The New Developing Treatment of Parkinson's Disease

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ABSTRACT: Parkinson's disease (PD) is the second most common neurodegenerative illness that affects the central nervous system, especially the motor nervous system and it is marked clinically by movement impairment. Its symptoms usually arise gradually over time. Tremors, limb stiffness and abnormal gait are all obvious in the early phase, and some PD patients also have non-motor symptoms like behavioral problems. Besides, decline of cognition is common in severely ill patients. While the pathogenesis of PD has not been fully studied, genetic and environmental factors are generally thought to play a role. There are a lot of potential mechanisms like mitochondrial dysfunction, neuroinflammation and abnormal metabolism. Drugs therapy is the major treatment for PD. But drugs may bring some side effects, it is urgent to find new treatment targeting at specific sites. This review introduces the current drugs and new developing drugs for PD.

1. Introduction

PD is the second most common and progressive neurodegenerative movement disorder characterized clinically by some motor symptoms like tremor at rest, bradykinesia and unsteady posture, often accompanied by non-motor symptoms like hyposmia and sleep disturbance. Furthermore, people with PD can also have cognitive and behavioral problems. Decline of cognition is common in severely ill patients. It's reported that PD affects about 1% of people aged over 65 in the whole world [1], bringing huge physical and mental burden to patients and their families.

The etiology and pathogenic mechanism of PD is still unclear, but it may be related to the following factors such as excessive oxidative stress, neuroinflammation, mitochondrial dysfunction and impaired Ca^{2+} homeostasis. In grey matter, α-synuclein aggregation and selective loss of dopaminergic neurons in the pars compacta of the substantia nigra (SN) in the midbrain are two major pathologies in PD [1]. More than 30 genes have been found to be associated with PD. There are several major risk genes like *LRRK2* [2]. Leucine-rich repeat kinase 2 gene (*LRRK2*) mutations generally cause mid- or late-stage PD. LRRK2 regulates a lot of functions such as cytoskeletal dynamics, mitochondrial function [3], neuroinflammation [4], and lysosomal degradation. Furthermore, diabetes is a risk of PD. Patients with diabetes are likely to get PD, meanwhile, PD patients also have abnormal glucose metabolism. Insulin resistance is common in PD patients [5]. N-methyl-D-aspartic acid (NMDA) receptor is a kind of excitatory glutamate receptors, which is associated with synaptic plasticity and development of nervous system. The activation of NMDA receptors is considered to be related to the pathogenesis of PD. For the reason that the activation of NMDA receptors leads to impaired Ca2+ homeostasis. As a result, a variety of neuronal necrosis or apoptosis.

At present, there is no potential way to cure PD. PD medications are effective obviously in the early stage of this disease. This period is called the "honeymoon period", which generally lasts for 3 to 5 years. "On-off phenomenon" (ON-OFF) is a complication in the late stage of drug treatment for PD. "On" means that the medication has an obvious effect on the patients, and they have ability to exercise; "off" means that after receiving drug treatment for a period of time, patients lose motor ability due to low levels of dopamine. Some patients have improved original motor symptoms such as stiffness, but other movement disorders have appeared. The population of PD is increasing every year, it is urgent to find innovative ways to treat patients. This review introduces new drugs and potential targets for treating PD in recent two years.

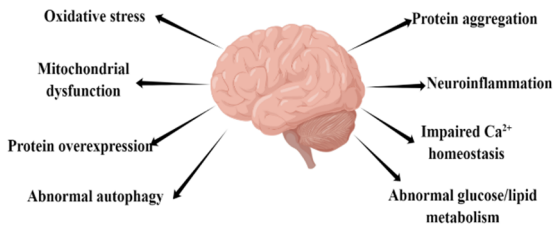

Figure1. The pathogenesis of PD

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2. New developing drugs for PD

2.1. Naturally occurring compounds

2.1.1. Withaferin A

Naturally occurring compounds plays a potential role in PD therapy due to their diverse biological activities related to neuroprotection. Withaferin A (WA) is regarded a neuroprotective agent. It is a natural small molecule compound with high fat-soluble steroid lipids, it has multiple pharmacological properties such as alleviating stress, enhancing autophagy and regulating glucose and lipid metabolism. In a mouse model of MPTP-induced PD, the mice given WA could prevent the loss of dopaminergic neuron and motor deficits. WA also attenuates the accumulation of α-synuclein. It functions through DJ1-Nrf2-STING axis. WA provides a new perspective for developing new drugs for PD [6].

