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MPTP-Induced Mouse Model of Parkinson's Disease: Advantages, Limitations, and Breakthroughs

Yi Luo, Bixiang Wang, Wenbiao Chen, Jiangying Chen *

Department of Neurology, Guangzhou Red Cross Hospital Affiliated to Jinan University, Guangzhou, Guangdong 510220, China
*** Corresponding author:** Jiangying Chen

Abstract: Parkinson's disease (PD) is a common neurodegenerative disorder characterized pathologically by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the formation of Lewy bodies, which are neuronal inclusions primarily composed of abnormally aggregated α-synuclein. To elucidate the pathogenesis of PD and explore therapeutic strategies, researchers have established various animal models. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) reliably triggers neuroimmune cascades in the animal brain that closely mirror the pathological hallmarks of PD and selectively destroys dopaminergic neurons. MPTP-based mouse models have become one of the most widely used PD animal models. This review systematically summarizes the in vivo metabolism of MPTP, common protocols for establishing MPTP-induced mouse models, their pathological features, and further discusses the trends and limitations of this model.

Keywords: Parkinson's Disease; MPTP; Animal Models; Neuroinflammation.

1. Introduction

Neurodegenerative diseases are a group of chronic disorders characterized by the progressive loss of neuronal structure and function. Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are among the most common types [1]. Due to the extremely limited regenerative capacity of neurons in the central nervous system, these diseases typically follow an irreversible and progressive course [2]. PD is the second most common neurodegenerative disease after AD, and its prevalence increases significantly with age. According to statistics, approximately 1% of people over the age of 60 are affected by the disease, while the prevalence can be as high as 3% in those aged 80 and above [3]. The primary pathological feature of PD is the progressive loss of dopaminergic neurons in the substantia nigra (SN). This loss results from neuronal degeneration and necrosis, leading to reduced dopamine (DA) synthesis in the nigrostriatal pathway. Recent studies have indicated that the loss of axonal integrity in this pathway is also a key factor in the onset and progression of the disease [4]. Another core pathological feature of PD is the misfolding and abnormal aggregation of α-synuclein (α-syn). These proteins aggregate within neuronal cell bodies and processes, forming insoluble, spherical, eosinophilic inclusions known as Lewy bodies (LBs) [5].

Currently, the exact etiology and complete pathophysiological mechanisms of PD remain to be fully elucidated. Current hypotheses regarding the causes of PD primarily involve genetic susceptibility gene mutations, environmental exposures (such as to pesticides, herbicides, and heavy metals), and mitochondrial dysfunction. Although drugs such as levodopa can effectively manage symptoms, there is currently no fundamental therapy that can halt or delay disease progression. Emerging strategies like stem cell therapy and CRISPR-Cas9 gene editing are still in the exploratory stage. While they show promise, they urgently require suitable research platforms for validation [6]. Therefore, preclinical research, particularly the application of animal models, is crucial for elucidating the pathogenesis of PD, discovering new therapeutic targets, and achieving early diagnosis. The establishment of animal models with good reproducibility, high stability, and pathological features closely matching those of clinical PD patients is key to in-depth research on PD pathogenesis and the development of new therapies.

Numerous animal models have been developed to investigate the pathogenesis and pathological characteristics of PD. Existing PD models each have their own advantages and limitations [7], and different modeling methods, administration routes, and dosages can significantly affect the mechanisms of action and experimental outcomes. This review focuses on the MPTP-induced mouse model of PD, providing a systematic overview of its metabolic characteristics, modeling methods, pathological features, and research progress.

2. Comparison of Common PD Animal Models

Current PD animal models are mainly divided into neurotoxin-induced models, transgenic models (e.g., parkin, PINK1, DJ-1), and combined models that integrate both approaches [8]. To some extent, PD animal models recapitulate pathophysiological features including the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the formation of Lewy bodies (LBs), and they mimic motor deficits similar to those observed in PD patients [9]. However, due to the complex pathophysiological mechanisms of PD, animal models cannot fully reproduce all the pathological and symptomatic features of the disease [10].

