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Research Progress on Pathological Mechanism and Treatment of Parkinson's Disease

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Abstract: *Parkinson's disease (PD) is a neurodegenerative disease caused by the degeneration and loss of dopaminergic neurons in the substantia nigra pars compacta. The hallmark pathological feature is the presence of Lewy bodies consisting of abnormal aggregation of α-synuclein. This paper summarizes and analyzes the latest relevant literature at home and abroad in recent years, and finds that the pathological mechanism of Parkinson's disease is complex and can interact with each other. At present, the drugs for the treatment of PD are single and have great side effects. Surgical treatment has a certain risk and high price, while acupuncture treatment has the characteristics of good effect, low cost and no side effects, and plays a huge role in the treatment of PD.*

Keywords: *Parkinson's disease; Pathological mechanism; Drug treatment; Acupuncture treatment*

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, and its prevalence is expected to increase greatly with the acceleration of global aging. In addition to the typical motor symptoms such as tremor, myotonia, and bradykinesia, the non-motor symptoms of PD can occur before the motor symptoms, including depression, anxiety, cognitive impairment, sleep disorders, and constipation, which are often ignored by people. The exact etiology of PD is still unclear. Genetic factors, environmental factors, aging and oxidative stress may be involved in the degeneration and death of dopaminergic neurons in PD. At present, drug therapy is the most important treatment method for PD, and surgical treatment is an effective supplement to drug therapy. Rehabilitation therapy and psychotherapy can also improve the symptoms to a certain extent. Acupuncture treatment has no side effects and fills the deficiency of drug treatment to a large extent.

2. Pathological mechanism of Parkinson's disease

2.1. Abnormal aggregation of α-synuclein

"α-synuclein (α-syn) A small protein of 140 amino acids that is located primarily at the tip of synapses and is abundant in the brain." When the balance between α-syn production and clearance is disrupted, soluble monomeric α-syn aggregates and misfolds into oligomers followed by the formation of amyloid fibrils and finally Louie bodies, a process that is largely irreversible [1]. α-syn oligomers can be cytotoxic in a number of ways, ultimately leading to neuronal cell death, including mitochondrial dysfunction, endoplasmic reticulum (ER) stress, loss of protein homeostasis, synaptic damage, apoptosis, and neuroinflammation. Thus, abnormal aggregation of α-syn plays a central role in the pathogenesis of PD. Many cellular and environmental factors related to PD (PTMs of α-Syn, such as C-terminal truncation, interactions of α-Syn with polyamines, pesticides, and metal ions) have been shown to enhance α-Syn aggregation [2]. Although factors favoring the aggregation of α-Syn have been demonstrated, the exact mechanisms that promote aggregation are not well understood. In addition, because PD is prone to be misdiagnosed in clinical diagnosis, α-syn can be used as a PD biomarker and early diagnosis basis.

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2.2. Mitochondrial dysfunction

Mitochondria are highly dynamic multi-functional organelles whose main function is energy supply and play important roles in oxidative stress, apoptosis, Ca2 + storage and neuronal survival. It is generally accepted that mitochondrial dysfunction plays a key role in the pathogenesis of PD. Studies have shown [3] that familial PD is associated with gene mutations in proteins, including PINK1, Parkin, DJ-1 and LRRK2, and the corresponding gene products are also involved in mitophagy, resulting in mitochondrial dysfunction. It has also been demonstrated that [4] the activity of mitochondrial complex I is found to be reduced in various tissues of sporadic PD patients postmortem, so the inhibition of mitochondrial complex I activity is hypothesized to be one of the main mechanisms leading to the death of dopaminergic (DA) neurons in PD. In addition, treatment of rodents with 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA), as well as rotenone, can inhibit the function of mitochondrial respiratory chain by disrupting mitochondrial complex I, leading to mitochondrial dysfunction and thus inducing many key features of PD [5-7]. Abnormal aggregation of α-syn is also closely related to mitochondrial dysfunction, and studies have shown that [8] gradual accumulation of α-syn may impair mitochondrial function at the level of mitochondrial complex I, resulting in reduced ATP synthesis and oxidative stress. At the same time, mitochondrial dysfunction can also lead to abnormal aggregation of α-syn, and the two can interact to form a vicious cycle.