2.1.2. Farnesol

Farnesol, a compound naturally found in flower, fruits and fungi, inactivates the PARIS protein. As a result, it prevents the loss of neurons which produce dopamine in the brain. In a study in mouse model of PD, the mice given farnesol behaved better on behavioral tests to detect motor ability. The healthy dopamine neurons in farnesol-fed mice were twice than that in control mice. PGC-1α is a major mediator that coordinates mitochondrial biogenesis, cellular respiration and energy metabolism, which was increased in farnesol-fed mice [7].

2.2. LRRK2 kinase inhibitor

New studies show that regardless of whether there is a mutation of LRRK2, LRRK2 mutation promotes the development of PD. Like idiopathic PD, patients also have excessive activation of LRRK2 protein and impaired autophagy function of neuronal cells, which leads to the excessive accumulation of α-synuclein [8].

LRRK2 kinase inhibitors have some neuroprotective effects to some extents [9]. The research about LRRK2 kinase inhibitor have got a lot development. There is a new drug called BIIB094 in the phase I of clinical trials. It is a LRRK2 antisense oligonucleotide (ASO) that reverses the abnormal endoplasmic reticulum calcium and the defects of mitochondrial phagocytosis [10]. ASO has good diffusivity in cerebrospinal fluid, it is beneficial to the application of ASO in Neurological disorders. It has been identified to be safe and tolerable [11]. DNL-201 and DNL 151 are non-ATP-competitive LRRK2 inhibitors. Both of them have been tested on early clinical trials. Among the subjects, DNL151 showed better tolerability in a wide dose range and improved the function of lysosome [12]. EB-42168, a novel LRRK2 G2019S inhibitor, is about 100 times more selective for LRRK2 G2019S mutation, it also lowers phosphorylation biomarkers of LRRK2 G2019S mutation [13].

2.3. G-coupled protein receptor inhibitor

CVN424 is a G-coupled protein receptor (GPCR) inhibitor targeting the dopamine D2 receptor-dependent indirect signaling pathway. It aims to produce the same positive effects as levodopa or deep brain stimulation, while at the same time, it avoids negative sides. The data in phase II of clinical trial showed that patients with PD in high-dose group improved the "off" period by 1.3 hours and increased the "ON" time without dyskinesia compared with placebo. Furthermore, CVN424 decreased some indicators during daytime in patients [14].

2.4. NMDA modulators

NMDARs is an ionotropic glutamate receptor that allows the passage of cations and is an important mediator of adults' synaptic plasticity and consolidating adaptive processes of memory and acquired neuroprotection. A study in a primate model of PD showed that those primates giving NYX-458 with higher dose 0.1mg/kg and 1mg/kg all had a significant improvement in Variable Delayed Response (VDR) performance than those in a group with low dose 0.03mg/kg (p =0.026, p < 0.02 respectively) [15]. It is a potential therapy for impaired cognition in PD. NYX-48 produced in Aptinyx company and SAGE-718 produced in Sage Therapeutics are NMDAR modulators, which are being tested in phase II of clinical trial to treat the progression of PD.

2.5. ABBV-951

Because ABBV-951 composed of foslevodopa and foscarbidopa has high water solubility and chemical stability, it's used in subcutaneous infusion continuously. This way is being studied to treat advanced PD where motor symptoms are not controlled by oral levodopa/carbidopa. The phase I of clinical had proved its safety and pretty tolerance [16]. The study about ABBV-951 in the phase III showed it was statistically superior to oral levodopa/carbidopa in reducing the motor fluctuations in patients with advanced PD. After 12 weeks of ABBV-951 treatment, the "ON" time increased by 2.72 hours, while "ON" time increased by 0.97 hours in the oral levodopa/carbidopa group. (The results of ABBV in phase III from AbbVie company)

2.6. Mesdopetam (IRL790)

Dopaminergic treatment has some negative effects such as dyskinesia and psychotic symptoms. Mesdopetam is a novel dopamine D3 receptor antagonist developed for the prevention and treatment of levodopa-induced dyskinesia (LID) in patients with PD. The safety and tolerability of this drugs had been proved in volunteers [17]. The completed phase Ib and 2a clinical trial revealed that patients given mesdopetam treatment had substantial improvements in experienced dyskinesia and prolonged "ON" period. (The results of IRL 790 in phase Ib and 2a from ipsen company)

2.7. Fibroblast Growth Factor21

Fibroblast Growth Factor21 (FGF21) regulates glucose and lipid metabolism. In mouse model of PD, the mice given FGF21 showed better memory and motor ability compared to PD mice without FGF21 treatment. It also reduced the expression of IL-1β and TNF-α which are the markers of microglia. Therefore, FGF21 attenuates neurodegeneration and neuroinflammation by regulating microglia polarization. It plays a neuroprotective role in central nervous system [18].

