ISSN 2959-6157

Application of Optogenetics in the Regulation of Neural Circuits in Parkinson's Disease

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Abstract:

This paper reviews the application of optogenetics in the study of Parkinson's disease and discuss how optogenetics stimulates specific neural circuits to regulate the symptoms and behaviors of Parkinson's disease. Optogenetics technology has a higher spatial resolution than traditional electrical stimulation, and optogenetics can accurately control specific neuron populations, providing a new perspective for studying PD and exploring potential treatments. The researchers found that selective optogenetic stimulation of the dorsal striatum was sufficient to induce levodopa-like dyskinesia in 6-hydroxydopamine (6-OHDA)-induced PD rat models. In addition, the researchers found that transplanted dopamine neurons can correct some of the motor deficits through their neural activity, including dopamine release and synaptic transmission. Although the utility of optogenetic techniques in human patients is unclear, the precise control of neural circuits in animal models provides an important way to understand the mechanisms and side effects of DBS therapy. The study also suggests that optogenetic stimulation of glutamatergic neurons in the mesocerebellar nucleus may improve motor function in PD mouse models, providing a new potential target for PD treatment. Finally, the article discusses how optogenetic technology can be transformed from a research tool into a treatment for PD, and how to repair damaged neural circuits through optogenetic technology to provide a more durable and effective treatment.

Keywords: optogenetics, neural circuits, Parkinson's disease

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by the progressive death of dopaminergic neurons in the substantia nigra pars compacta and ventral tegmental area, leading to motor dysfunction such as motor weakness and muscle rigidity. With the aggravation of the disease, patients may also develop non-motor symptoms such as cognitive impairment and affective disorders. Currently, levodopa is the most effective drug for the treatment of PD, but long-term use can cause motor complications, such as levodopa-induced dyskinesia (LID). The occurrence of these complications seriously reduces the quality of life of patients and becomes a major challenge in the treatment of PD.

In recent years, optogenetic technology has provided a new research tool for studying the neural circuit mechanism of PD. Optogenetic technology uses light-sensitive proteins (such as opsin) to precisely stimulate specific neuronal populations with high spatial resolution, which can analyze neural function at the level of cells and neural circuits. Through optogenetic technology, researchers can model the pathological processes and behaviors of PD in living animal models and explore new treatment strategies.

This article reviews the application of optogenetic techniques in the regulation of neural circuits in PD, focusing on the effects of optogenetic activation of specific neural circuits on the behavior of PD model animals, and how optogenetic techniques can provide important information for understanding the neural mechanisms of PD and developing new treatments. By analyzing recent progress in optogenetic PD research, this paper aim to provide new perspectives and strategies that could potentially inform clinical treatments for PD.

2. Application of Optogenetics in the Regulation of Neural Circuits in Parkinson's Disease

2.1 Optogenetic Striatal Activation

This paper mainly to investigate the relationship between long-term levodopa treatment and levodopa-induced dyskinesia in Parkinson's disease (PD). Optogenetic techniques were used to induce motor deficits in rats to mimic the side effects of levodopa treatment in humans with Par-

kinson's disease [1]. While levodopa-induced dyskinesia is a well-known side effect of long-term PD treatment, the precise mechanisms underlying these movement disorders remain elusive. This gap in their understanding hinders the development of more effective treatments.

The researchers then came up with the idea of using photogenetic stimulation to induce motor disorders in rats with partial Parkinson's disease models and injecting 6-OHDA into the medial forebrain tract to induce unilateral striatal dopamine depletion. Adeno-associated viruses expressing photosensitive proteins were used optogenetically to stimulate striatal mesenchymatous spiny neurons by a laser source. To ensure the validity of their model, researchers assessed dopaminergic depletion in all rats following behavioral studies. This was done through TH (tyrosine hydroxylase) immunostaining in coronal brain sections. Only rats showing more than 95% loss of TH staining were included in the experiment, ensuring they were working with a severe Parkinson's model.