2.3. Oxidative stress

Studies have found [9] that reactive oxygen species (ROS) is an important factor in the loss of dopaminergic neurons, and oxidative stress is an important pathological process of PD. Oxidative stress results from an imbalance between oxidants and antioxidants in biological systems that results from excessive ROS levels or improper function of the antioxidant system.

Oxidative stress interacts with other pathological mechanisms. The brain consumes 20% more oxygen than the rest of the body and is therefore more susceptible to oxidative stress [10]. In the brain, reactive oxygen species arise primarily from dopamine metabolism, mitochondrial dysfunction, and neuroinflammation. In dopaminergic neurons, DA catabolism produces a toxic metabolite, 3, 4-dihydroxyphenylacetaldehyde (DOPAL), which can generate hydroxyl radicals in the presence of H2O2. Moreover, DOPAL catechol groups have a tendency to autooxidize to semiquinone radicals and o-benzoquinone. The resulting ROS can exacerbate oxidative stress in neurons [11]. Mitochondria produce ROS under physiological conditions. However, dysfunction of the mitochondrial electron transport chain (ETC) in damaged mitochondria can lead to excessive ROS production, which is very harmful to cells [12]. Through activation and proliferation, microglia can release a large amount of ROS, causing inflammation and degeneration of dopaminergic neurons [13].

2.4. Neuroinflammatory mechanisms

Neuroinflammation is a basic immune response that can protect neurons from injury and compensate for neuronal damage. However, excessive neuroinflammation is harmful, leading to inflammatory damage of dopaminergic neurons, which is an important pathological mechanism of the occurrence and development of Parkinson's disease.

Various studies in vivo and in vitro have shown [14] that microglial activation plays an important role in neuroinflammation in PD. Studies have found [15] that significant microglial activation can be observed in the postmortem brain of PD patients, and microglial activation can be experimentally triggered by α-synuclein. The expression of cytokines IL-1α, IL2, IL-1β, TNF-α, IL-6, TGF-β, and IFNγ was associated with the degeneration of DA neurons in SNpc following microglial activation.

The role of microglia in PD has been widely demonstrated, but less is known about the role of peripheral immune cells [T cells, B cells, natural killer (NK) cells, and dendritic cells (DC)]. Natural killer (NK) cells are innate effector lymphocytes that target and kill malignant cells. Recently, a study has shown [1] that NK cells can clear α-synuclein aggregates and that systemic depletion of NK cells leads to worsening neuropathology in a mouse model of α-synucleinopathy. Williams et al. [16] confirmed that IFNγ-producing CD4 T cells are essential for the CNS bone marrow MHCII response and the loss of TH+ substantia nigra neurons caused by α-syn overexpression. Increasing evidence has shown [17] that regulating CD4+T cells (Treg) has the ability to inhibit the inflammatory response of Th1 and Th17 cells, which has become a key role in reducing neuroinflammation and neurodegeneration. The key to future use of T cell therapies will be to further demonstrate the signals

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produced by these T cells and their role in PD.

2.5. Microbiota-gut-brain axis

In the past decade, emerging evidence has shown the existence of a tight connection between the brain and the gastrointestinal system, the so-called "gut-brain axis". Braak speculated that α-syn may be produced in the gut and then spread to the central nervous system (CNS) via the vagus nerve [18-19]. Non-motor symptoms such as gastrointestinal dysfunction appear decades before motor function, and about 80% of PD patients suffer from constipation [20]. Therefore, the role of "gut-brain axis" has begun to receive more attention in the study of the pathogenesis of PD.

