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REVIEW —*Current Perspective*—

The Parkinsonian Models: Invertebrates to Mammals

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ABSTRACT—In contrast to Alzheimer's disease, effective therapeutic options are available for Parkinson's disease. Therapy of dopamine replacement such as levodopa improves the symptoms of this disease, but does not inhibit neurodegeneration in the substantia nigra. Numerous studies have suggested that endogenous and environmental neurotoxins, and oxidative stress may participate in this disease, but the detailed mechanisms are still unclear. Recent genetic studies in familial Parkinson's disease and parkinsonism show several gene mutations. This new information regarding pathogenesis offers novel prospects for therapy. To develop novel neuroprotective drugs, it is necessary to have a model for each type of parkinsonism. This review summarizes current findings regarding parkinsonian models in vertebrates and invertebrates and discusses their value.

Keywords: Parkinsonian model, MPTP, Gene knockout mice, Transgenic animal, Invertebrate

1. Introduction

Parkinson's disease (PD), an age-related neurodegenerative disorder, was originally described by James Parkinson in 1817 (1 – 3). The clinical features of PD consist of resting tremor, cogwheel rigidity, bradykinesia and loss of postural reflex. The pathologic hallmarks are loss of dopamine (DA) neurons and the formation of Lewy bodies (LBs), which are found in the remaining neuronal cytoplasm in the substantia nigra. Recent studies on PD have been inspired by the discovery of a DA neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is a by-product of the synthetic heroin 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP, a meperidine analog). Exposure to MPTP rapidly causes parkinsonism in humans (4, 5). Although the age of onset in the sporadic PD is usually older, recent findings have shown a young and/or juvenile age of onset in several cases of parkinsonism. PD is always sporadic (about 95%), and only fewer patients are familial PD or parkinsonism. Parkinsonian symptoms are found in many disorders such as dementia with LB [DLB, also known as diffuse LB disease (DLBD)], autosomal recessive juvenile parkinsonism (AR-JP), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), hereditary progressive dystonia [HPD, also known as dopa-responsive dystonia (DRD) or Segawa's disease], pure akinesia, multiple system atrophy (including striatonigral degeneration, sporadic olivopontocerebellar atrophy and Shy-Drager syndrome), progressive supranuclear palsy, structural lesions (due to infarct, tumor or hydrocephalus), brain injury (including encephalitis or punch-drunk encephalopathy), treatment with multiple drugs (to block D_2-receptors), poisoning by carbon monoxide or manganese, etc., suggesting that the parkinsonism can have several causes. Several gene mutations have also been identified as possible causes such as mutations of the α-synuclein, parkin, tau, ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1) and GTP cyclohydrolase I (GCH-1) genes (Table 1). Other as yet unidentified genes involved have been linked to chromosomes 2P and 4P (1, 3).

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2. Pathogenesis of parkinsonism

A loss of tyrosine hydroxylase (TH)-positive DA neurons and LB formation are found in the pars compacta of the substantia nigra of PD patients. LBs contain predominantly α-synuclein but also ubiquitin, UCH-L1, parkin, cytochrome c, synphilin-1, etc. (3, 6 – 8). α-Synuclein in mammals is expressed abundantly in the presynaptic terminals but not specifically in DA neurons (7, 9). In several autosomal dominant PD families, two mutations in the amino-

Table 1. Parkinsonism and related neurodegenerative disorders in which gene mutations have been identified