Commonly used neurotoxins include MPTP, 6-hydroxydopamine (6-OHDA), paraquat, and rotenone [11]. 6-OHDA cannot cross the blood-brain barrier and requires intracerebral injection via stereotaxic surgery, making it suitable for drug screening studies [12]. Rotenone is suitable for studying oxidative stress and neuroinflammatory responses and is often used in research on environmental etiologies [13]. The paraquat model is suitable for PD research related to environmental factors. The MPTP model

can effectively simulate the clinical motor symptoms of PD patients [14], and some studies have also found that it can reproduce certain non-motor symptoms. It is an ideal tool for studying early neuroinflammation and mitochondrial dysfunction induced by environmental toxins in PD, although the formation of Lewy bodies is rarely reported in this model [15].

Transgenic models can reveal pathogenic mechanisms at the genetic level but have limitations such as weak phenotypes and long experimental cycles [16].

3. Mechanism of MPTP Toxicity

In 1983, MPTP was accidentally discovered to induce acute parkinsonism in drug users [17]. Subsequent studies found that this compound selectively destroys dopaminergic neurons in the substantia nigra in both primates and mice. The neurotoxicity of MPTP primarily derives from its metabolite, 1-methyl-4-phenylpyridinium (MPP^+). MPTP is highly lipophilic and can cross the blood-brain barrier to enter the central nervous system. Once in the brain, MPTP is catalyzed by monoamine oxidase B (MAO-B) to form an unstable intermediate, 1-methyl-4-phenyl-2,3-dihydropyridinium ($MPDP^+$), which then spontaneously oxidizes to MPP^+ [18]. The chemical structure of MPP^+ is similar to that of DA, allowing it to be selectively taken up by dopaminergic neurons via the dopamine transporter. It then inhibits the electron transport chain function of mitochondrial complex I, ultimately leading to dopaminergic neuron degeneration and death [19]. Therefore, the MPTP animal model offers unique advantages for studying PD-related mitochondrial dysfunction.

The neurotoxicity of MPTP can also induce dysfunction of the autophagy-lysosomal pathway (ALP), primarily manifested as impaired autophagosome-lysosome fusion and decreased lysosomal degradation capacity, leading to defective clearance of misfolded α-syn and consequently promoting its abnormal accumulation within cells. Recent studies have shown that MPTP impairs autophagic flux by activating the transient receptor potential vanilloid 4 (TRPV4) calcium channel [20]. Of note, MPTP-induced α-syn aggregation can first occur at synaptic terminals, and this event precedes the onset of neuronal death [21].

Neuroinflammation is an important phenotypic feature of the MPTP model. Following MPTP treatment, microglia in the substantia nigra are rapidly activated, as evidenced by an increase in the number of Iba-1-positive cells and a morphological transformation from a branched to an amoeboid shape. Activated glial cells release pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and iNOS, while the expression of the anti-inflammatory cytokine TGF-β decreases. These inflammatory mediators further exacerbate neuronal injury, creating a vicious cycle [22]. This phenomenon is highly consistent with the chronic neuroinflammation characteristic observed in the brains of PD patients.

4. MPTP-Induced Mouse Models of PD

The MPTP animal model has been widely used in PD research. The neurotoxic effects of MPTP have been demonstrated in various experimental animals, including monkeys, mice, pigs, and fruit flies. Non-human primate models are closer to human pathological features but are less commonly used due to high costs and ethical concerns [23]. Compared with primates, rodents have become the mainstream choice because of their low cost and ease of handling. The effect of MPTP induction is species-specific, with the C57BL/6 mouse strain exhibiting higher sensitivity; therefore, most studies focus on mice [24]. Common MPTP-induced PD mouse models can be classified into three types: acute, subacute, and chronic injury models. Additionally, MPTP can be used in combination with transgenic animals to generate combined models. MPTP reliably induces highly selective, rapid, and predictable dopaminergic neurotoxic injury. Model mice exhibit motor symptoms such as tremor, bradykinesia, and balance impairment, as well as non-motor symptoms including olfactory dysfunction [25], cognitive impairment [26], depression [27], and anxiety [28].