They divided the rats included in the experiment into two groups. One group is experimental group (dopamine was depleted and ChR2 was expressed), and another group is control group (non-dopamine depleted but expressing ChR2). What's more they divided two methods in this experiment method A is 3-min basal period (no stimulation), followed by continuous optogenetic stimulation over 3 min, and finally by laser off for another 3 min. And then method B is a 3-min basal period followed by continuous optogenetic stimulation over 10 s, followed by nine repetitions of the 30-s laser with off.

Finally, they got their results experimentally: direct and indirect optogenetic stimulation of striatal cortical spiny neurons induced levodopa-like dyskinesia. Double immunostaining of FosB in combination with dynorphin B, a marker of direct pathway neurons (DR1), showed that FosB was expressed primarily in dynorphin containing neurons known to be present in LID (Fig. 1). FosB expression, a molecular marker of L-dopa-induced dyskinesia, is increased in medium spiny neuron in the direct pathway of the dopamine-depleted hemisphere.

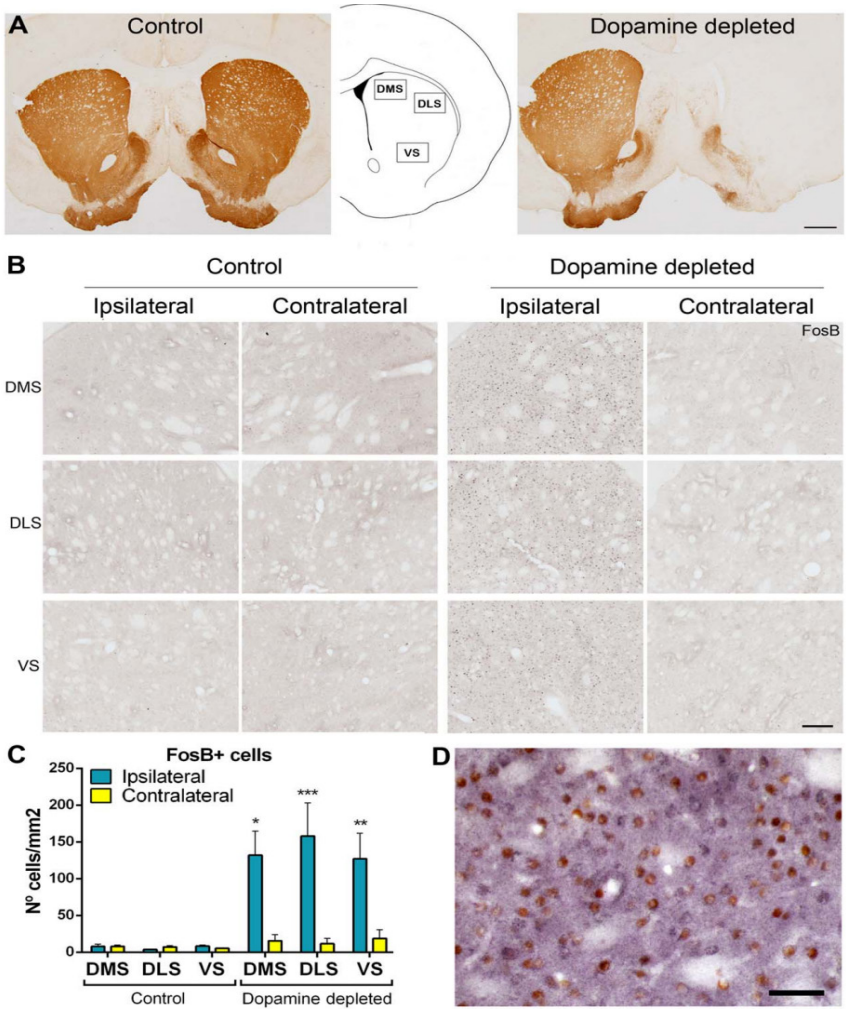

Fig. 1 FosB expression increased in dopamine-depleted animals after optical stimulation [1].

Their findings demonstrate that selective optogenetic activation of the dorsolateral striatum is sufficient to induce dyskinesia in their 6-OHDA rat model of Parkinson's disease. Importantly, this effect appears to be mediated primarily through activation of the direct striato-substantia nigra pathway. These results provide crucial insights into the neural circuits involved in levodopa-induced dyskinesia, potentially opening new avenues for therapeutic interventions in Parkinson's disease. These results also provide the possibility to reveal the synaptic mechanisms and striatal microcircuits involved in LID pathogenesis [1].

