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Modeling Mechanisms and Applications of Parkinson's Disease Animal Models

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Abstract

Parkinson's Disease (PD) is a neurodegenerative disorder characterized by the progressive and irreversible loss of Dopaminergic (DA) neurons in the midbrain substantia nigra and the formation of intracytoplasmic inclusion structures or Lewy Bodies (LB's). However, the etiology and pathogenesis of PD remain unclear. Animal models are essential to study the pathogenesis of PD and identify novel therapeutic targets for its treatment. The first PD model developed was the reserpine model, which was followed by the 6-hydroxydopamine, MPTP, rotenone, and gene models. Several animal models have been used to elucidate different aspects of the molecular mechanisms of DA neuron death and potential therapeutic drugs. The specific modeling mechanisms and applications of each model are therefore different. In this paper, we review the modeling mechanisms and applications of PD animal models in recent years.

Keywords: Parkinson disease; Animal models; Modeling mechanism; Neurodegenerative disease

Introduction

Parkinson's disease (PD) is a common chronic neurodegenerative disease whose exact etiology and pathogenesis are unclear. The mechanisms involved in PD pathogenesis include energy metabolism dysfunction, oxidative stress, gene mutation, and abnormal protein accumulation. There is general consensus among researchers that PD is caused by the combined effect of genetic and environmental factors. Further analysis of the role and mechanisms of various factors in the PD disease process are therefore of great clinical and scientific interest. Animal models are essential to elucidate the mechanisms underlying the development and progression of PD and identifying novel therapeutic targets. This article reviews the modeling mechanisms, applications, and progress of several major PD animal models developed in recent years.

Literature Review

Chemical drug models

Reserpine model: The earliest PD model was established by intraperitoneal reserpine injection. Reserpine blocks vacuolar monoamine transporters and causes short-term depletion of monoamine substances including DA, 5-hydroxytryptamine, and norepinephrine, in the central and peripheral regions without neurodegeneration. This model can be applied in mice, rabbits, guinea pigs, cats, and monkeys. The most significant use of this model was to confirm that L-dopa could be applied as a therapeutic drug for PD [1-5]. The limitation of this model is that it does not completely reproduce the pathological changes of PD but only simulates PD symptoms in a short duration. It is mainly applicable in efficacy studies of striatum DA substitutes and DA agonists.

6-OHDA model: The chemical structure of 6-OHDA is similar to that of DA, and it can therefore be taken up intracellarly by dopaminergic neurons in the brain. It is then metabolized to products including hydrogen peroxide and superoxide radicals, which cause oxidative stress, neuronal damage, and eventually cell death. 6-OHDA also inhibits the activity of the mitochondrial respiratory chain complex, disrupting neuronal energy metabolism and causing mitochondrial damage. 6-OHDA cannot penetrate the Blood-Brain Barrier (BBB); it has to be injected into the brain in animal models modeling. The main injection sites include the Medial Forebrain Bundle (MFB), Substantia Nigra Pars Compacta (SNpc), and striatum. In 1968, Ungersted injected 6-OHDA into the SNpc of rats, which directly damaged the DA-ergic neurons, causing degeneration and death, and the tyrosine hydroxylase positive (TH+) nerve fibers projected onto the striatum were lost. The PD model was successfully established, and the models constructed by this method typically showed severe neuronal damage. The 6-OHDA model was subsequently constructed in mice, cats, dogs, and monkeys; however, rats were most sensitive to 6-OHDA. The most common method of 6-OHDA application is a unilateral injection into the rat MFB. The MFB injection of 6-OHDA model is suitable for studying the specific function of striatal interneurons in PD pathogenesis. Unilateral 6-OHDA injection into the rat MFB of rats can cause limb stiffness, cognitive and memory impairment, and significant reduction in TH+ cells in the striatum and SNpc [5-10]. Some studies have focused on the injection of 6-OHDA into the striatum; unilateral injection of 6-OHDA into the striatum of rodents caused a significant reduction in TH expression and DA content [9,10]. 6-OHDA injection into the striatum also induced retrograde DA neuron degeneration in the SNpc and decrease of TH+ projection fiber density in the cingulate gyrus and motor cortex, indicating that this model can be used to study the mechanism of PD pathology and cognitive decline in the cortex. The