4.1. Acute Injury Model

The acute injury model uses a high-dose, short-duration dosing regimen. A typical protocol involves intraperitoneal injections of 20 mg/kg MPTP every 2 hours for a total of 4 injections. This model exhibits significant dopaminergic neuron loss in the substantia nigra (70%-80% reduction) within 1-3 days post-modeling, accompanied by pronounced motor behavioral deficits [29]. Its main advantages include rapid modeling, low cost, and high uniformity of lesion severity. The limitations are that neuronal death is too acute, differing substantially from the chronic progressive pathological process of PD, and the model lacks α-syn aggregation and Lewy body formation.

4.2. Subacute Injury Model

The subacute injury model uses a medium-dose, continuous dosing regimen. A typical protocol involves daily intraperitoneal injections of 20-30 mg/kg MPTP for 5 consecutive days. This model achieves stable pathological changes 7-14 days post-modeling, with a reduction of tyrosine hydroxylase (TH)-positive neurons in the substantia nigra by approximately 50%-60%, accompanied by mild to moderate glial activation [30]. The subacute model is currently the most widely used subtype of MPTP model. Because it achieves a good balance between modeling efficiency and pathological progression, it is particularly suitable for evaluating the efficacy of drug intervention studies. However, this model shares the major limitation of lacking Lewy body formation.

4.3. Chronic Injury Model

The chronic injury model uses a low-dose, long-term dosing regimen. A typical protocol involves intraperitoneal injections of 10-15 mg/kg MPTP, 3-5 times per week, for 4-5 weeks [31]. Probenecid inhibits the renal clearance of MPTP metabolites, thereby improving the modeling success rate of the MPTP-induced Parkinson's disease model. The chronic model established by prolonged low-dose MPTP administration not only recapitulates the pathological features of PD observed in the acute model, but some studies employing MPTP combined with probenecid have also reported α-syn aggregation, thereby more closely resembling the chronic and progressive pathological evolution of human PD [32]. Therefore, it more closely resembles the chronic, progressive pathological evolution of human PD.

4.4. MPTP-Transgenic Combined Models

PD has a long disease course, encompassing a prodromal phase lasting years to decades followed by a phase of clinical

symptoms. During this period, compensatory changes may occur in the patient's brain, features that cannot be recapitulated in acute toxin models [33]. The inherent limitations of single neurotoxin models prevent them from fully replicating all the symptoms and pathological changes of human PD.

Meanwhile, some transgenic models (e.g., DJ-1 knockout models) have the drawback of weak phenotypes. However, when DJ-1 knockout mice [34] and A53T α-syn transgenic mice [35] are treated with MPTP, the combined model mice exhibit more pronounced dopaminergic neuron degeneration and increased cell death compared with either modeling method alone, and their neurons are more sensitive to oxidative stress. Further studies have shown that this loss of protection is related to impaired DJ-1 function in reducing reactive oxygen species (ROS) levels [36]. Moreover, differential expression of DJ-1 in brain regions such as the olfactory bulb and hippocampus may explain why olfactory dysfunction precedes cognitive impairment in PD patients [37].

Sporadic PD accounts for the vast majority of all PD cases and is generally considered to result from the combined effect of genetic susceptibility and environmental factors. The MPTP plus transgenic mouse model simulates a "genetic background + environmental trigger" pathogenic pattern, which can explain why only some individuals develop the disease under the same environmental exposure. Compared with the MPTP model alone, the combined model can utilize sub-toxic doses, more closely resembling real-world exposure scenarios, and is an important tool for studying gene-environment interactions in PD. Furthermore, this model can better simulate early non-motor symptoms. By comparing the differential responses of transgenic and wild-type mice to MPTP, it is possible to identify susceptibility genes and protective genes, and it is also more convenient for testing gene therapy strategies such as CRISPR and ASO [38].

These findings indicate that a combined strategy integrating neurotoxins with genetic models can more accurately reproduce the complexity of human PD and holds significant value for exploring disease mechanisms.