2.2 Advances in neural circuit mechanisms in Parkinson's disease

It is concluded that Parkinson's disease is a common neurodegenerative disease, and its clinical symptoms are highly heterogeneous and will gradually aggravate. Apoptosis of nigrostriatal dopaminergic neurons, a central pathological feature of the disease, explains only part of the symptoms

With the development of neuroelectrophysiological monitoring, functional magnetic resonance imaging (fMRI), optogenetics and other technologies, it is generally believed that neural circuit dysfunction caused by dopaminergic neuron apoptosis is an important mechanism of the occurrence and development of Parkinson's disease, and it is also the intervention target of various therapeutic measures such as deep brain stimulation. This article reviews the research progress of the neural circuit mechanism of Parkinson's disease in recent years, including the common symptoms of Parkinson's disease, neural circuit models and abnormal neural electrical activity patterns, so as to provide ideas for clinical research [2].

2.3 Optogenetics in Parkinson's Therapy

Investigators achieved precise control of the activity of human embryonic stem cells (hESCs) by inserting an inhibitory chloride pump, halorhodopsin (HALO), into hesCs and then differentiating these cells into cells that mimic dopamine neurons. Activation of HALO by light triggers an influx of chloride ions and reduces neuronal activity, including transmitter release and synaptic transmission. A mouse model of PD was established by injecting the neurotoxin 6-hydroxydopa (6-OHDA) to destroy dopamine neurons on one side of the brain. These animals will lean toward the diseased side during stimulation and use the ipsilateral paw for feeding. It has been shown that when Halo-expressing grafts are photoinhibited, the motor defects that were originally cured by the graft reappear immediately. This suggests that transplanted cells correct motor deficits through their neural activity, including dopamine release.

The researchers made an interesting discovery: stimulating nearby brain regions (specifically the corpus callosum) could trigger dopamine release from the implanted cells. This release, in turn, generated excitatory responses in striatal GABA neurons. Importantly, these responses could be blocked by drugs that inhibit D1 receptors. This suggests that the transplanted dopamine neurons are functionally integrating with the host brain, specifically by activating D1 receptors on striatal GABA neurons (Fig.2).

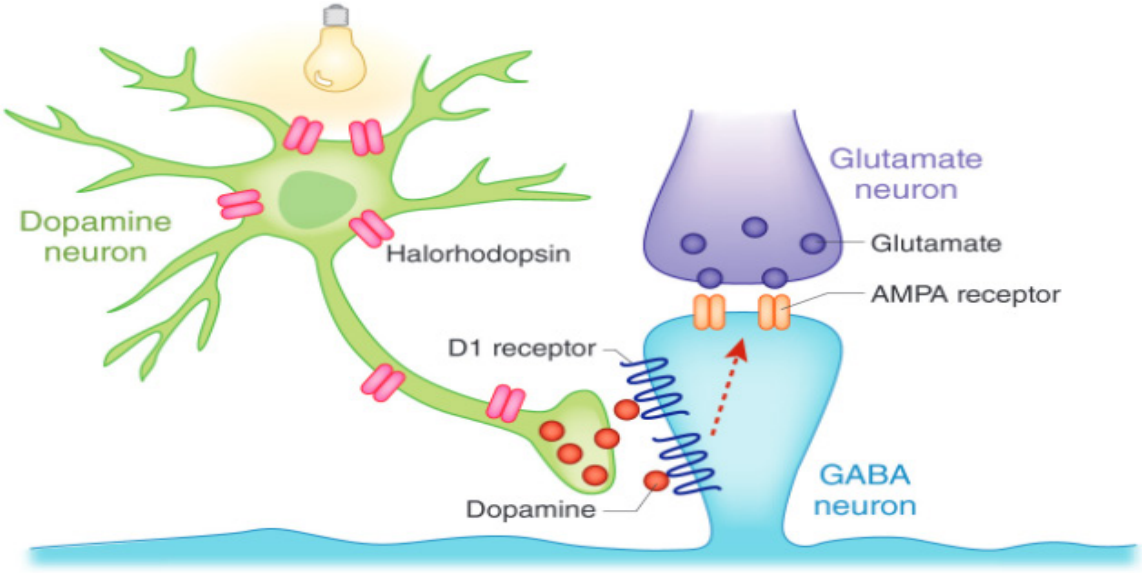

Fig. 2 The relationship between Glutamate and AMPA receptor [2].

