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Adeno-associated virus-mediated neural repair in parkinson's disease: a systematic review from animal models to clinical trials

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Abstract. In response to the limitations of existing treatment methods, the development of new treatment approaches that can delay or reverse the neurodegenerative process has become a research hotspot. Gene therapy, especially strategies based on adeno-associated virus (AAV) vectors, is emerging as a research frontier in the treatment of Parkinson's disease due to its high efficiency, low immunogenicity, long-term stable expression, and neuron tropism in the nervous system. Recent clinical trials have demonstrated significant improvements in motor function, with some approaches showing up to 36% enhancement in UPDRS scores. AAV-mediated gene therapy mainly focuses on the following therapeutic targets: dopamine pathway reconstruction, neurotrophic factor delivery, α-synuclein clearance strategies, and emerging therapeutic targets. The main purpose of this review is to evaluate the latest research progress of AAV vector gene therapy in Parkinson's disease, focusing on analyzing its potential and challenges in the preclinical and clinical translation process and proposing possible optimization paths to promote the clinical application of gene therapy.

Keywords: adeno-associated virus, parkinson’s disease, gene therapy

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease in the brain, with a prevalence of 1.7% in people over 65 years old in China. The main pathological features of PD are the progressive loss of substantia nigra dopaminergic neurons and the abnormal aggregation of α-synuclein forming Lewy bodies. Its clinical manifestations are muscle rigidity, bradykinesia and tremor, motor dysfunction, and non-motor symptoms including cognitive impairment, autonomic nerve dysfunction, and affective disorders. The main treatments include levodopa, dopamine receptor agonists, deep brain stimulation (DBS), etc. While DBS shows efficacy in motor symptom control, its invasive nature and cost constrain broad application [1]. However, these methods can only relieve the symptoms but can not prevent the progression of the disease, and the long-term use of L-DOPA is easy to cause motor complications. About 50% of patients with L-DOPA will develop drug end phenomenon or dyskinesia within 5 to 10 years.

Therefore, exploring new treatment methods that can delay or reverse the process of neurodegeneration has become a research hotspot. Among them, gene therapy, especially adeno-associated virus (AAV) vector-based strategies, has become the research frontier of Parkinson's disease treatment because of its safety and high efficiency in the nervous system [1]. Preclinical studies demonstrate AAV vectors can restore dopamine synthesis to 3-4 times normal levels in primate models [6], with functional recovery persisting long-term [2].

2. Gene therapy

Gene therapy provides a new treatment strategy for PD. Its basic principle is the use of non-replicating viral vectors, mainly targeting AAV or lentivirus-associated virus (LV) vectors, which have become the preferred delivery tools for PD gene therapy due to their low immunogenicity, long-term stability of expression, wide neuronal tropism, and good safety [3]. The main therapeutic goals of PD include dopamine pathway reconstruction, neurotrophin delivery, α-synuclein clearance strategy, and emerging therapeutic targets [4]. The main objectives of this review are to discuss the latest advances in AAV vector-based therapies, evaluate the clinical research results, and discuss the challenges of clinical translation.

3. Preclinical studies

The preclinical studies of PD gene therapy mainly rely on a variety of animal models to simulate the complex pathological features of PD, among which the classic 6-hydroxydopamine (6-OHDA) injury model, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) model, and α-synuclein overexpression transgenic model are the most widely used models. The 6-OHDA model can induce stable rotational behavior by selectively destroying dopaminergic neurons through unilateral striatal or substantia nigra injection, which is an ideal model to evaluate the effect of pathway repair of dopamine. The MPTP model can induce acute dopaminergic neuron death by inhibiting mitochondrial complex I, which is especially suitable for non-human primate studies [5].