Disorder	Related gene	Pathology and inclusions	Levodopa-response (side-effects)
Parkinsonism			
Sporadic PD	?	loss of DA neurons, LBs (α-synuclein)	+ (+)
Heroin addicts (with MPTP exposure)	—	loss of DA neurons, few LB-like inclusions or no LB	+ (+)
Drug-induced parkinsonism	—	—	—
Vascular parkinsonism	—	infarcts	—
Familial PD	α-synuclein	loss of DA neurons, LBs (α-synuclein)	± (+)
Familial PD	UCH-L1	unknown	+ (?)
AR-JP	parkin	loss of DA neurons, no LB	+ (+)
DLB	?	LBs (α-synuclein)	± (+)
HPD/DRD	GCH-1	loss of DA production, no LB	+ (−)
MSA	?	glial inclusions (α-synuclein)	—
FTDP-17	tau	phospho-tau	—
Others			
Familial AD	PS, APP	SP (Aβ, NAC), NFT (phospho-tau)	—
Familial ALS	SOD1	LB-like hyaline inclusions	—
HD	huntingtin	nuclear inclusions (poly-Gln)	—

PD, Parkinson's disease; AR-JP, autosomal recessive juvenile parkinsonism; DLB, dementia with Lewy body; HPD/DRD, hereditary progressive dystonia/dopa-responsive dystonia; MSA, multiple system atrophy; FTDP-17, frontotemporal dementia and parkinsonism linked to chromosome 17; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease; APP, amyloid precursor protein; LB, Lewy body; SP, senile plaque; NFT, neurofibrillary tangle; +, effective (appearance of side-effects); −, ineffective (no side-effect); ?, unknown.

terminal region of α-synuclein have recently been identified, i.e., substitutions of alanine at amino acid position 30 by proline (A30P) and at position 53 by threonine (A53T) (7, 9). It is known that the full-length of wild-type and mutant α-synuclein proteins are self-aggregated and such aggregation is facilitated by cytochrome c, oxidative stress or synphilin-1 (7, 8). On the other hand, a fragment of α-synuclein (amino acid residues 61−95, an extremely hydrophobic region) has been considered to be a non-amyloid β component (NAC) in amyloid plaques in Alzheimer's disease (AD) brains (7). Thus, α-synuclein may be implicated in the etiology of neurodegenerative disorders such as PD, DLB and AD (7, 9).

AR-JP patients, who have loss-of-function mutations for the parkin, show a good response to levodopa (3). Although there is a severe loss of DA neurons, LBs are absent in AR-JP brains. In sporadic PD brains, however, the level of parkin protein production is unchanged compared to that in vehicle control brains, and few LBs contain parkin protein. These observations suggest that a loss of nigral DA neurons may participate in the aggregation of α-synuclein in LBs or loss of parkin. However, several questions are raised: i) why does the aggregation of full-length α-synuclein cause neurodegeneration predominantly in DA neurons, ii) what role does α-synuclein play in AR-JP patients, and reversely, iii) what role does parkin play in DA neurodegeneration in autosomal dominant or sporadic PD patients? Further studies are needed to answer these questions.

3. MPTP-treated models among mammals

Dysfunction of mitochondrial complex I and oxidative stress may be in critical components of nigral DA neurodegeneration. Insight into the molecular mechanisms of DA neuronal death has come from the studies using 6-hydroxydopamine (6-OHDA) and MPTP (4, 5). It has been speculated that sporadic PD is caused by endogenous and environmental neurotoxins such as *N*-methyl-(*R*)-salsolinol, *N*-methyl tetrahydroisoquinoline and β-carbolines. However, the actual toxin that is more neurotoxic than MPTP has still not been identified (1−3). MPTP is converted by monoamine oxidase B (MAO-B) to 1-methyl-4-phenylpyridinium (MPP^+), which is accumulated intracellularly in neurons via DA transporter (DAT). MPP^+, a potent inhibitor of mitochondrial complex I, causes the production of reactive oxygen species (ROS), which induces apoptotic death in DA neurons. Since 6-OHDA and MPP^+ can not pass through the blood-brain barrier (BBB), these toxins should be directly microinjected into the substantia nigra or striatum. MPTP is a relatively stable substance and passes through the BBB. In contrast, 6-OHDA is such an unstable substance that it must be used in the presence of antioxidants such as ascorbic acid. Therefore, MPTP can be administered systemically (4, 5). In primates such as human, monkey and baboon, MPTP causes irreversible and severe parkinsonian symptoms that are indistinguishable from those in sporadic PD, with a degeneration of nigral DA neurons and a few microinclusions (but not typical LBs) such as eosinophilic inclusions and α-synuclein aggre-