By applying optogenetics, this study directly reveals how transplanted dopamine neurons restore motor function. However, because the HALO transgene is expressed by the synapsin promoter under all neuron types and the

hesC-derived cell population may include non-dopamine neurons, a contribution of other neuron types to function cannot be excluded [3].

2.4 Optogenetic Striatal Function Evaluation

Mainly explains how optogenetics has been used in the last decade to probe striatal circuits associated with Parkinson's disease, a neurodegenerative disorder involving motor and cognitive abnormalities caused by degeneration of dopaminergic neurons in the midbrain. The exact mechanisms by which the striatum contributes to cognitive and motor dysfunction in PD remain unclear. Although optogenetic approaches are somewhat detached from clinical applications, insights from these studies can help identify novel therapeutic targets and may inspire new therapies for PD. They discuss how optogenetics can be used to explore striatal circuits and motor symptoms in animal models of PD, and how optogenetics can be used to explore cognitive dysfunction in animal models of PD [4].

2.5 Restoring Neural Circuits with Optogenetics

Optogenetic technology offers significant advantages over traditional electrical stimulation methods. Its high spatial resolution allows for precise control of specific neurons. This level of precision makes optogenetics a promising tool not only for studying Parkinson's disease, but also for exploring potential treatments for a range of neurological and psychiatric disorders, including affective disorders. Behavioral approaches were used to evaluate the therapeutic effects of light stimulation in a unilateral PD rat model, including an adjusted gait test, a forearm use asymmetry test (cylinder test), and a drug-induced rotation test.

While optogenetic stimulation offers unprecedented specificity compared to electrical stimulation, there are still challenges to overcome. One key limitation is the need for more refined combinations of promoters and light-sensitive proteins. This would allow for even more precise targeting of specific neuron populations, potentially improving therapeutic outcomes and reducing side effects. Developing these tools requires further research at the intersection of genetics and neuroscience. The safety of prolonged deep brain irradiation has not been verified and requires the use of functional generators to adjust the frequency and amplitude of the laser or LED light source to minimize light-induced damage.

Optogenetics has emerged as a powerful tool in neuroscience, with applications rapidly expanding across various fields. Their research demonstrates its promising potential in developing novel therapies for Parkinson's disease. As researchers continue to refine this technology and overcome current limitations, they anticipate that optogenetics will play a crucial role in understanding and treating a wide range of brain circuit disorders. The future of neurological and psychiatric treatment may well be shaped by the insights gained through optogenetic research [5].

2.6 Translating Optogenetic Insights to Parkinson's Therapies

Parkinson's disease (PD) is a movement disorder caused by the degeneration of dopamine neurons in the substantia nigra pars compacta. Deep brain stimulation (DBS) has been shown to be a key development in the treatment of movement disorders, but efforts are ongoing to improve the effects and mechanisms of DBS technology. Optogenetics, a technology to control neural activity through light-sensitive ion channels (opsins), provides an important approach to understand the mechanisms of DBS treatment and side effects. Although optogenetics is currently impractical in human patients, precise control of neural circuits is possible through studies in animal models.

This article reviews how optogenetics as a research tool can inspire the next generation of DBS-based therapies, discusses how basal ganglion cell type diversity can shape clinical approaches to treat PD, and how optogenetics can provide insights into the neural circuits underlying the mechanisms and therapeutic effects of DBS.

In conclusion, optogenetics has proven to be an invaluable research tool in researchers' quest to understand and treat Parkinson's disease. Unlike traditional approaches that often merely mask symptoms, optogenetics offers the potential to guide us towards therapies that can repair damaged neural circuits. This paradigm shift from symptom management to circuit repair could lead to more durable and effective treatments. As researcher continue to refine and apply optogenetic techniques, they are optimistic about its potential to revolutionize not just Parkinson's disease treatment, but their approach to a wide range of neurological disorders [6].