2.8. Dipeptidyl peptidase -4 inhibitor (DPP4)

Dipeptidyl peptidase -4 inhibitor (DPP4) is a drug for Diabetes. It regulates blood sugar by inhibiting the release of glucagon and increasing insulin secretion. A recent study showed that the patients in diabetic group previously treated with a DPP4 inhibitor had lower rate of levodopa-induced dyskinesia than that in diabetic group without DPP4 inhibitor [19]. DPP4 inhibitors may help patients alleviate dopamine degeneration and improve motor ability. This effect may contribute to non-diabetic PD patients.

2.9. Nicotinamide riboside supplementation

Nicotinamide riboside (NR) is an initial form of Vitmin3. According to a study in fly model of PD, the flies given feed containing NR had better motor ability than that in flies given feed without NR. Besides, after NR treatment, new mitochondrial are produced [20]. Research conducted a test about NR in phase I of clinical trial, an obvious increase in NAD levels in the brains of patients following NR supplementation was observed, along with a decrease in inflammatory markers. Moreover, their symptoms related to PD had obvious changes. The improved NAD metabolism may provide a potential therapy for PD [21].

3. New developing non-drugs for PD

3.1. Gene therapy

Different gene therapy drugs currently undergoing clinical trials can be categorized based on their mechanisms: 1. Nutritional factors, such as CERE-120 and AAV2-GDNF, they are able to relieve symptoms by nourishing the dopamine neurons; 2. Gene replacement therapy for key genes in dopamine synthesis or in metabolic pathways, such as AADC, PR001A regulates the energy metabolism in patients with PD; 3. Gene expression regulation, BIIB094 blocks protein translation in *LRRK2*-mutant patients.

Aromatic L-amino acid decarboxylase (AADC) is an enzyme that converts levodopa to dopamine. As the development of PD, the numbers of nigrostriatal cells where AADC is produced are reduced. Therefore, patients need to increase their levodopa dose and other treatments to control their motor fluctuations and dyskinesia. Gene therapy can provide durable, potentially lifelong clinical benefits in patients with PD after a single dose. Adeno-associated virus serotype 2 (AAV2) gene therapy, NBIb-1817 (VY-AADC01), aims to stimulate the production of dopamine by delivering the AADC gene directly to the dopaminergic cell. During phase 1b of clinical trial, there was no severe adverse events. At 36 months of this treatment, the two highest-dose cohorts had a 21-30% reduction in requirements of taking PD medications. The quality of patients' lives and their motor ability were improved compared to placebo [22].

3.2. Stem cell therapy

During the past few years, stem cell therapy has developed rapidly in many aspects such as fields of regenerative medicine and establishment of disease models. Stem cells may self-renewal and differentiate in multi-direction, which results in regenerating and repairing nerves in damaged tissues.

Mesenchymal stem cells (MSCs) therapy is regarded as an ideal therapy for PD. MSCs have some characteristics like high self-renewal ability, low immunogenicity and low probability of tumorigenicity after transplantation into human body. MSCs have the ability to differentiate into astrocytes or neuron-like cells in the brain, then they transform into dopaminergic neurons which replace damaged cells [23]. At the same time, they can secrete a variety of bioactive factors which regulates immunity and resists apoptosis. this therapy improves the nigrostriatal system. A study using autologous MSCs to treat 12 patients with PD showed that the severity of motor and non-motor symptoms after MSCs transplantation was significantly reduced [24].

3.3. Noninvasive vagus nerve stimulation (nVNS)

Vagus nerve stimulation is an adjunctive neuromodulation therapy for epilepsy through surgically implanted device. This treatment has been simplified with the introduction of hand-held non-invasive VNS (nVNS) devices, which has the ability to conduct intervention trials for diseases without the risk of surgical and postoperative complications. It also has the anti-inflammation characterize.

In the advanced stages of PD, patients tend to have frozen gait, describing a feeling of "being stuck to the ground". The symptom is progressively worsening with the degeneration of substantia nigra system. A study conducted to evaluate the effect in PD-patients with frozen gait after one-month nVNS treatment. Their motor abilities including walking speed, standing time and stride length were obviously improved after treatment compared to placebo. Furthermore, some inflammatory cytokines like TNF-α and glutathione were reduced. nVNS therapy can improve motor function and decrease the level of inflammatory cytokines in PD patients [25].