gations (4, 5, 7, 9). In contrast, the rodents such as rats and mice are less sensitive to MPTP neurotoxicity (4, 5). In brief, MPTP-induced DA depletion requires a higher dose and permanent behavioral symptoms like parkinsonism are rarely appear. In rodents, the appearance of parkinsonian behaviors requires the complete blockade of the DA-response by D_2-receptor antagonists, while relative DA-depletion is insufficient. Thus, MPTP-treated monkeys may be the most suitable model for sporadic PD. However, since the C57BL/6 strain mouse is the most sensitive rodent to MPTP, MPTP-treated C57BL/6 mouse may also be a useful model. We previously found that MPTP-induced DA depletion was inhibited by deprenyl (MAO-B inhibitor) and nomifensine (DAT inhibitor) (10).

4. MPTP-treated models among invertebrates

Previous studies have shown MPTP toxicity in lower animals such as frogs and leeches. The frog *Rana pipiens*, a vertebrate amphibian, showed a decrease in DA content and motor dysfunction with MPTP and MPP^+ (11). However, MPP^+ was more toxic and effective at lower doses than MPTP in frogs. The medicinal leech *Hirudo medicinalis*, an invertebrate segmented worm, also decreased DA content and motor dysfunction with MPTP, but the American leech *Macrobdella decora* showed no MPTP-sensitivity (4, 5).

Recently, we developed a novel MPTP-treated model using planaria (*Dugesia japonica*), an invertebrate flatworm (12). Planaria is the most primitive species to have acquired a centralized nervous system. This flatworm also has neurotransmitters such as DA, noradrenaline, serotonin, etc. In addition, treatment with levodopa or reserpine induces an increase or a decrease in DA content, respectively, and DA agonists and antagonists influence planaria behaviors. Therefore, this flatworm is considered to be an ancestor of mammalian brains (13). Although planaria have a high capacity for regeneration and reorganization (13, 14), we found that MPTP markedly induced autolysis (like apoptosis) and then individual death in comparison with 6-OHDA and MPP^+ (12). In addition, MPTP-induced autolysis in planaria was completely rescued by the novel anti-parkinsonian drugs talipexole and pramipexole (12). Thus, MPTP-induced apoptosis-like death may occur even in an invertebrate flatworm. Table 2 shows MPTP neurotoxicities in vertebrates and invertebrates.

Table 2. MPTP-treated models in vertebrates and invertebrates

Species	DA content or DA neurons	Movement or survival
In vivo MPTP-treated models		
Vertebrates		
Mammals		
Primates		
monkeys	↓	↓
Rodents		
rats	—	no change
mouse (C57BL/6)	↓	↓ (acutely) or no change
Gene-mutant mice		
human SOD1-transgene	resistance	unknown
nNOS (–/–)	resistance	unknown
iNOS (–/–)	↓ (no change)	unknown
PARP (–/–)	resistance	unknown
GSHPx (–/–)	↓ (enhancement)	unknown
VMAT2 (+/–)	↓ (enhancement)	unknown
Amphibian		
frog (*Rana pipiens*)	↓	↓
Invertebrates		
fruit fly (*Drosophila*)*	unknown	unknown
nematode (*C. elegans*)*	unknown	unknown
segmented worm (leech)	↓	↓
flatworm (planaria)	↓	↓ (autolysis, death)
In vitro culture models		
DA neuron-like cell lines (PC12, SH-SY5Y, etc.)	↓	apoptosis
primary neuronal cells (from rat brains)	↓	apoptosis or necrosis
mesencephalic organ slices	↓	apoptosis or necrosis

* MPTP toxicity was not tested in fruit fly or nematode. (–/–), null mutation; (+/–), heterozygous deficiency.