6-OHDA model shows many biochemical and pathological similarities to human PD, and can closely simulate the DA decrease, loss of DA neurons, and some neurobehavioral defects. However, the main motor disorder observed in this model is lateral rotation, which is not fully consistent with the common clinical symptoms of human PD such as static tremor, weakened motor function, and muscle rigidity. Further, the pathological characteristic of Lewy Body (LB) formation is not observed. Despite these limitations, this model has been widely used, because of easy availability, low cost, and stable and lasting behavior changes, to confirm the efficacy of anti-PD complexes, evaluate the therapeutic effect of neurotropic factors, and more. This model has some additional advantages: the rotation behavior induced by 6-OHDA can be quantitatively evaluated, and this model is the only PD model in which quantitative detection on behavioral changes is possible. Moreover, complete or partial substantia nigra striatum bundle damage can be induced in the unilateral 6-OHDA model by adjusting the dose and site of administration individually or simultaneously, to simulate the pathological changes in patients with PD in the early, middle, and late stages. This offers a solution to the high mortality observed in the bilateral total brain injury model, and also allows the use of the undamaged hemisphere as a control in each model animal.

3-Nitrotyrosine (3-NT) model: The nitrite peroxide anion (ONOO-) is a prominent reactive nitrogen species involved in oxidative stress *in vivo*. It nitrifies free tyrosine residues or tyrosine in protein structures to produce 3-NT, which can cause protein denaturation, functional changes, and eventually cell damage [11-14]. At present, 3-NT is considered a relatively specific marker of oxidative stress. Several patients with neurodegenerative diseases including PD have shown elevated levels of 3-NT in the brain, suggesting that protein nitrification could play a role in PD neurodegeneration. Intra striatal injection of free 3-NT resulted in decreased TH-positive nerve endings, decreased DA neurons in the substantia nigra, and abnormal behavior in mice, suggesting that 3-NT can induce neurodegeneration in animal models. The 3-NT model is an acute model, and it is not clear whether the protein aggregation and emergence of intracellular inclusion bodies observed are related to PD. However, this model is an oxygen stress PD model, and could be valuable in exploring the pathogenesis and developing treatment methods against the stress-induced aspect of PD.

Biological toxicity models

Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) model: MPTP is converted to the Methyl-Phenyl Pyridine ion (MPP+) by Monoamine Oxidase (MAO)-B. MPP+ has a high affinity for the Dopamine Transporter (DAT), and can be transported by DAT to DA neurons, where it inhibits oxidative phosphorylation by selectively inhibiting the activity of mitochondrial complex I, causing mitochondrial dysfunction and Reactive Oxygen Species (ROS) accumulation, and eventually DA neuron degeneration by necrosis or apoptosis. MPTP treatment simulates PD in several species including mice, dogs, and primates. The toxicity of MPTP is different in different species; the highest sensitivity is observed in humans and primates, followed by mice. Rats and guinea pigs have a high tolerance to MPTP, and not preferred for use as MPTP PD models. MPTP can be administered by several methods including brain stereotaxic injection and systemic administration. The most commonly used systemic administration methods are subcutaneous, intravenous, abdominal, or intramuscular injection. Single intraperitoneal injection of MPTP only reduces TH expression without the loss of SNpc DA neurons. Primate MPTP models can induce clear, persistent, and irreversible behavioral responses, pathological and biochemical changes, and responses to drugs (including adverse reactions) similar to those observed in patients with PD. They are therefore the most ideal PD animal model. However, their application is limited by the availability and cost of primates. Rodents have the advantage of availability, ease of maintenance, and low cost, and the behavioral changes after MPTP treatment have a short duration and can be completely reversed. Therefore, the mouse model is a classic model for exploring the molecular pathway of PD neuronal death and evaluating the efficacy of neuroprotective agents. The monkey model is mainly used to identify the behavioral aspects and symptoms of PD, and is typically used in the last stage of PD treatment research before testing in humans [14-23]. There have been reports on the production or absence of LBs-like inclusions in MPTP models. Low-dose MPTP is likely insufficient to promote the formation of LB's. The formation of inclusion bodies may be related to an increase in lactic acid levels in the brain of MPTP-treated mice, because it can activate AMP-activated protein kinase and promote the accumulation and phosphorylation of α-synuclein.