The gut-brain axis interaction may be influenced by the gut microbiota. In a PD transgenic mouse model overexpressing α-syn, the presence of gut microbes may exacerbate motor and GI disorders, microglia activation, and pathological aggregation of α-syn, while antibiotic treatment reduces PD-related motor deficits [21]. Therefore, the pathogenesis and clinical manifestations of PD are related to the dysregulation of the "microbiota-gut-brain axis".

Studies have shown [22] that changes in intestinal microbiota may lead to defects in intestinal barrier function and increased intestinal permeability, which will promote the translocation of microorganisms and microbial products (such as LPS), and then trigger inflammation and oxidative stress, leading to the development of Parkinson's disease. Treatments for the dysregulation of the microbiota-gut-brain axis in PD include the administration of antibiotics, fecal microbiota transplantation, and dietary interventions (e.g., caffeine). Treating PD by regulating microbiota dysregulation, reducing intestinal permeability, and reducing oxidative stress and intestinal inflammation is a direction that can be deeply studied.

3. Treatment of Parkinson's disease

3.1. Drug therapy

It is well known that levodopa (LD) is currently the main and most effective therapeutic agent in the treatment of PD, often in combination with carbidopa or benserazide (aromatic acid decarboxylase inhibitor), which prevents its peripheral metabolism and significantly reduces the risk of nausea [23-24]. However, serious adverse reactions such as switching phenomenon and dyskinesia may occur during long-term use of LD.

It was found that increasing the ratio of carbidopa: levodopa from the current standard of 1:4 was shown to increase dyskinesia free time and to reduce closure time [25]. In addition, the side effects of oral LD can also be improved by changing the route of administration. CVT-301 is a levodopa inhaled powder that can be administered by inhaler, allowing LD to bypass the GI tract and rapidly enter the bloodstream through the pulmonary system, and is safe and well tolerated. Moreover, clinical trials have shown that CVT-301 can rapidly improve motor function and significantly reduce the daily "off" time during "off" episodes [26]. Levodopa/carbidopa enterogel (LCIG; Also known as carbidopa/levodopa enteral suspension) has been used to treat motor fluctuations in patients with advanced PD. LCIG is delivered directly into the patient's jejunum by a portable pump through a surgically inserted permanent tube, which avoids the problem of unstable gastric emptying. LCIG can reduce the "off" time and improve other motor complications of oral levodopa through continuous dopaminergic stimulation [27-28]. ND0612, a continuous subcutaneous levodopa/carbiddopa delivery system [29], is currently under development for patients with PD and motor fluctuations, but more experimental studies are needed to confirm this.

In addition to levodopa, many other classes of drugs are available to treat PD-related motor symptoms: Dopamine receptor agonists (amantadine, apomorphine, pramipexole, ropinirole, rotigotin), monoamine oxidase inhibitors (selegiline, rasagiline) and catechol-O-methyltransferase inhibitors (entacapone, tolcapone), anticholinergic drugs, dopamine-releasing drugs, etc [30].

At present, PD cannot be cured by drug treatment, so the principle of PD medication is to improve symptoms, avoid or reduce adverse reactions, and improve work ability and quality of life. Adverse drug reactions and motor complications can be avoided, delayed, or reduced as much as possible by changing the route of administration and adjusting the drug ratio.

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3.2. Surgical treatment

The first treatment for PD patients is drugs. With the progress of the disease, the efficacy of drugs gradually decreases and serious side effects appear, at this time, surgical treatment can be considered. Deep brain stimulation (DBS) is currently the most mature and effective surgical treatment for PD. It can improve the patients' tremor, rigidity, bradykinesia and other disorders, reduce the dose of oral drugs, and significantly improve the patients' quality of daily life and ability [31].