5. In vitro culture models

As described above, 6-OHDA and MPP^+ are unsuitable for systemic administration. However, since their uptake activity into the brain synaptosomes is similar among primates and rodents, these neurotoxins are useful in neuronal cultures in vitro. On the other hand, recent studies suggest that DA neuronal death is also caused by glutamate and nitric oxide (NO). In vitro cultures of mesencephalic organ slices (from newborn rats), dissociated mesencephalic neurons (from fetal rats) and DA neuron-derived cell lines (human SH-SY5Y, rat PC12, etc.) are suitable for studying neuronal networks (15) and detailed mechanisms (16, 17). We recently found that MPP^+ induces ROS production, changes in levels of pro- and anti-apoptotic Bcl-2 family members, cytosolic cytochrome c release and caspase-3 activation, and then causes apoptosis in human SH-SY5Y cells (17).

6. The DA system and MPTP in gene-mutant mice

DA is produced by several synthetic enzymes (such as TH) with co-enzymes such as GCH-1, which is a synthetic enzyme of tetrahydrobiopterin, a TH cofactor. Recent gene-targeting and transgenic strategies have generated several mouse lines that have mutations in the DA system. TH- or DA-deficient mice die at a late embryonic stage or shortly after birth (18), suggesting that these mutant mice are unsuitable for parkinsonian models. Although mice lacking GCH-1 have not been generated, human HPD/DRD patients, who exhibit dystonia at juvenile onset without a loss of DA neurons, are associated with mutations in the GCH-1 gene (19). Since such patients only lack tetrahydrobiopterin synthesis and have lower TH activity, they are responsive to levodopa and do not exhibit side-effects.

In contrast, mice that lack D_2-receptors show a decrease in spontaneous movements as in drug-induced parkinsonism (20), while mice that lack D_1, D_3 or D_4-receptors do not show marked reduction in locomotive activity. Thus, D_2-receptor-deficient mice may be one of useful models for parkinsonism. However, it is unknown whether parkinsonism involves mutation in the D_2-receptor gene. Table 3 summarizes the current findings regarding gene-knockout and transgenic animals.

On the other hand, MPTP neurotoxicity has also been examined in other mutant mice (Table 2). Mice over-expressing human wild-type Cu/Zu-superoxide dismutase (SOD1) and those that lack neuronal NO synthase (nNOS) or Poly(ADP-ribose) polymerase (PARP) are resistant to the neurotoxic effects of MPTP (8). Mice that lack inducible NO synthase (iNOS) are resistant to the MPTP-induced decrease in TH-positive neurons, but show no change in DA-depletion. In contrast, glutathione peroxidase (GSHPx)-homozygote deficient mice and vesicular monoamine transporter 2 (VMAT2)-heterozygotes had enhanced MPTP neurotoxicity (21, 22). Since MPTP sensitivity varies among mouse strains, it is very important to consider animals with a similar genetic background.

7. Other mutants and parkinsonian models

The gracile axonal dystrophy (*gad*) mouse shows sensory ataxia at an early stage, followed by motor ataxia at a later stage. In this mutant mouse, an in-frame deletion was recently identified in the UCH-L1 gene, which causes a loss-of-function (23). A missense mutation in the UCH-L1 gene

