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Rodent Model of Parkinson's Disease: Unilateral or Bilateral?

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Abstract

Parkinson's disease (PD) is one of the most common neurodegenerative diseases affecting the aging population worldwide. Levodopa (L-DOPA) is the gold standard of PD therapy, which is administrated for symptomatic treatment. However, long-term application of L-DOPA leads to less effectiveness and a dose-dependent side effect of dyskinesia. Therefore, to help understand the pathogenesis and clarify potential therapeutic strategies, a great effort is made for the preclinical research on experimental PD models. Since the variety of the animal models is employed in the research work of PD, a controversy has arisen over the reproducibility of experimental models to clinical Parkinsonism. The experimental paradigms are diverse, with which partial Parkinsonism features can be induced in rodents, while others may be limited. Rodent models need to be validated for further use in pathophysiological and therapeutic investigations. This review summarizes the characteristics of the commonly used experimental PD models on rodents, including both unilateral and bilateral models, which may provide useful ideas on selection the most applicable animal model on specific aims of PD research. In conclusion, bilateral models are more consistent with the natural pathogenic process of PD, although there currently exists no model completely reproducing the clinical characteristics of human patients.

Keywords: Parkinson's disease; Animal model

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder with the features of movement disorders and cognitive deficits. Over 1–2% of the general population over the age of 60 years is affected and about 5 million peoples in total are interrelated all over the world [1]. The pivotal pathological characteristic of PD is the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), which results in the decrease of dopamine (DA) in striatum [2]. The accumulation of intracellular α-synuclein is histopathologically observed in PD patients [3]. Recent studies suggest that the inflammatory response is involved in pathogenesis as well [4]. The DA deficiency causes the subsequently functional changes in the basal ganglia circuitry, which represent the externally parkinsonian motor dysfunction as well as cognitive disturbance [5,6]. Levodopa (L-DOPA) is considered as the current standard treatment for symptomatic Parkinsonism. The decreased DA content in the basal ganglia circuitry of PD leads to the logical use of L-DOPA for substrate supplement. Along with the concerns about the less effectiveness and dose-dependent side effect of the administration of L-DOPA, a number of studies are placed in exploring the effective therapeutic strategies for PD patients [7,8].

Animal models which mimic the human Parkinsonism are required to enhance our understanding of the pathophysiology and optimize the treatment of PD. Rodents models are commonly used both for its experimental value and economic reasons. Neurotoxic agents are employed initially to destroy the DA neurons in SN, which induces the Parkinsonism in animal models. PD-mimetic toxins are frequently used, including 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its active metabolite 1-methyl-phenylpyridinium (MPP+), pesticides rotenone, paraquat and pesticide manganese ethylene-bis-dithiocarbamate (Maneb) and inflammogen lipopolysaccharide (LPS) [9]. The toxic agents mimic partially the mechanisms of PD pathogenesis and lead to the loss of dopaminergic neuron, which eventually results in the motor dysfunctions as well as sensorial and memory deficits [10]. According to the application route, PD animal models are divided into unilateral and bilateral models, that is, the focal or the systemic administration of the neurotoxicity. The focal injection usually applies the stereotactic injection to introduce the neurotoxic agent into the unilateral side of the SN. This method results in hemiparkinsonism. The systemic models usually apply the subcutaneous (s.c) or intraperitoneal (i.p) administration to induce the bilateral Parkinsonism. In addition, the discoveries of gene deficiency in familial PD and the mutation of proteins/enzymes in PD patients provide the possibility to utilize the transgenic models in research of PD [11].

In this review, we examine the commonly used PD rodent models in past decades, including both unilateral and bilateral models. Each of the experimental models has own specificities and limitations. Therefore, Utilization of the PD rodent models should depend on the specific aims for the variety of studies.

Unilateral Parkinsonism Model

6-OHDA model

6-hydroxydopamine (6-OHDA) is the primarily utilized agent for inducing animal PD [12]. 6-OHDA is a toxin to elicit the neural degeneration. 6-OHDA inhibits the complex I of the mitochondrial respiratory chain, resulting in the increase of reactive oxygen species (ROS) and the decrease of ATP. The oxidative stress leads to the apoptosis and cell death of DA neurons [4]. The neurotoxin-induced neurodegeneration reproduces the DA deficiency aspect of PD, which is utilized for the investigation on PD pathologic hallmarks.