DBS surgery uses a minimally invasive technique to implant electrodes in the subthalamic nucleus (STN) or globus pallidus internus (GPi) to send electrical stimulation to suppress abnormal cranial nerve signals. STN is the main site of DBS implantation, but GPi targets are significantly increased and selected for patients with poor cognitive and emotional indexes [32]. In addition, the pedunlopontine nucleus (PPN) has been used as a new target for DBS to improve gait and posture abnormalities in PD patients [33]. Studies have found that patients are prone to emotional deterioration after DBS, and although motor symptoms are improved, the risk of suicide is increased [34]. Therefore, suicide is one of the important potential risks of death after DBS. The depression of patients should be carefully evaluated and treated after DBS, and regular evaluation and follow-up are recommended. With the development of technology, DBS technology has also been continuously improved, such as the introduction of wireless connections for monitoring and programming devices, the use of adaptive stimuli, and the incorporation of commercial platforms into the system [35]. However, the development of technology also faces the problems of ethics, privacy and security.

In addition, the latest surgical treatment for PD is stem cell transplantation, in which somatic cells (e.g., skin fibroblasts or blood cells) derived from PD patients are reprogrammed into autologous stem cells, which are then differentiated into a true midbrain dopamine cell population and transplanted into the brain of PD patients [36]. At present, this technology for the treatment of PD is still in the clinical research stage, which is not widely used and lacks large sample data support.

Surgery, like other treatments for PD, can only improve symptoms, but cannot cure the disease. Medications are still required after surgery, but the dose can be reduced.

3.3. Acupuncture treatment

PD belongs to the category of "tremor syndrome" in traditional Chinese medicine, which is based on the deficiency of essence and the reality. The disease is mainly in the liver and kidney, and the location is in the brain. Therefore, the acupoints of acupuncture are mostly selected on the head and the liver and kidney meridians, and then added or subtracted according to different syndrome types. There are many methods of acupuncture for PD, such as body acupuncture, scalp acupuncture, electroacupuncture, fire acupuncture, eye acupuncture, warming acupuncture, and acupuncture combined with other therapies. Studies have found that acupuncture can play a therapeutic role in PD by regulating multiple targets, such as mitochondrial dysfunction, oxidative stress, and "brain-gut axis".

Based on the theory of "brain-gut axis", Zheng Zhijun et al. [37] confirmed that acupuncture could regulate PD by down-regulating the expression of JNK in the substantia nigra of PD model rats and reducing the levels of inflammatory factors TNF-α, IFN-γ and IL-1β. Huang Kai et al. [38] applied electroacupuncture to the bilateral choreiform tremor areas of the head of PD model mice, and the expression of TH in the substantia nigra of midbrain, the activity of mitochondrial complex I and the level of mitochondrial membrane potential increased after treatment. These results suggested that EA could improve mitochondrial dysfunction by increasing the activity of mitochondrial complex I. CAI Weibin et al. [39] improved the ability of anti-oxidative stress and motor function of PD mice by increasing the activity of mitochondrial complex I and reducing the content of mitochondrial ROS in brain tissue through electroacupuncture.

4. Summary

Mitochondrial dysfunction, abnormal aggregation of α-synuclein, oxidative stress, neuroinflammatory mechanism, and "microbiota-gut-brain axis" are involved in the pathological mechanism of PD, and these mechanisms do not exist independently, but interact with each other to form a vicious circle. At present, the clinical treatment of PD is still mainly symptomatic treatment, which can only improve symptoms. Drug therapy is the first choice in clinical practice, but with the progress of the disease, the efficacy of drugs gradually decreases and there are great side effects. With

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the development of medicine, surgical treatment is gradually emerging, which has a good effect on improving the motor symptoms of advanced PD and can improve the quality of life of patients. However, surgery has a certain risk and high price, and is not the first choice of patients in clinical practice. Acupuncture has the characteristics of good curative effect, low cost and no side effects in the treatment of PD. It can not only improve the motor symptoms of PD patients, but also play a good role in the non-motor symptoms such as constipation, insomnia and anxiety. In the future, the treatment of PD needs to play a multidisciplinary treatment model, play the combined role of drugs, surgery, acupuncture and psychological intervention, and improve the patients' work ability and life treatment as the main goal, and pay more attention to the patients' mental health.

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