Table 3. Gene-knockout and transgenic animals

Species	DA neurons	Inclusions	Movement or survival
Knockout mice			
TH (–/–)	↓	— (?)	almost embryonic death
DA (–/–)	↓	— (?)	neonatal death
DAT (–/–)	no change (?)	— (?)	premature death
D1R (–/–)	no change (?)	— (?)	slight increase in locomotor activity
D2R (–/–)	no change (?)	— (?)	dysfunction of locomotion
D3R (–/–)	no change (?)	— (?)	increase in locomotor activity
D4R (–/–)	no change (?)	— (?)	no change
α-synuclein (–/–)	no change	—	dysfunction of DA-dependent locomotion
Transgenic mice			
human WT α-synuclein	↓ (?)	α-synuclein	dysfunction of locomotion (?)
human WT tau	no change (?)	tau	no change (?)
human Mut. PS1/APP	no change (?)	Aβ-amyloid	learning and memory dysfunction
Mutant mouse			
Gad (mutation in UCH-L1)	no change (?)	spheroid body	↓ (ataxia, axonal dystrophy)
Transgenic fly (*Drosophila*)			
human WT α-synuclein	↓	LB-like	dysfunction of locomotion
human Mut. α-synuclein	↓	LB-like	dysfunction of locomotion

R, receptor; (–/–), null mutation; WT, wild-type; Mut., mutant; APP, amyloid precursor protein; PS1, presenilin-1; other abbreviations are referred from the text.

(leading to I93M) that causes about a 50% reduction in catalytic activity has only been identified in one PD family in Germany (1, 3). However, the pathological and clinical features in patients with this familial PD are different from those in *gad* mice. Therefore, *gad* mouse is not a suitable for this PD model, although it is the first mammalian model of neurodegeneration with a defect in the ubiquitin system.

Point mutations in the tau gene have been identified in the parkinsonism FTDP-17, which also shows dementia with filamentous hyperphosphorylated tau deposits but an absence of Aβ amyloid plaques in the brain (6). Human wild-type tau-transgenic mice were recently generated, but these mutants also did not exhibit parkinsonism. Thus, although mice with a mutation in a parkinsonism-related gene have been generated, they may not be suitable as parkinsonian models. Therefore, several changes are necessary to develop a model for these parkinsonisms such as transfer of mutant human genes.

Mice that lack α-synuclein are normal; they exhibit an intact brain architecture with normal DA neurons and display only a dysfunction of the nigrostriatal DA system such as reduced DA release and amphetamine-stimulated locomotion (24). More recently, very interesting mutants have been generated for PD models in mouse and fruit fly (*Drosophila melanogaster*). Masliah et al. described transgenic mice that expressed a high level of human wild-type α-synuclein (25), whereas Feany and Bender have engineered transgenic flies to overexpress either human wild-type α-synuclein or mutant forms in familial PD such as A30P and A53T (26). Mice that overexpressed human wild-type α-synuclein showed the formation of cytoplasmic and nuclear microinclusions with α-synuclein and ubiquitin and a reduction of striatal TH activity and motor performance. However, since mouse wild-type α-synuclein was natively expressed, the decreases in TH activity and locomotion were relatively lower levels. They did not measure DA content in the striatum or the number of cell deaths among TH-positive neurons in the substantia nigra. Genetically, mouse and rat carry the A53T allele as these normal sequences in the α-synuclein protein, while A30 is the same as the human wild-type. Therefore, more suitable mouse models may be needed for a higher expression level of A53 α-synuclein (human wild-type) or A30P-mutant α-synuclein or a further combination of transgenes such as cytochrome c, synphilin-1, etc.

In contrast, transgenic flies are more suitable as a PD model. Transgenic flies show an age-dependent loss of TH-positive neurons and the accumulation of intracellular aggregations including α-synuclein that resemble LBs in PD brains. In addition, locomotor dysfunction is more apparent in transgenic flies that overexpress A30P-mutant α-synuclein than in those with A53T-mutant and wild-type α-synuclein. Thus, transgenic flies fulfill most of the criteria for an excellent PD model, including progression, age dependence, selective loss of DA neurons and formation of α-synuclein inclusions (8). Thus, since the body plans, neuronal networks and motor functions in invertebrates are very simple, invertebrate models may be useful as PD models.

