reuptake inhibitors, such as fluoxetine, has been found to increase the neurogenesis in the hippocampus in a transgenic α-synuclein mouse model of PD [120].

6-OHDA injection into SNpc of rat results in memory and other cognitive deficits, which can be used as possible model for either dementia with LB or PD with dementia [121]. Nicotine administration in these rats showed a convincing improvement in the short-term memory, as examined on the Y-maze task and the shuttle-box task having a decreased number of escape failures, and an increased number of conditioned avoidance responses [121]. In a similar study, pergolide, a DA agonist, improves spatial memory in a rat model of PD [122].

Recent DAergic Drug Studies on Animal Models of PD

Intranasal Levodopa

Certain motor tests like turning behavior in an open field, foot slips on a horizontal grid, and postural motor asymmetry in a cylinder may be assessed after intranasal levodopa administration with and without benserazide in a unilateral 6-OHDA-lesioned rat model [123]. Intranasal levodopa treatment reduces ipsilateral turning, and contralateral forelimb slips on the grid [123]. These results suggest that intranasal levodopa can bypass the BBB and attenuate the motor impairments in the parkinsonian 6-OHDA-lesioned rat model.

Sustained-Release Formulation of Levodopa Methyl Ester/Benserazide

When administered in the form of microspheres into 6-OHDA-lesioned rat model, levodopa methyl ester/benserazide achieves sustained release and markedly attenuates apomorphine-induced rotations and rectifies the imbalance steps of the parkinsonian rats [124].

Transdermal Rotigotine Patch

Non-ergot DA agonist rotigotine can be used as a single drug or in combination with levodopa [125]. Continuous transderma delivery of rotigotine has been shown to provide "true" constant DAergic stimulation in MPTP animal model of PD [126]. Rotigotine has been found to be effective in early, as well as advanced PD, to treat early morning and nocturnal motor symptoms, and also in non-motor symptoms such as sleep disturbances, depression, and pain [127].

Continuous Subcutaneous Infusion of Ropinirole via Osmotic Minipumps

Ropinirole is a long-acting, non-ergot DA agonist that has a potential to provide more continuous DAergic stimulation [10]. Ropinirole continuous infusion with subcutaneous administration in MPTP-treated marmoset can reverse motor

deficits and cause less dyskinesia when compared with the orally administered form [128].

Therapeutic Strategies for LIDs in Animal Models of PD

Chronic administration of levodopa is often compromised by numerous side effects, such as LIDs in PD patients [10]. Modulation of DA, glutamate,adenosine, and other systems has been explored in various animal models of LIDs [129–145].

DA Receptor Antagonists

To address the question whether inhibition of various DA receptors can be used to treat LIDs, selective D1, D2, and D3 DA receptor antagonists have been tested in 6-OHDA-lesioned rat model with LIDs and found that these antagonists are able to inhibit the LIDs without disrupting the therapeutic potential of levodopa [129]. This result suggests that the anti-parkinsonian effects of levodopa and its dyskinetic side effects are mediated through different DA pathways.

N-Methyl-D-Aspartate Receptor Antagonists

Mixed *N*-methyl-D-aspartate (NMDA) receptor antagonist and serotonin agonist amantadine and dextromethorphan have proven to be effective in attenuating LIDs in PD patients and LIDs in 6-OHDA rat model [130, 131]. However, pure NMDA agonists like dizocilpine (MK-801) show no effect on suppressing LIDs in low doses when used in a parkinsonian rat model [131]. But when used in high doses, they reduce the LIDs and also suppress levodopa-induced contralateral rotations [131]. In a clinical trial conducted on PD patients, the use of NMDA receptor 2B selective NMDA glutamate antagonist CP-101,606 improves LIDs, but left patients with side effects, such as dose-dependent dissociation and amnesia [130].

AMPA Receptor Antagonists

Selective AMPA antagonist GYKI-47261 has proven efficacious in the treatment of LIDs in rat model, particularly when combined with NMDA antagonists [132]. AMPA and NMDA antagonists exhibit greater potential in alleviating LIDs when used in combination than when administered individually [132].