2.7 Optogenetic Glutamatergic Stimulation

Parkinson's disease is characterized by the progressive loss of dopaminergic neurons in the midbrain. This neuronal loss leads to a cascade of effects, culminating in severe motor deficits. Two particularly debilitating symptoms are freezing of gait, where patients suddenly feel as if their feet are glued to the floor, and akinesia, a marked difficulty in initiating movement. Recent research has shed light on the crucial role of the midbrain locomotor region (MLR) in these motor deficits. The MLR, a key brainstem area involved in movement control, shows reduced activity in Parkinson's disease. This finding suggests that the motor symptoms may not just be a direct result of dopamine loss, but also due to downstream effects on other brain regions critical for movement initiation and control. Clinicians are exploring MLR with deep brain stimulation

as a treatment option to improve motor function, but with mixed results. However, within the MLR, clinicians targeted only the crural pontine nucleus and did not explore the cerebellar interpeduncular nucleus. This study breaks new ground by exploring a previously overlooked area: the cerebellar interpeduncular nucleus. Despite its potential importance in motor control, the effects of stimulating this nucleus have never been investigated in any animal model of Parkinson's disease. This represents a significant gap in their understanding, which this research aims to address. Here, researchers address this question in a mouse model of PD based on bilateral striatal injections of 6-OHDA, which impairs the nigrostriatal pathway and reduces motor activity. They show that selective optogenetic stimulation of glutamatergic neurons in the cerebellar interpeduncular nucleus increases the number of motor primes, increases the duration of movement, and controls the speed of movement in mice with channel rhodopsin expressed in a Cre-dependent manner in VGLUT2-positive neurons. A particularly exciting finding came from researchers' deep learning-based motion analysis. Researchers discovered that the limb movements induced by their optogenetic stimulation in Parkinsonian mice closely resembled those of healthy animals. This suggests that their approach not only improves motor function but does so in a way that restores natural movement patterns. This could have significant implications for developing therapies that aim to restore normal motor function in Parkinson's disease patients. Their research has identified a promising new target for Parkinson's disease treatment: the glutamatergic neurons in the cerebellar interpeduncular nucleus. By demonstrating the ability to improve motor activity through stimulation of these neurons, they've opened up a new avenue for potential clinical interventions. This finding could lead to the development of more targeted and effective treatments for Parkinson's disease, potentially improving the quality of life for millions of patients worldwide. Their study should open avenues for the development of deep brain stimulation, drug therapy, or optogenetic tools targeting these neurons.

This study suggests that increasing the activity of glutamatergic (VGLUT2-positive) neurons in the cerebellar intercrural nucleus is a relevant approach to improve motor function in PD conditions. Future studies should aim to manipulate these neurons using pharmacological treatments, optimized deep brain stimulation (DBS) protocols, optogenetic or chemical genetics tools to improve motor control and allow smooth navigation in PD conditions [7].

2.8 Optogenetic Techniques in Neural Circuit Studies

This article introduces optogenetics, an approach that uses light-sensing targeted control tools to study and regulate specific cellular functions. In the field of neuroscience, optogenetic technology allows scientists to use optical means to precisely control the electrical activity of specific subsets of neurons or individual neurons, and then study the function and regulation mechanism of neural circuits under physiological and pathological conditions. Combined with calcium ion imaging technology, optogenetics technology can observe neuronal activity in real time, which is helpful to locate neuronal clusters with specific functions in multiple dimensions, reveal their roles in neural circuits, and then explain the impact of brain diseases on the overall brain functional network. In this paper, researchers reported that the investigators obtained detailed information of striatal MSNS, interneurons and afferent neurons by optogenetics, and thus unraveled the basic pathology of PD [8].

3. Conclusion

In summary, optogenetic technology has shown great potential and value in the research and treatment of Parkinson's disease (PD). By precisely controlling the activity of specific neural circuits, optogenetics not only deepens our understanding of the pathological mechanisms of PD, but also opens the possibility of developing new therapeutic approaches. Future research should focus on optimizing optogenetic tools, enhancing their safety profiles, and improving their clinical applicability. Continued exploration of optogenetics may lead to novel treatments not only for Parkinson's disease but potentially for other neurological disorders as well.

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