5. New Breakthroughs in the MPTP Model

Although the MPTP model has been widely used, its inherent limitations regarding α-syn pathology and chronic progression have remained controversial. However, recent studies are re-examining these "limitations" from new perspectives and, with the support of new technologies, are developing novel application scenarios for this model.

Ferroptosis is a form of regulated cell death that is iron-dependent and characterized by lipid peroxidation. A comparative study systematically analyzed three PD models (6-OHDA, MPTP, and lipopolysaccharide [LPS]) and found that the MPTP model showed prominent changes in ferroptosis-related indicators (decreased FTH1 and GPX4, increased MDA and ROS), suggesting that this model has unique value for research on ferroptosis pathways [39].

The MPTP model has also seen new advances in neuroinflammation research. Traditionally, the MPTP model was considered unsuitable for studying gut-brain axis propagation of α-syn due to its lack of α-syn aggregation. However, recent studies suggest that MPTP can induce significant gut microbiota alterations and intestinal inflammation via circulating inflammatory factors, providing a unique platform for exploring the "gut microbiota — neuroinflammation — dopaminergic neuron injury" pathway [40].

At the molecular mechanism level, the dynamic monitoring capability of the MPTP model has also been newly developed. The "overly acute neuronal death" characteristic of the MPTP model has traditionally been viewed as a drawback. However, recent studies have re-examined this issue: in certain research scenarios, investigators can precisely administer drugs at specific time points before, simultaneously with, or after MPTP injection (e.g., 2 hours, 6 hours, 24 hours), thereby determining whether a drug acts during the preventive, early intervention, or post-injury repair phase.

Previous oxidative stress studies mostly detected end products or indirect markers, making it difficult to capture dynamic changes of specific reactive molecules in real time. ClO^- is a highly reactive oxidant produced by myeloperoxidase (MPO). Cheng et al. developed an innovative method combining in vivo brain microdialysis with fluorescent carbon dot probes, achieving real-time tracking of striatal ClO^- levels during PD progression [41]. This provides more direct evidence for oxidative stress and inflammatory pathways in PD. This dynamic monitoring capability is difficult to achieve with other models and is of great significance for elucidating drug mechanisms.

Meanwhile, the application of novel imaging technologies has further expanded the research dimensions of the MPTP model. A recent study combined the MPTP model with artificial intelligence (AI)-enhanced molecular magnetic resonance imaging (MRI) to achieve "visualized" quantitative analysis of brain metabolites. Due to its relatively predictable disease course and well-defined lesion targets, the MPTP model has become an ideal platform for validating and optimizing this cutting-edge imaging technology [42].

In a chronic MPTP/probenecid model study, the number of dopaminergic neurons in the mouse substantia nigra was significantly reduced at 1 month post-modeling but showed partial recovery at 12 months. Through proteomic analysis, the researchers identified two key proteins, Bmpr2 and Gstm2, that may drive this endogenous repair. This finding challenges the traditional view of the MPTP model as causing "irreversible injury" [43].

Based on the anatomical proximity of the olfactory mucosa to the central nervous system and the relatively weak blood-brain barrier in the olfactory bulb region, the MPTP intranasal administration model has validated Braak's hypothesis that "PD pathological changes begin in brain regions such as the olfactory bulb and gradually spread to motor control centers such as the substantia nigra" [44].

6. Conclusion

The MPTP model has been successfully used to evaluate the ability of novel neuroprotective strategies to reverse or delay disease progression. However, considerable gaps remain between this model and the actual pathological changes and clinical symptoms of PD patients, particularly its inherent limitations regarding α-syn pathology and chronic progression. The MPTP model holds great potential for elucidating the etiology and pathogenesis of Parkinson's disease, and recent evidence continues to challenge traditional views. Therefore, it is particularly necessary to optimize existing modeling protocols to better recapitulate the full

pathological spectrum of PD and to construct animal models that more closely match clinical characteristics using new technologies.

Looking forward, deep integration with emerging technology platforms, expanded application of model variants, and in-depth exploration of neuroendogenous repair mechanisms will be important directions for MPTP model research. These efforts are expected to promote the continued indispensable role of the MPTP model in elucidating PD pathogenesis and developing therapeutic strategies.

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