Metabotropic Glutamate Receptor Modulators

Metabotropic glutamate receptors 5 (mGluR5), found in the basal ganglia, amygdala, hippocampus, peripheral sensory nerves, and dorsal horn of the spinal cord, have been postulated to mediate control of movements, emotion, learning, and nociception. MRZ-8676 (6,6-dimethyl-2-phenylethynyl-7,8-dihydro-6H-quinolin-5-one), a novel mGluR5 modulator, has been found to have high efficacy in a rat model of LIDs without any detrimental effects on motor performance, as determined by open field and rotarod tests [133]. Other mGluR5 inhibitors, such as AFQ056 and dipraglurant, have been found in animal models to improve LIDs, but it is not clear whether these findings will translate into similar improvement in patients with PD [11, 134].

Adenosine A (A2A) Receptor Antagonists

Results from animal models suggest that adenosine A (A2A) receptor activity contributes to motor deficits in PD [135]. A2A receptors co-localize with striatal D2 receptors on GABAergic medium spiny neurons which project via the "indirect" striatopallidal pathway to the GPe; A2A receptor activity is increased in the putamen of PD patients with LIDs [135]. Application of A2A receptor antagonists *in vivo* can reverse parkinsonian features, improve levodopa-related complications, and even may have neuroprotective effects, but the clinical results are variable [135, 136]. While some A2A receptor antagonists such as istradefylline (KW-6002) and tozadenant [11] have shown benefit to motor fluctuations or LIDs in clinical trials of PD patients, other A2A antagonists, such as preladenant, have demonstrated only minimal or no improvement (http://www.dailyfinance.com/2013/05/23/merck-provides-update-on-phase-iii-clinical-progra/). Chronic administration of A2A receptor antagonist MSX-3 has provided motor benefits in MitoPark mice [137].

Adrenoceptor Antagonists

In 6-OHDA induced parkinsonian rat model, selective α1 adrenoceptor antagonist HEAT, the α2 adrenoceptor antagonist idazoxan, and the nonselective ß1/ß 2 adrenoceptor antagonist propranolol attenuate LIDs without affecting the normal locomotion of the rats in the open field, indicating that the antidyskinetic potential is not due to reduced motor function [138].

5-Hydroxytryptamine Receptor Agonists

5-Hydroxytryptamine receptor agonists have been shown to potentiate levodopa therapy by accentuating its motor effects and suppressing LIDs in a 6-OHDA-lesioned rat model [139].

Nitric Oxide Synthase Inhibitors

Daily use of levodopa manifests some changes in signaling molecules, including ΔFosB, phospho-DARPP32, and phosoho-GluA1AMPA receptor subunits, and also increases nitric oxide production in the striatum [140]. Using unilateral 6-OHDA lesioned rats to examine the effect of nitric oxide synthase (NOS) inhibitors in preventing LIDs, the

nonselective NOS inhibitor, N(G)-nitro-l-arginine methyl ester, and nNOS inhibitor 7-nitroindazole have been found to ameliorate the development of LIDs, but the inducible NOS inhibitor aminoguanidine does not show such effect [140].

Cyclin-Dependent Kinase 5 Antagonists

Cyclin-dependent kinase 5 (Cdk5) has been implicated in the pathogenesis of LIDs, which is known to increase the expression of Cdk5 receptor [140]. To this effect, the Cdk5 inhibitor roscovitine has been tested in 6-OHDA-lesioned rat model for its efficacy against LIDs and found that roscovotine can reduce the apomorphine-induced rotations in PD rats, but fails to decrease LIDs [141].

δ-Opioid Receptor Antagonists

Stimulation of striatal δ-opioid receptors that are positioned on the glutamatergic corticostriatal projection releases glutamate and DA, which may cause LIDs [142]. Administration of the selective δ-opioid receptor antagonist naltrindole in hemiparkinsonian rats has reduced the LIDs, and the use of the selective δ-opioid receptor agonist [D-Pen (2), D-Pen (5)]-enkephalin has enhanced LIDs, indicating the beneficial role of δ-opioid receptor antagonists in the treatment of LIDs [142].