The advantage of the MPTP model is that it can accurately simulate PD-related movement disorders, and the neurons of substantia nigra and striatum are highly sensitive to MPTP. This model also reflects the inhibition of mitochondrial respiration during PD pathogenesis. The disadvantages include the high mortality, and the variations produced by different drug dosages and methods on the modeling results. It is also difficult to observe the production of LBs, and the behavioral dysfunction and substantia nigral lesion of the mouse model can be reversed quickly, making it difficult to simulate the characteristics of PD as a chronic neurodegenerative disease. Drinkut et al., used the PD model of MPTP mice with deficiency of the tyrosine kinase receptor Ret and overexpression of Brain-Derived Neurotrophic Factor (BDNF) in the striatum. Immunohistochemistry (IHC) and Enzyme-Linked Immunosorbent Assay (ELISA) were used to detect the number of TH and Nissl-positive substantia nigra neurons. Quantification of DA fiber density and determination of DA content in the striatum was performed by HPLC [20]. This confirmed that the lack of Ret completely offsets the neuroprotective and regenerative effects of BDNF on the DA energy system in the midbrain in the mouse PD model. Thus, Ret signaling is likely necessary for BDNF to prevent and compensate for the degradation of the DA system and Ret activation is the main mechanism underlying the effects of BDNF in the treatment of PD.

Rotenone model: The agricultural insecticide rotenone is a highly lipo-soluble neurotoxin that can easily penetrate biological barriers including the BBB. It can selectively destroy substantia nigra striatum DA neurons by inhibiting the activity of mitochondrial respiratory chain complex I and disrupting the mitochondrial respiratory chain, resulting in ROS production and mitochondrial dysfunction.

The Rotenone model reproduces several anatomical, neurochemical, neuropathological, and behavioral characteristics of human PD, including the accumulation of α-synuclein. autophagy damage, and reduced mitochondrial protein input, and can be used to study the relationship between environmental factors and PD etiology. The simulation of chronic progression makes it suitable for testing PD neuroprotection. The generated inclusion bodies are useful in studies aimed at elucidating the mechanism of LB formation. Combinations of PD rotenone and gene models can be used to study gene-environment interactions. The hallmarks of the chronic rotenone rat model are the

induction of α-synuclein. inclusion bodies similar to LB's in surviving DA neurons and the simulation of neuropathological features of LB's in substantia nigra neurons, which are lacking in the 6-OHDA and MPTP models. Further, rotenone is easier to administer than 6-OHDA owing to its lipophilicity, and can be administered by gavage, subcutaneous injection, intravenous injection, and intraperitoneal injection. Rotenone exposure is considered a health hazard; therefore, chronic subcutaneous injection with an osmotic pump is the most common drug delivery scheme. Different animals show different relativities to rotenone, which makes the amount, location, and degree of DA melanocytic striatum damage in the rotenone model variable, with poor reproducibility. In addition, rotenone exposure can cause multiple organ damage, and high animal mortality.

Betarbet et al., established the rotenone PD model in 2000. They implanted Alzet micro osmotic pumps subcutaneously into the back of rats, and performed low-dose intravenous injections of rotenone (3 mg/kg/day) for 33 days [21]. They observed selective degeneration of DA neurons in the striatum, and the rats exhibited characteristic PD features including dyskinesia, flexion posture, gait instability sometimes with rigidity, and tremors, and LB-like -nielcunys-positive inclusion bodies. However, rotenone (3 mg/kg/day) administered subcutaneously to rats for 28 days caused no damage to DA neurons and caused extensive toxicity to peripheral organ. Intracerebral injection of rotenone could be used to facilitate the expression and aggregation of DA neurons and α-synuclein in the SNpc and progressive neuronal, without related peripheral toxicity.