Since the poor penetration of the blood brain barrier, 6-OHDA

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is usually applied directly into the brain by stereotaxic injection. The three common administrated locations are substantia nigra pars compacta (SNpc), the median forebrain bundle (MFB) and striatum. The dopaminergic cell bodies distribute in the SNpc and 6-OHDA is able to permeate directly into the nigrostriatal tract. The dopaminergic nigrostriatal tract ascends through the median forebrain bundle and project into the striatum. The SNpc is the area usually avoided to damage unless the initial region is targeted. Therefore, the MFB area is the most preferred to applied [13,14]. However, the surgical technique of the stereotaxic injection becomes the major drawback of the 6-OHDA model of PD. Recently, perinatal administration of 6-OHDA is indicated to be potent to inducing lifelong animal model [15]. Unilateral administration of 6-OHDA leads to the ipsilateral dopaminergic neurons death, which results in the contralateral neuronal deficits [6]. In some studies, a bilateral lesion is devoted to induce the bilateral symptoms, which is proposed to mimic the naturally systematic onset of disease. However, the dysplasia and dysphasia after operation result in the tube feeding, which decreases the welfare of the animals [16].

6-OHDA intoxicated PD model has been used successfully to develop rodent models of behavioral deficits, including locomotor dysfunction, akinesia, sensory-motor deficits and cognitive impairment [17-20]. The presence of abnormal involuntary movements (AIMs) is observed in 6-OHDA PD model and also after L-DOPA treatment, which allows the investigation on the L-DOPA-related dyskinesia [21,22]. The unilateral 6-OHDA model also provides self-control for the intervention. While the discrepancy that the ipsilateral Parkinsonism is different to the natural Parkinsonism in human patients exists either. Therefore, the application of 6-OHDA intoxicated PD model largely depends on the objects of different studies.

LPS PD model

Bacterial endotoxins lipopolysaccharide (LPS) triggers inflammation reactivation when infused into the nigrostriatal pathway. The neurotoxicity of LPS is exerted through the microglial activation and subsequent release of cytotoxic molecules. LPS indirectly leads the neural degeneration of the nigrostriatal pathway [23]. The LPS PD model mimics the inflammation process in PD pathogenesis, which is recently indicated as a key factor to induced Parkinsonism.

Unilateral LPS injection into SNpc results in contralateral lesion presenting the rotational behavior deficits. The administration is implemented by the stereotaxic injection. The striatum is another location to prefer [24]. Anti-inflammation treatment based on this model is investigated for neural protection in PD process [25].

The concerning of this model mainly focused on the limited reproducible pathophysiology to clinical PD. The limitation unavoidably incurs a narrow range of investigation on the potential mechanism and treatment for PD. Similarly to 6-OHDA model, the unilateral onset of Parkinsonism is inconsistent to the natural PD process.

Bilateral Parkinsonism Model

MPTP model

The discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a selective nigral toxicity, leads to a new field of view to the animal model of PD. MPTP crosses blood–brain barrier rapidly when systematically administrated. MPTP is converted into 1-methyl-4-phenylpyridinium (MPP+) by MAO-B and subsequent spontaneous oxidation once permeated inside the brain. MPP+ inhibits the complex I of the mitochondrial respiration chain, therefore triggers the cell death. The DA neurons in SNpc areas of rodents are sensitive to MPTP toxicity [26]. However, there are some certain strains of mice are spared. The C57BL/6, Swiss Webster mouse and SD rat are commonly used in the establishment of MPTP-induced PD model.

One of the remarkable characteristics of this model is the systematical administration route, usually via i.p or s.c injection, which makes it more feasible to establish than the 6-OHDA model. The systematic application results in the bilateral lesions that mimic the natural situation of human beings.

The regimens of MPTP vary from each study. The different dosage and route affect the stability of this model and bring about the discrepancies. MPTP-induced PD models are categorized into acute, sub-acute and chronic models according to the period and dosage of MPTP treatment. Acute intoxication causes a respectable extent death of dopaminergic neuron, which is the premise and guarantee of the success of this model. However, the acute and mega dose of MPTP leads to considerable mortality, which is the key limitation of this model. Therefore, the divided doses rather than acute bolus are preferred for establishing the MPTP rodent model [27,28].

Rodents treated with MPTP present the Parkinsonism symptoms, such as tremor, grooming and gait disturbance. However, it is reported in previous studies that the MPTP fails to elicit dyskinesia in rodent's model but not in the primate, that may suggest that the MPTP-targeted pathways are different between rodents and primates. It is probably one reason, for which some treatments cannot be translated between rodents to human.