Studies of Neuroprotective and Disease-modifying Strategies on Animal Models of PD

Drugs Protective Against Oxidative Stress

There are many drugs that have been tested in animal models as potentially exerting neuroprotective effects through their antioxidant properties. For example, by blocking the generation of ROS, minocycline has been found to prolong the survival of a *Drosophila* model of PD [143]. Another example is lycopene, a potent antioxidant used in cancer prevention, which has been found to protect against oxidative stress through elevating the levels of antioxidants superoxide dismutase and GSH in rotenone-treated rats [144]. Other examples include centrophenoxine, which protects against rotenone-induced motor dysfunction, attenuates oxidative stress, and enhances the activity of catalase and superoxide dismutase in the rat model of PD [145], and gallic acid, which is a potent antioxidant and free radical scavenger, and is shown to improve motor function in 6-OHDA-lesioned rats [146]. Finally, the green tea extract polyphenol, a potent inhibitor of the ROS–NO pathway, has been found to exhibit protective effects against 6-OHDA-induced nigral injury in rat model of PD [147].

Rasagiline Mesylate

Rotenone-treated Wistar rats show PD-like symptoms, such as akinesia [148]. The application of rasagiline mesylate, especially when used in the form of poly lactide-co-glycolide microspheres rather than a solution, attenuates akinesia (and catalepsy) and improves swim tests in the rotenone-injected rat model [148]. An *in vivo* model in which we produced nigrostriatal DAergic denervation by injecting a UPS inhibitor lactacystin into the MFB of mice showed that administration of both selegiline and rasagiline reduces the loss of DA neurons, striatal DA levels, and B-cell lymphoma-2 protein levels, but the effects are much more robust with rasagiline than with selegiline [149]. Another mechanism by which rasagiline could exert neuroprotective effects is through inhibiting the MAO metabolite of DA, 3,4-dihydroxyphenylacetaldehyde (DOPAL) that has been found to facilitate α-synuclein aggregation *in vitro* and *in vivo* models, and DOPAL-induced DA neuron loss and accumulation of high molecular weight oligomers of α-synuclein [150]. Thus, rasagiline, in addition to its irreversible MAO B inhibition and potential anti-apoptotic effects, may have additional neuroprotective effects in PD by preventing the formation of the endogenous neurotoxin DOPAL [151].

GSH

Intravenous GSH is one of the most controversial anti-PD treatments [152]. In a *Drosophila* model, supplementing glutathione S-transferase omega, which is down-regulated in parkin mutants, can protect DA neurons via the regulation of mitochondrial adenosine triphosphate synthase activity [153].

Mitochondrial Antioxidant Properties

Baicalein, a flavonoid isolated from the roots of scutellaria baicalensis, is known to modulate the γ-aminobutyric acid type A receptor and, when tested in 6-OHDA-lesioned rats, it markedly reduced tremor [154]. It also reduces the cytochrome oxidase subunit I mRNA expression in the subthalamic nucleus and attenuates the intracellular Ca^{2+} increase induced by glutamate. When baicalein is used in isolated rat brain mitochondria pre-treated with rotenone, it reduces ROS production, and halts adenosine triphosphate deficiency and mitochondrial swelling, as well as boosting mitochondrial respiration, showing its potent mitochondrial antioxidant properties [154]. Diapocynin (200 mg/kg, three times per week, intraperitoneally), a proposed nicotinamide adenine dinucleotide phosphate oxidase inhibitor improves the performance on pole and rotor-rod in the $LRRK2^{R1441G}$ mice, demonstrating that diapocynin is a viable agent for the protection of neurobehavioral function [155]. The bioflavinoid antioxidant quercetin has been tested

in MPTP-treated mice, showing significant improvement in balance and coordination [156]. Mitochondrial complex I and complex IV activity enhancers, such as near infrared light, have been tested as a putative neuroprotective strategy in α-synuclein transgenic mice [157].