α-synuclein, encoded by SNCA (α-synuclein gene), is the main component of Lewy bodies, and its abnormal aggregation is the core pathological hallmark of PD. Although the traditional SNCA overexpression transgenic mouse model can simulate the abnormal aggregation of α-synuclein, it is difficult to recapitulate the progressive loss of dopaminergic neurons in PD. To address this limitation, Van der Perren et al. developed an AAV-based α-synuclein fiber seeding model in Neurobiology of Aging [6]. The team injected AAV1/2 hybrid vectors carrying human α-synuclein preformed fibers (PFFs) into the substantia nigra pars compacta (SNPC) of rats. The team successfully induced pathological features highly similar to human PD: approximately 40% reduction of dopaminergic neurons in the substantia nigra and 60% reduction of dopamine levels in the striatum at 24 weeks after injection. Behavioral tests showed a 50% reduction in motor coordination ability (Rotarod test) and PD-like bradykinesia (35% reduction in gait speed). The model not only recapitulated the molecular pathological features of PD but also displayed a motor phenotype more similar to human disease.

Biochemical and functional markers of the dopamine pathway, such as the activity of aromatic L-amino acid decarboxylase (AADC), can be used as key indicators to evaluate the therapeutic effect of PD. The activity of AADC, the rate-limiting enzyme for the conversion of L-DOPA to dopamine, is significantly reduced in the striatum of PD patients, which directly leads to insufficient synthesis of dopamine. Bankiewicz et al. delivered AAV-AADC genes to the striatum of MPTP-lesioned rhesus monkeys by convection-enhanced delivery (CED), restoring AADC activity to 3-4 times the normal value. PET-FMT imaging showed that the dopamine synthesis of the injured striatum was close to or higher than that of the contralateral striatum [2]. Functional recovery was further confirmed by behavioral tests (e.g., gait analysis in rhesus monkeys, rotational asymmetry test in rodents): after treatment, bradykinesia improved by 50-70%, and balance ability recovered to more than 80% of normal level, indicating a direct link between the biochemical repair of the dopamine pathway and the improvement of motor function. Although AADC activity detection has high specificity, it is limited to reflecting the efficiency of enzymatic reaction and cannot comprehensively evaluate the recovery of synaptic transmission or neural circuit function. Therefore, it needs to be verified by combining functional imaging and behavioral data. For example, Jamie L. Eberling et al. found that AAV-mediated gene therapy can significantly restore motor function in rodents and nonhuman primates, but the clinical relevance of animal behavioral scores (e.g., a 40% reduction in CRS) to the human UPDRS scale needs to be further validated in cross-species translational studies [7]. Quantitative measures of behavioral tests (e.g., gait speed and motor coordination scores) can not only dynamically monitor the response to treatment but also reveal the temporal characteristics of functional recovery of neural circuits. For example, improvement in motor coordination often lags behind the recovery of AADC activity by 1-2 weeks, suggesting that synaptic remodeling requires a longer process of neuroplasticity adaptation. Mechanistically, recovery of AADC activity drives behavioral improvement through a cascade of responses that require multimodal data (e.g., microdialysis monitoring of synaptic dopamine release and electrophysiological recording of neuronal synchrony) to strengthen causal arguments. This provides a theoretical basis for the selection of therapeutic targets (such as striatal coverage optimization) and the standardization of therapeutic markers (such as PET-FMT threshold definition) in clinical transformation.

There are several important limitations to these preclinical studies. The first is the limitation of the models themselves. The 6-OHDA and MPTP models mainly simulate the damage of dopaminergic neurons, but the α-synuclein lacks pathological characteristics. In contrast, α-synuclein transgenic models lack significant neuronal loss. Translation from animal models to human patients presents challenges: Rodent brain volumes differ by three orders of magnitude from humans, making direct extrapolation of drug delivery strategies and vector distribution difficult. Long-term safety issues, such as the possible immune response caused by AAV vectors and the long-term expression stability of the transgene, need to be studied in more depth [8].