The dominant limitation of MPTP-induced PD model is the safety issue. The toxicity is originally found in peoples with the illegal abuse of drugs, from which it results in a novel approach to PD animal model establishment. MPTP, when absorbed into the blood, is rapidly delivered to the brain and affect the dopaminergic neurons of the human. Therefore, for investigators, special attentions should be paid to the biosafety of handling MPTP. MPTP irritates respiratory tract, digestive tract and skin, on which the investigators should highly notice when disposing the MPTP-contaminated animal cadavers, animal bedding and the material used during MPTP injection [29,30].

Rotenone model

Rotenone presents the neuronal toxicity, similar to the MPTP, through inhibiting the complex I of mitochondria and subsequently produces ROS. The depletion of glutathione plays an important role in Parkinsonism inducing, rather than the decrease of ATP, which is quite different to MPTP-induced Parkinsonism. In addition, rotenone elicits oxidative stress to the DA neurons [31]. Rotenone is highly lipophilic which the premise for systemically administration is. It crosses blood-brain barrier rapidly and easily diffuses in the SNpc and striatum.

The recent studies illustrate that the inflammatory responses contribute to Parkinsonism in the rotenone PD model. Rotenone upregulates the expression of NF-κB, a pro-inflammatory transcription nuclear factor. The pathophysiological process is similar to the human PD. The inflammation response is linked to mitochondrial dysfunction in the progress [32,33].The reproduction of clinical PD features through the intragastric administration of rotenone uncovers a novel view on the gut-brain transmission of PD [34].

Considering of the high systematic toxicity of rotenone, the rotenone is now employed commonly for the exploration of mediating the certain pathway of PD pathogenesis. In which the studies specifically

focused on the mitochondrial inhibition and neuroinflammatory responses in PD.

Paraquat model

Paraquat is herbicide used to trigger PD pathogenesis through the toxicity to mitochondrial complex I [35]. Paraquat cannot cross blood brain barrier, but enter the cells through neutral amino acid transporter when systematically administrated [36]. Recent studies elucidate that the permeability via mitochondrial membrane of dopaminergic neurons plays an important role in paraquat-induced Parkinsonism [37].

The partial reproduction of the clinical PD pathogenesis gives the possibility of paraquat to induce the Parkinsonism on the experimental model. A combination of paraquat with another pesticide manganese ethylene-bis-dithiocarbamate (Maneb) is an alternative formula for PD rodent model establishment. The combination increases the concentration of paraquat and enhances the toxicity to the dopaminergic neurons [38-40]. Maneb is a fungicide and used independently to induce PD via a similar mechanism to paraquat, which targets on the mitochondrial complex III [41]. The paraquat PD models are employed to investigate the neuroprotective treatment [42]. The high mortality of this model is essential to be taken into consideration, which might be the result of respiratory damage [43].

Gene-related PD model

In recent years, the genetic method has revolutionized the way we develop the pre-clinical animal studies. The enabled techniques of gene deletion, overexpression, and mutation *in vivo* make it possible for generating the transgenic model of PD. PD-related gene modulated model, including α-synuclein transgenic mouse model, Leucine-rich repeat serine/threonine kinase 2 (LRRK2) and other transgenic model, are mainly employed for studies on PD. Except for the technique for genetic modification, once generated, the transgenic mouse model is easy to use subsequently than the toxic model.

α-synuclein is a presynaptic neuronal protein and genetically correlative to familial PD in the first place [3,44]. α-synuclein is identified as a major component of Lewy bodies in idiopathic PD and plays an important role in neurodegenerative conditions [45,46]. Lacking, Mutation or duplication of the -synuclein contributes to PD pathogenesis. Several transgenic models are generated to investigate the role of α-synuclein in physiology and pathology of PD. The transgenic model is generally divided into two categories, the lacking or overexpression of α-synuclein. α-synuclein knockout or α-synuclein null mice show loss of α-synuclein function and reduced dopamine level in the striatum [47,48]. Interestingly, this model displays resistant to MPTP toxicity, while more sensitive to rotenone than wild-type mice. The locomotor functions are largely preserved in this model, except subtle abnormal performance on rearing ability in the open field test [47]. This category of α-synuclein transgenic mice provide a new information regarding its physiological role in PD. On the other hand, overexpression of alpha-synuclein is committed as a model of synucleinopathies. Mice overexpressing either wild-type or mutated human α-synuclein, including A30P or/and A53T, are generated via utilizing different promotors [49,50]. Early start of progressive motor deficits is demonstrated in α-synuclein transgenic mice [51]. α-Synuclein transgenic mice develop neuronal mitochondrial degeneration, however lack of dopaminergic neuronal loss [52,53]. Although none of the above α-synuclein transgenic models demonstrate dopaminergic neuronal death in the substantia nigra, the characteristics of synucleinopathies and the potential role of alpha-synuclein in Pathogenesis of PD are pivotal for the pre-clinical researches. Therefore, α-synuclein transgenic mouse model reproduced the sporadic PD on a certain degree.