Miyazaki et al., chronically exposed C57BL/6J mice to low-dose rotenone (2.5 mg/kg/day) for four weeks by subcutaneous implantation of an osmotic minipump to generate a rotenone mouse PD model [22]. The model mice showed dyskinesia and gastrointestinal dysfunction. The dyskinesia was evaluated by open field, roller, and cylinder tests. In addition to a decrease in the number of DA neurons in the SNpc and injured striatum nerve endings, a significant decrease in cholinergic neurons in the dorsal motor nucleus of the vagus and the intermuscular plexus of the intestine was observed. In addition, Rotenone-treated mice accumulated -synuclein in the neurons of SNpc, DMV, and intestinal intermuscular plexus. No obvious Lewy-like inclusion body was observed in this model. Thus, the behavior, and central and peripheral nerve degeneration characteristics of PD could be replicated in a low-dose rotenone mouse model, which could prove invaluable for studying the pathogenesis of PD.

The rotenone model has attracted much attention for two main reasons. Firstly, epidemiological studies show that organic pesticides are closely related to a high incidence of sporadic PD in rural areas. Second, the rotenone model simulates most of the motor symptoms and histopathological features of PD in humans, particularly the formation of LB's. However, the model has several disadvantages including high cost, effort, and variability, and a low success rate. Moreover, like the MPTP and 6-OHDA models, the rotenone model has a low survival rate in bilaterally injured model animals, which limits the application of this model.

Lipopolysaccharide (LPS) model: The microinjection of LPS into the substantia nigra or striatum, globus pallidus, and ventricle of the brain, induces neuroinflammation that can replicate some characteristics of PD, including excessive microglial activation, progressive and selective DA neuron damage in the substantia nigra striatum system, and accumulation of phosphate α-synuclein in the surviving DA neurons.

LPS is an endotoxin produced by gram-negative bacteria. LPS can enter the brain to internally bind to the CD14-like receptor on the microglial membrane and activate Toll-like receptor 4, which leads to microglial activation and neuronal damage. Recent studies on the ' gut-brain axis have explored the pathogenesis of PD, and have suggested that LPS plays a role in PD. Intestinal microbial membrane metabolites have neural regulatory effects in PD pathophysiology. The excessive growth of intestinal bacteria or excessive stimulation of the innate immune system caused by intestinal malnutrition and enhanced intestinal permeability could induce a systemic inflammatory response. The activation of intestinal glial cells and intestinal neurons may induce the production of synuclein aggregates in the intestinal nervous system, which may proliferate and spread to the central nervous system in a prion-like manner through the vagus nerve. Combination with LPS would expose the protofibrillated core of α-synuclein, which would act as a template for further aggregation of α-synuclein. The LPS model is an ideal model to study the effect of the microglia-mediated inflammatory response on PD pathogenesis. However, the long modeling cycle is a disadvantage.

Gene models

In recent years, the discovery of certain familial PD-related genes has improved the development of PD animal models. Familial PD is associated with specific genes including α-synuclein, LRRK2, Parkin, PINK1, and DJ-1.

αSynuclein transgenic model: The SNCA gene encoding-synuclein is the first identified autosomal dominant PD-related gene. Misfolding and abnormal aggregation of α-synuclein are typical pathological features of PD. α-synuclein oligomers cause mitochondrial dysfunction, endoplasmic reticulum stress, oxidative stress, and neuroinflammation, and inhibit proteasome activity and autophagy. Grassi et al., identified smaller, conformational-synuclein aggregates called α-synuclein*. Their studies showed that p α-syn* was a shear-synuclein produced by the failure of cells to degrade fiber-synuclein aggregation [23]. The p α-syn* is a neurotoxic substance that can cause mitochondrial damage, division, and autophagy, and plays an important role in PD pathogenesis. The toxicity of α-synuclein is caused by p α-syn*. Mutations could increase the expression, or cause abnormal processing of α-synuclein, which lead to PD. α-synuclein PD models could have been effectively induced using viral vectors, synthetic α-synuclein precursor fiber inoculation, or transgenic technology. At present, over-expression mediated by a viral vector is widely used. The viral vector targeting DA neurons is usually injected unilaterally into the substantia nigra striatum, and directly transmits wild type and mutant α-synuclein to simulate the PD disease process. Lentiviral and adeno-associated viral vectors can drive the expression of substantia nigra α-synuclein to mimic PD features, including the accumulation of α-synuclein in substantia nigra, loss of DA in the striatum, dysfunction of surviving DA striatum terminals, the degeneration and loss of DA neurons and axon lesions. Overexpression of pathogenic proteins by viral vectors can be applied to a variety of species, including rodents and non-human primates. Mulcahy et al., injected adeno-associated virus α-synuclein into the unilateral substantia nigra striatum of rats, and found that the striatum overexpressed α-synuclein, which could be transmitted to the end of axons and aggregated in the cell, resulting in the loss of substantia nigra striatum neurons and processes, and significant