8. Evolution of apoptotic processes

Nigral DA neuronal death is caused by apoptosis in PD patients (1, 2). More recently, it has been reported that caspase-3 may participate in the vulnerability and apoptosis of DA neurons in PD brains and MPTP-treated mouse brains (27). Recently, the genes of many participants in apoptotic processes have been identified in human, fruit fly (*Drosophila*) and nematode (*Caenorhabditis elegans*). In brief, EGL-1, CED-9, CED-4 and CED-3 in nematode are known as a BH3 domain only protein (Bad/Bid/Bik), Bcl-2/Bcl-x, Apaf-1 and caspases in human, respectively (28). Human Apaf-1 has the binding domains for ATP, caspases and cytochrome c, while nematode CED-4 lacks a cytochrome c-binding domain, suggesting that CED-4 activates CED-3 in a cytochrome c-independent manner. In addition, CED-4 is usually inhibited by CED-9, while Apaf-1 is not directly regulated by Bcl-2 or Bcl-x. In contrast, human anti-apoptotic Bcl-2 and Bcl-x inhibit cytochrome c release from the mitochondria to the cytosol, while pro-apoptotic Bax and Bak induce cytochrome c release (29). On the other hand, *Drosophila* has two isoforms of Apaf-1/CED-4, Dapaf-1S (CED-4 type) and Dapaf-1L (Apaf-1 type). Therefore, *Drosophila* caspases are activated by both cytochrome c-dependent and -independent pathways (30). Unfortunately, the apoptosis-related participants in planaria are unknown. These observations suggest that cytochrome c-dependent activation of a caspase cascade by Apaf-1 have been acquired during the evolution in animals. Therefore, when invertebrate models are used, it is necessary to consider different apoptotic mechanisms. Table 4 summarizes current findings regarding apoptotic processes by CED-4/Apaf-1-dependent pathways in vertebrates and invertebrates.

9. Outlook

Recent gene technology has led to the development of several parkinsonian models. On the other hand, the lifespan in rodents (about 3 years) is much shorter than that in humans. Therefore, they are limited with regard to their use as models for age-dependent disorders. However, since mice that have received double mutant human genes of both amyloid precursor protein and presenilin-1 exhibit the formation of amyloid plaques, which resemble senile plaques in AD brains already at 2 months of age, the age-dependency may be overcome by neurotoxin treatment,

Table 4. CED-4/Apaf-1-dependent apoptosis in mammals and invertebrates

Species	BH3/EGL-1	Bcl-2/CED-9	Apaf-1/CED-4	Caspases/CED-3	Survival
Mammals (human and rodents)					
	Bad/Bid	Bcl-2/Bcl-x (?)	ATP/dATP		
MPTP → MPP$^+$ → ROS →		Cytochrome *c*	Apaf-1	Caspase-9 → Caspase-3 →	Apoptosis
		Bax/Bak			
Fly (*Drosophila*)					
MPTP neurotoxicity: Unknown					
			ATP/dATP		
		Cytochrome *c*	Dapaf-1L (Dark, HAC1)	DRONC (Dredd ?)	drICE (DPC1 ?) → Cell death
		Drob-1 (?)			
			ATP		
			Dapaf-1S		drICE → Cell death
Nematode (*C. elegans*)					
MPTP neurotoxicity: Unknown					
	EGL-1	CED-9	ATP		
			CED-4		CED-3 → Cell death
Flatworm (planaria)*					
			ATP/dATP (?)		
MPTP → MPP$^+$(?) → ROS (?)			?	?	Individual death (Autolysis)

* The apoptosis-related genes in planaria are unknown.

multiple gene-transfer and/or -deficiency. Since none of the models generated thus far exhibit typical LBs, further work is needed. Recently, analysis of the outline of the human genome was analyzed, which should facilitate linkage analysis in human diseases. In the future, patients may be treated with each benefit therapy (tailor-made therapy). To develop new potential neuroprotective therapies, it is necessary to have a suitable model for each parkinsonism.

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