4. Conclusion

The traditional methods for PD are mainly drugs and surgical treatment, they only alleviate symptoms, but they both can't control the progression of PD and rescue

impaired nerve cells. Furthermore, these two ways bring some negative effects such as behavioral or mental disorders and dyskinesia. Surgical intervention easily leads to intracranial hemorrhage and has no obvious effect on cognitive impairment and neurological symptoms. It is more traumatic and has poor long-term effect.

There are several reasons leading to the failure of developing new drugs: Firstly, the pathogenesis of PD is complicated and not clear, so that it is difficult to predict the ideal targets. A variety of genetic factors and environmental risks account for the different changes of pathologies in PD. Secondly, any model of PD can't summarize the pathogenesis of PD in humans. Therefore, the effects of new drugs observed and concluded in preclinical trails can't stand for the treating behaviors in PD patients. Furthermore, there is a lack of biomarkers in the early stage of PD, so it's hard to identify and recruit patients who are in early stage to attend clinical trials where new drugs are further evaluated.

In the future, despite the challenges, more studies developing new drugs can follow in these ways: 1. Neuroinflammation, mitochondrial dysfunction are new targets. 2. "Brain insulin resistance" is related to the pathogenesis of PD, so GLP1R agonists provide a new perspective of treating PD. Meanwhile, GLP1R agonists also focus on neurotrophic factors which act as a protective role in the brain. 3. Stem cell therapy is an innovative treatment. Different types and sources of stem cells can all promote nerve regeneration and repair of neuron. It also differentiates into dopaminergic neurons to replace damaged ones. 4. Most drugs for PD have negative effects and the dose of drugs increase as the disease progresses. The Gene therapy is a new way aiming to treat diseases by genetically modifying cells to relieve symptoms without drugs-induced side effects. Hoping that this review can be helpful in the field of developing new treatments for PD.

Table 1. New developing drugs of PD.

Name	Mechanism	Effect	Company	Phase (being conducted)
Withaferin A (WA)	A natural small molecule compound with high fat-soluble steroid lipids	Enhances autophagy and regulating glucose and lipid metabolism	/	Preclinical
Farnesol	Inactivates the PARIS protein	Prevents the loss of dopamine neurons	/	Preclinical
DNL-201	LRRK2 kinase inhibitor	Inhibits LRRK2 kinase	Denali	Phase 1 (NCT04551534)
DNL-151	LRRK2 kinase inhibitor	Inhibits LRRK2 kinase	Denali; Biogen	Phase 1 (NCT04557800)
EB-42168	LRRK2 G2019S inhibitor	Lowers phosphorylation biomarkers of LRRK2 G2019S mutation	MedChemEa press company	Preclinical
CVN424	G-coupled protein receptor (GPCR) inhibitor	Improved the "off" period by 1.3 hours; increased the "ON" time without dyskinesia	Cerevance company	Phase 1 (NCT03657030)
NYX-48	NMDA modulators	Enhances attention and cognition	Aptinyx company	Phase 2
SAGE-718	NMDA modulators	Enhances synaptic plasticity and memory	Sage Therapeutics	Phase 2 (NCT04476017)
ABBV-951	Composed of foslevodopa and foscarbidopa	It reduces the motor fluctuations in patients with advanced PD.	AbbVie company	Phase 3 (NCT04750226)
Mesdopetam	A novel dopamine D3 receptor antagonist	Improves dyskinesia and prolonges "ON" period.	Ipsen company	Phase 2 (NCT04435431)
Fibroblast Growth Factor21	A classical metabolic regulator	Showed better memory and motor ability	/	Preclinical
DPP4	Dipeptidyl peptidase -4 inhibitor	Has beneficial effect on dopamine degeneration and motor ability.	/	Clinical trial
NR	Nicotinamide riboside supplementation	Improves motor ability	/	Phase 1 (NCT03568968)
NBIb-1817 (VY-AADC01)	Gene therapy	Increases dopamine production	Voyager Therapeutics Company	Phase 2 (NCT03562494)
Mesenchym-al stem cells	Stem cells therapy	Differentiate into astrocytes or neuron-like cells in the brain, then they transform into dopaminergic neurons	/	Phase 1 (NCT02611167)

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