Drugs that Prevent α-Synuclein Accumulation

Passive immunization using monoclonal α-synuclein antibody (9E4) against the C-terminus of α-synuclein crosses the BBB and binds to the α-synuclein-aggregated cells and augments their clearance through the lysosomal pathway [56, 158]. Thus, passive immunization may have disease-modifying effects in α-synucleinopathies related to PD, dementia with LB, and multiple system atrophy [56, 157]. Lithium also has been shown to exert neuroprotective effects by preventing oxidative stress-induced protein aggregation in α-synuclein transgenic mice [159]. Propyl endopeptidase induces neuronal damage by augmenting the aggregation of α-synuclein [160]. The propyl endopeptidase inhibitor, KYP-2047, can attenuate α-synuclein aggregation in a transgenic mouse strain [160]. Administration of copper (II)-diacetyl-bis(N(4))-methylthiosemicarbazone in several PD animal models can improve the motor and cognitive deficits, and attenuate nigral DA neuronal loss, possibly by inhibiting the formation of nitrated α-synuclein intraneuronal inclusions [161]. Phosphoprotein phosphatase 2A (PP2A) dephosphorylates α-synuclein at serine 129, and this dephosphorylation is increased by carboxyl methylation of the catalytic C subunit of PP2A [162]. By using eicosanoyl-5-hydroxytryptamide, a PP2A methylation enhancer, α-synuclein accumulation in mouse brain is markedly attenuated [162].

Recently, Stefanova et al. [163] reported that mannitol, a Food and Drug Administration-approved diuretic drug used in the treatment of brain edema, interferes with aggregation of α-synuclein in both *in vitro* and *in vivo* models. In the mThy1-human α-synuclein transgenic mouse model, application of mannitol can result in a decrease in α-synuclein accumulation in several brain regions, suggesting that mannitol promotes α-synuclein clearance in cell bodies [163].

LRRK2 Kinase Inhibitors

Several LRRK2 kinase inhibitors, including CZC-25146, GW5074, and sorafenib, have been tested in rodents, as well as in *Caenorhabditis elegans* and *Drosophila* models, and have been shown to protect against $LRRK2^{G2019S}$ induced neurodegeneration [164]. These findings indicate that increased kinase activity of LRRK2 is neurotoxic and that inhibition of LRRK2 activity can have a disease-modifying effect [164].

Toll-like Receptors

Toll-like receptors (TLRs) support innate immunity, and their loss may play a role in the pathogenesis of α-synucleinopathies [165]. Deletion of TLR4 in α-synuclein transgenic mouse model enhances motor disability and exaggerates the loss of nigrostriatal DA neurons [165]. In contrast, TLR4 promotes α-synuclein clearance and improves the survival of nigrostriatal DA neurons, thus providing a protective role in PD [165].

Nurr1 Activator

Nurr1 is a member of the orphan nuclear hormone receptors family, which is critical for midbrain DA neurons differentiation and survival [9, 99]. Nurr1 has been shown to regulate the expression and function of aromatic amino acid decarboxylase, TH, and DAT [99]. *Nurr1* is a potential susceptibility gene for PD [166]. All these observations led to the hypothesis that activating Nurr1 in degenerating DA neurons might delay or modify the disease progression [167]. A synthetic low molecular weight Nurr1 activator named SH1, which increases the transcription of Nurr1, has been tested in a lactacystin-induced nigro-striatal degeneration model in mice [60]. Chronic use of SH1 in a UPS-impaired mouse model can significantly improve locomotion and coordination, attenuate nigro-striatal DA neuron loss and DA content reduction, increase DAT and VAMT2 levels, and alleviate microglial activation [60]. These results suggest that the Nurr1 activator may be able to modify the disease course of PD [60].

Wnts Signaling

Wnts are a family of secreted proteins that regulate multiple steps of neural development and stem cell differentiation [168]. Wnt1 and Wnt5a have been found to regulate midbrain DA neuron development involving Nurr1, Lmx1a, and Ngn2 pathways [168]. Activation of Wnt1 and Wnt5 may improve the generation and differentiation of midbrain DA neurons from neural and embryonic stem cells, suggesting that a Wnts signaling modifier can be used for the development of stem cell-based therapies for PD [168]. In PD, neurogenesis is impaired in the subventricular zone of human and animal models of PD [169]. Use of Wnt/ß-catenin signaling with RNA interference-mediated GSK-3 knockdown can reverse MPTP-induced neurogenic impairment [169]. Collectively, these results suggest the possibility of modulating Wnt/ß-catenin signaling to achieve the DAergic neuroprotection.