contralateral motor dysfunction [24]. The PD monkey model established by adeno-associated viral vector-mediated overexpression of α-synuclein closely mimicked human pathological changes. Injection of synuclein into the brain of rodents and non-human primates can induce endogenous-synuclein fibrosis. The Bacterial Artificial Chromosome (BAC) transgenic mouse model has a more representative PD phenotype (including non-motor symptoms) and can be used to evaluate therapeutic strategies for promoting protein degradation and reducing α-synuclein aggregation. In addition, there are α-synuclein transgenic models in non-lactating animals such as *C. elegans* and Drosophila.

LRRK2 transgenic model: LRRK2 is a leucine-rich repeat kinase 2 encoded by the PARK8 gene. LRRK2 gene mutation is a common genetic feature of PD (autosomal dominant inheritance). Mutations in the LRRK2 gene may cause disease by enhancing its substrate phosphorylation kinase activity through active region recombination.

Maio et al., used the rotenone rat PD model to prove that rotenone activated LRRK2 in striatum DA neurons and increased the phosphorylation of the LRRK2 substrate Rab10 [25]. Sloan et al., observed an age-dependent movement defect in LRRK2 BAC transgenic rats expressing human G2019S or R1441C gene mutation in the roller experiment, but there was no such movement defect in rats expressing wild-type human LRRK2 [26].

PINK1 transgenic model: PINK1/PARK6 is the first known mitochondrial PD-related gene. PINK1 (PTEN-induced kinase 1) is a mitochondrial serine/threonine kinase, which exists in the inner and outer membrane of brain tissue and cell mitochondria, and has anti-apoptotic and anti-oxidation effects [27-38]. Mutation of the PINK1 gene disrupts its function, and the resulting oxidative damage could cause autosomal recessive premature PD. Studies accelerating mitochondrial genome error accumulation and mitochondrial stress induced by unfolded proteins in animal models have supported the view that PINK1 and Parkin play a role in the survival of DA neurons by correcting dysfunctional mitochondria [39-48]. Loss of PINK1 function leads to motor deficits and DA neuron degeneration in mouse models. PINK1 knockout (Knockout, KO) rats exhibit pathological characteristics associated with endogenous α-synuclein, and show clear progressive loss of substantia nigra neurons. These models can be used for targeted therapy of mitochondrial dysfunction and research on therapeutic strategies to remove or reduce α-synuclein inclusion bodies.

Parkin transgenic model: Parkin, encoded by the PARK2 gene, is the earliest discovered recessive genetic PD gene [49-52]. Mutations in this gene can lead to autosomal recessive genetic PD. Parkin is an E3-ubiquitin ligase, which is expressed in relatively high levels in the central nervous system, and can recognize specific proteins, including α-synuclein for degradation. Loss-of-function Parkin gene mutations cause abnormal E3-ubiquitin ligase function, affecting protein regulation and the removal of abnormal proteins, causing α-synuclein aggregation due to the blocked degradation pathway, and consequently cellular toxicity [53-57]. Meanwhile, Parkin degrades dysfunctional mitochondria through autophagy, and is further implicated in mitochondrial dysfunction as an important cause of PD pathogenesis. In Drosophila and mammals, Parkin acts on the same pathway downstream of PINK1. Aging or damaged mitochondria lose membrane potential, resulting in PINK1 translocation to the outer mitochondrial membrane. PINK1 recruits Parkin there and mediates its activation by phosphorylation, releasing Parkin from its usual self-inhibition. Parkin then mediates the aggregation and subsequent clearance of these mitochondria through mitophagy. Parkin and PINK1 therefore cooperate closely in regulating mitochondrial quality control, depending on the function of Parkin.