LRRK2 is a protein with the armadillo repeats (ARM) region, an ankyrin repeat (ANK) region, a leucine-rich repeat (LRR) domain, a kinase domain, a RAS domain, a GTPase domain, and aWD40 domain. LRRK2 is expressed in subcellular part of neurons [54]. Mutation of LRRK2 is prevalent to the inherited PD [55]. The pathogenesis is probably owing to aberrant kinase activity, the abnormal phosphorylation of substrates, and misregulation of binding partners and regulators [56]. The abnormal autophagy and neuroinflammation regulation involve in the process [57]. To further investigate the function of LRRK2 involved in the pathophysiology of PD, transgenic model either with the mutated or the lack of LRRK2 are employed. Transgenic mouse model expressing mutant LRRK2 R1441G or G2019S are commonly used since the same missense mutation and high incidence in familial PD patients.

Transgenic mice [58,59], LRRK2 R1441G mice express high levels of tau protein and develop progressive motor deficits along age, which is similar to many PD patients with LRRK2 mutations. The mutant mice largely preserve the dopaminergic neurons, despite the presence of axonal degeneration in the nigrostriatal pathway [58]. However, LRRK2 G2019S shows a decline of DA content in striatum with the abnormal kinase activity [59]. LRRK2 knockout model is utilized to investigate the physiological role of LRRK2. LRRK2 knockout mice demonstrate the similar PD pathophysiology in kidney, despite the absence of DA alteration. The process includes the accumulation of α-synuclein inclusions and ubiquitinated proteins, inflammatory responses, and oxidative damage, which give an insight of LRRK2 dysfunction *in vivo* [60,61]. In sum, the features of the LRRK2 transgenic model provide a perspective for the biological and molecular mechanism of inherited PD.

In addition to the α-synuclein and LRRK2 transgenic model, Mitochondrial genetic models of PD are used for mimic the increased oxidative stress and mitochondrial dysfunction in neurodegeneration. The mutations in PTEN-induced putative kinase1 (PINK1) results in an autosomal recessive PD, which is the first evidence of mitochondrial dysfunction causing Parkinsonism. PINK1 knockout mice elucidated a decline catecholamine level at the synapse and reduced striatal DA content. The motor deficits are also observed in this model. However, PINK deficient model fails to mimic the dopaminergic neuron loss [62,63]. DJ-1 is a small protein that is wildly expressed in cells and targets to the mitochondria. DJ-1 plays a pivotal role in protecting against increased ROS through its antioxidant properties and clearance of the defective mitochondria via autophagy [64,65]. Recent studies illustrate that DJ-1 stabilizes α-synuclein and involves in the Nrf2-dependent oxidative stress response through regulating 20S proteasome [66]. Mutations in DJ-1 results in an autosomal recessive PD [67]. DJ-1 null mice display reduced DA neurons in the tegmental area (VTA) [68]. Parkin is an E3 ubiquitin-protein ligase and also one of the largest genes in the genome. Mutations in the parkin gene are associated with juvenile PD as well as sporadic PD [69,70]. Parkin knock-out mice showed cognitive impairment on depression domain without dopaminergic neurons loss [71,72], which are utilized for investigating parkin function and the specific pathogenesis of the disease. Other mutations of genes related to the juvenile-onset form of PD, including ATP13A2 (PARK9), PLA2G6 (PARK14) and FBX07 (PARK15), are also the potential loci for transgenic models. Even though seldom DA neuron degeneration in the above models, genetic method provides a platform of which we

may study some certain aspects of PD pathogenesis. The absence of the DA neuron loss may due to common intrinsic genetic factors in the mouse strain [73].

Conclusion

The emergence of the PD experimental models makes it possible for expanding our understanding of PD pathogenesis and investigating the potential therapeutic targets of PD. Rodents model have the irreplaceable values for research in preclinical studies. The reproducibility of both clinical features and pathogenesis of PD is the crucial issues of animal models. Either the unilateral or the bilateral model has its own pros and cons. Unilateral toxic model locates the exact onset of neuron damage and meanwhile conserves a self-control for the potential treatment. However, the unnatural process of pathogenesis results in the main controversy of unilateral Parkinsonism. The variety of bilateral model mimics the different phases of PD pathogenesis and each reproduces partial features of clinical conditions. Even though bilateral models are more commonly used and consistent with the natural process of PD, currently none of the animal models can completely reproduce the clinical characteristics of PD. The translation from preclinical animal studies to the human application is still the discussable issue for future studies.

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