Drugs Helpful in Neovascularisation

Angiogenin, which promotes neovascularization, is noted to be markedly reduced in a transgenic α-synuclein mouse

model of PD [170]. This drug has been shown to be neuroprotective against MPP^+- and rotenone-induced cellular models of PD [170].

Anti-apoptotic

Melatonin, a major secretary product of the pineal gland, may offer protection against rotenone-induced cell death by inhibiting Bax expression and by preventing the release of omi into the cytoplasm [171]. Melatonin is also reported to play a protective role against the rotenone-induced autophagy in the PD model [171].

Chaperon Activators

Sirtuins (SIRT) are nicotinamide adenine dinucleotide (+)-dependent protein deacetylases that may have an anti-aging effect [172]. In an A53T mutant α-synuclein transgenic mouse model, overexpression of SIRT1 increases the life span of mouse and decreases the accumulation of α-synuclein in their brains, while knockout of *SIRT1* causes the reverse effect [172]. SIRT1 shows this effect by deacetylating heat shock factor 1 and increasing the heat shock promoter 70 RNA and protein levels [173]. SIRT1 responds to α-synuclein induced stress by activating molecular chaperones and contributing to neuroprotection in PD [172]. Sodium 4-phenylbutyric acid, a chemical chaperone mimic, attenuates the pathogenic potency in human $\alpha\text{-synuclein}^{A30P+A53T}$ transgenic mice through the anti-neuroinflammatory and antioxidant activities [174, 175].

Anti-microglial Activation and Anti-inflammation Drugs

Central infusion of granulocyte macrophage colony stimulating factor into the SN or its systemic administration prevents the loss of SNpc DA neurons against PQ and/or LPS-induced neurotoxicity [176]. Riluzole application in a 6-OHDA lesioned rat model shows considerable reduction in DAergic neurodegeneration in SNpc, attenuation of amphetamine induced rotations, and inhibition of reactive astrocytosis [177]. Meloxicam, an oxicam non-steroidal anti-inflammatory drug has been tested in MPTP mouse model of PD, showing the improvement of motor function [178].

Increased Expression of VMAT2

3-Methyl-1-phenyl-2-pyrazolin-5-one (edaravone), a free radical scavenger, has demonstrated its neuroprotective effect in a chronic rotenone rat model by inhibiting ROS and apoptotic promoter Bax expression, and by enhancing the expression of VMAT2 [179]. It obliterates rotenone-induced catalepsy, mitochondrial damage, and DA neuron degeneration in rotenone-treated rats [179].

Resveratrol and Idebenone

Found to activate the AMPK/SIRT1/autophagy pathway in cellular models of PD [172], reseveratrol and idebenone have been shown to increase longevity and delay age-related deterioration of motor functions in HtrA2 knockout PD mice [180].

Nicotine, Lycopene, Centrophenoxine, Pioglitazone, and Rotenoic Acid

Nicotine, lycopene, centrophenoxine, pioglitazone, and rotenoic acid have been shown to ameliorate the motor deficits induced in a rotenone-lesioned rat model [121, 144, 181, 182].

Conclusions

Nonhuman models of PD are crucial for better understanding of the pathogenesis of neurodegenerative disorders and for the development of new therapeutic modalities. There are both toxic and genetic animal models, each with its own merits and limitations. Although the studies of the various PD animal models provide new insights into pathogenesis and treatment of PD, they do not exactly reproduce the human disease; therefore, findings from animal studies may not be fully generalizable. For example, most neuroprotective drugs that show robust improvement effects in the current animal models have failed to be validated in clinical trials. Future models should involve a combination of neurotoxin and genetic animal models in an attempt to mimic the genetic-environmental pathogenesis, presumed to cause the progressive neurodegeneration associated with PD.

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