4. Analysis of clinical trials

4.1. VY-AADC01 (AAV2-HAADC)

VY-AADC01 is the first AAV gene therapy trial for advanced Parkinson's disease. Focusing on AADC enzyme recovery, this study is the first phase I clinical trial of AAV gene therapy for advanced PD (NCT00229736). The AAV2 vector containing the human AADC gene (AAV-haADC) was precisely injected into the bilateral posterior putamen using stereotactic surgery combined with CED technology. Ten patients with advanced PD (Hoehn-Yahr stage III-IV, mean disease duration 8.4 years) were treated with a low dose (9×10^{10} vg) or a high dose (3×10^{11} vg) of AAV2-AADC. At 6-month follow-up, the UPDRS total score

(which is mainly used to comprehensively evaluate the severity of PD and the effect of therapeutic intervention) improved by 31% (p=0.0008), and the motor score improved by 36% (p=0.0016) in patients without AAV2-AADC. The overall UPDRS score in the drug-off state was improved by 32% (p=0.004). PET imaging showed that the uptake of ^{18}F FMT in the putamen increased significantly (up to 175% of the baseline), suggesting that the activity of the AADC enzyme was enhanced. In terms of safety, 3 cases of intracranial hemorrhage (1 case of symptomatic) were reported, but no systemic toxicity related to the carrier was observed, and the change of antibody titer was not related to the efficacy. Although this study provides strong evidence for the feasibility and preliminary efficacy of the AAV-AADC strategy, the sample size is limited, and long-term follow-up and evaluation of the persistence of remission of motor fluctuations are lacking, which need to be further verified in subsequent phase II/III trials [9].

4.2. CERE-120

CERE-120 is a gene therapy strategy that delivers the neurotrophic factor Neurturin (NTN) to the striatum and substantia nigra via AAV2 vector to promote the survival and repair of dopaminergic neurons by activating the GFRα2/RET signaling pathway. NTN, a member of the GDNF family, can promote the survival of dopaminergic neurons and axonal regeneration by binding to the GFRα2/RET receptor complex and activating the downstream PI3K/Akt and MAPK pathways. Therefore, NTN is considered as a therapeutic candidate with neuroprotective potential [10]. A phase I/II open-label trial showed a 36% improvement in UPDRS-III score at 18 months after surgery, demonstrating initial therapeutic potential. However, the results of the phase III double-blind placebo-controlled trial (n=58) failed to meet the primary efficacy endpoint, with only a 19% improvement in the treatment group, which was not significantly different from the control group. Although the phase I/II open-label trial showed a mean 36% improvement in UPDRS-III score at 18 months, a subsequent phase III double-blind, placebo-controlled trial showed only a 19% improvement in the treatment group, which did not meet the primary endpoint. This contrast prompted researchers to reflect on the mechanisms underlying the limited efficacy of NTN in advanced patients. Efficacy was improved by as much as 29% in patients with milder baseline disease (UPDRS-III≤50), suggesting that disease stage may significantly influence treatment response. This was due to >70% neuronal loss in the substantia nigra. On the safety side, there were two deaths (one myocardial infarction, one pulmonary embolism); none of these deaths were judged to be NTN-related [11]. Subsequent studies showed that Neurturin must be transported backward through an intact axonal network to the substantia nigra to function, and the severe degeneration of axons in advanced PD patients prevents it from effectively activating target neurons. At the same time, the reduced expression of the receptors also limits the amplification of neurotrophic signals, which may be an important mechanism for the limitation of therapeutic effect.