DJ-1 gene knockout model: Mutations in the PARK7 gene encoding DJ-1 could cause autosomal recessive early-onset PD, which may be related to LB accumulation. The interaction between DJ-1 and α-synuclein can affect the aggregation of pathological α-synuclein. As a redox-dependent molecular chaperone, DJ-1 can directly inhibit the early aggregation of α-synuclein. DJ-1 deficiency would cause an increase in oxidative stress, facilitating protein (including α-synuclein) aggregation. Therefore, DJ-1 plays a role in inhibiting α-synuclein aggregation. DJ-1 binds to the subunit of mitochondrial complex I and regulates its activity, which plays a role in resisting oxidative stress, neuroprotection, and maintaining mitochondrial function in PD. Compared with wild-type control rats, mitochondrial DJ-1-KO rats showed significant changes in mitochondrial respiration. DJ-1 KO in mice could cause loss of DA neurons and accumulation of defective mitochondria in the substantia nigra striatum. This phenomenon could be reversed by adeno-associated virus-mediated DJ-1 overexpression, indicating a special role for DJ-1 in mitochondrial function.

Generating models by transgenic technology is time-consuming and complex. Mixed side effects caused by the compensatory expression of some genes and the extensive-expression of PD-related genes are often observed. However, the construction process of the viral vector model is simple and rapid. The application of the viral vector model in adult rats could prevent the compensatory expression of corresponding genes, and the expression of related genes can be limited to local areas, such as the substantia nigra. Transduction is limited to one side of the brain hemisphere, and the opposite side can be used as a control. The α-synuclein overexpression transgenic model, which has been widely used in scientific research, can closely simulate the disease process induced by pathogenic genes, and is a good animal model to study the PD pathogenesis, gene therapy, and drug intervention. Moreover, compared to neurotoxin models, the α-synuclein overexpression transgenic model accurately reflects the characteristics of progressive slow degeneration of human PD substantia nigra DA neurons. However, these also have some shortcomings. For example, in most cases, the substantia nigra lacks obvious DA neuron loss, or the neuronal loss is present in non-PD related areas, such as the spinal cord. Moreover, no characteristic LBs have been observed in such models, even long-term.

Discussion

The Medial Forebrain Bundle (MFB) contains a large number of projections from DA neurons in the substantia nigra to DA neurons in the striatum. It is also the pathway of retrograde transport of striatum-derived neurotrophic factors to the SNpc and nutrition to the DA neurons. Mechanical injury to the MFB can damage substantia nigra neuron projections to the striatum, and cause the death of DA neurons in the substantia nigra due to lack of neurotrophic factors. The mechanical injury method requires the use of brain stereotaxic apparatus and stereotaxic technology to perform MFB axon cutting. The advantages of this method are its high success rate and low cost. DA neurons in the substantia nigra show a progressive death process, which is suitable for the study of drugs to improve the clinical symptoms of PD and neuronal regeneration. However, it is not suitable for exploring the causes of substantia nigra neuron death in PD.

Conclusion

Several different animal models for the pathogenesis of PD have been developed, and each has its advantages and disadvantages. Substantive substantia nigra striatum degeneration is common, and the motor symptoms of PD have been accurately replicated. Neurotoxin models, such as the 6-OHDA, MPTP, and rotenone models, have features consistent with the pathological characteristics of human PD. Genetic studies have elucidated the genetic principles and pathogenesis of PD. The neurotoxin models simulate the late stage of PD, and are not ideal to study potential cures. These are more suitable for the screening of symptomatic treatment drugs. Genetic models use overexpression or gene knockout technology to simulate early stages of PD. There is no progressive loss of DA neurons, which is more helpful in evaluating the role of genes in PD.

In summary, any PD animal model cannot fully simulate the clinical symptoms and pathological processes of PD. The choice of optimal animal model and experimental conditions should therefore be made according to factors such as the purpose of the study, detection indicators, operability, and research funding, in order to accurately explore the pathogenesis of PD and potential therapeutic targets.

Conflicts of Interest

The authors have no competing or conflicting interests to declare.

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