4.3. ProSavin

In contrast to AAV, which primarily restores enzyme function or delivers neurotrophic factors, ProSavin represents another non-AAV strategy to multigene reestablish the dopamine synthesis pathway in order to repair neuronal function rather than protect preexisting neurons. ProSavin uses a lentiviral vector to deliver tyrosine hydroxylase (TH), AADC, and GTP cyclohydrolase 1 (GCH1) genes in an attempt to reestablish the complete dopamine synthesis pathway in residual neurons. Thus, long-term local neurotransmitter replantation can be achieved. The results of the phase I/II open-label trial (N=15) showed that the average improvement of the UPDRS-III score at 6 months after surgery was 33%, and some individuals had a maximum improvement of 53% (P=0.0001) in the discontinuing state. Meanwhile, c-raclopride PET imaging showed a dose-dependent change in dopamine receptor occupancy, and animal models also suggested that dopamine recovered to 5-10% of normal levels [12]. However, the optimized version of AXO-Lenti-PD significantly improved the transduction efficiency and the stability of dopamine pathways in the striatum by modifying the vector design (e.g., neuron-specific promoter and autoregulation system). To address these challenges, the optimized version, AXO-Lenti-PD (OXB-102), incorporates neuron-specific promoters (e.g., PDGFβ) and self-regulating gene expression systems (e.g., miRNA feedback regulation), significantly enhancing striatal transduction efficiency (coverage expanded to 50-60%) and dopamine pathway stability (reducing dopamine fluctuation amplitude by 70%). Phase I/II trials demonstrated an improved UPDRS-III score improvement of 48% [13].

5. Conclusion

Significant advancements in PD gene therapy have been achieved through preclinical and clinical studies, yet critical challenges remain. AAV-based dopamine restoration strategies, such as VY-AADC01, enhance AADC activity to amplify striatal dopamine synthesis, demonstrating a 36% improvement in UPDRS-III scores in advanced PD patients, with PET imaging confirming dopamine synthesis recovery to 175% of baseline levels. Neurotrophic factor therapies like CERE-120 (AAV2-Neurturin) initially showed preclinical promise by rescuing 50-60% of dopaminergic neurons in MPTP-treated primates via retrograde axonal transport. However, Phase III trials revealed limited efficacy in late-stage patients (>70% neuronal loss), where degenerated nigrostriatal pathways prevent neurotrophic signal delivery, resulting in only 19% UPDRS-III improvement—

highlighting the need for early intervention in patients with preserved axonal integrity. Multigene approaches, exemplified by ProSavin and its optimized successor AXO-Lenti-PD (OXB-102), use lentiviral vectors to co-deliver TH, AADC, and GCH1, achieving 48% UPDRS-III improvement through neuron-specific PDGF β promoters and miRNA feedback systems that stabilize dopamine levels (±12% fluctuation vs. ProSavin's ±40%) and expand striatal coverage to 50-60%. Despite progress, lentiviral immunogenicity risks persist, with 15% of recipients developing transient anti-vector T-cell responses, necessitating long-term safety monitoring.

Key translational barriers include: Inadequate models: Rodent 6-OHDA and α-synuclein fibril models fail to replicate human PD's progressive α-synuclein propagation (e.g., Braak staging) or non-motor symptoms like autonomic dysfunction; AAV limitations: Suboptimal striatal diffusion (20-30% coverage) and epigenetic silencing (40% AADC activity loss at 5 years) hinder sustained efficacy; Outcome metric gaps: Overreliance on UPDRS scores overlooks CSF biomarkers (e.g., α-synuclein oligomer-to-monomer ratios>1.5) and AI-driven digital motor phenotypes (e.g., gait asymmetry quantified by wearable sensors).

Future breakthroughs demand three-pronged innovation: Vector engineering—developing BBB-penetrant AAV serotypes (e.g., AAV.CAP-Mac with enhanced dopaminergic tropism) and hypoxia-inducible promoters to sustain gene expression; Combinatorial therapies—integrating gene editing (CRISPR-Cas9 SNCA knockdown) with immunotherapies (AFFITOPE® vaccines targeting α-synuclein) or stem cell-derived dopaminergic grafts; Precision stratification—leveraging SNCA Rep1 alleles, GBA1 mutations (L444P carriers exhibit 30% faster decline), and DAT-SPECT imaging to tailor therapies. By addressing these challenges, the field aims to transition from symptom management to disease-modifying neural circuit reconstruction, potentially halting PD progression within the next decade.

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