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Optogenetics - Treatment of Parkinson Disease and Challenges Ahead

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Abstract: Optogenetic tools such as photosensitive opsins and LEDs are used for attaining spatial and temporal precision in neurons to study many neurodegenerative disorders, particularly Parkinson Disease (PD). This novel light-based technology has been reported in studying basal ganglia to understand the direct and indirect pathways. The role of optogenetics in unveiling the molecular basis of PD: α-synuclein aggregation and its association with the loss of dopaminergic neurons is also highlighted. The very frequently used 6-OHDA model has also been manipulated optogenetically to study the progressive loss of dopaminergic neurons. Optical stimulation of neurons at high frequencies has been observed to be helpful in the amelioration of PD motor symptoms such as Bradykinesia and Hypokinesia. PD treatment methods such as Deep Brain stimulation and Levodopa treatment have also been optogenetically modulated by many researchers to understand the basal ganglia circuitry revealing the inner mechanism of PD.

Keywords: α-synuclein, 6-OHDA, Deep brain stimulation, Parkinson disease, Opsins, Optogenetics.

I. Introduction

Optogenetics can be defined as a technique involving gene and neuro-engineering technology that can control the specific population of neurons within intact neural tissues of animals with light [1]. It allows high spatial and temporal resolution which were used to study neural circuits in PD. Light of a larger wavelength can penetrate deeper than that of a shorter wavelength. In an experiment performed by illuminating a rodent's brain at different wavelengths; UV, Blue Green, Yellow, Red, and NIR (Near Infrared), NIR showed the maximum penetration into the mice's brain. Hence red light can be used for non-invasive optogenetic manipulation of even the deepest brain structures in animal models [2]. Optogenetic tools to dive deeper into neural circuitry comprise photosensitive proteins called Opsins, waveguiding systems for light delivery; LEDs, micro-LED or laser, and in vivo neural probes spatial light modulator-based systems (SLMs); microelectromechanical (MEMS) based SLMs, liquid crystals, and vectors for gene delivery to manipulate neural circuits. Light-driven Channelrhodopsin (ChR) and Halorhodopsin are majorly used in optogenetic research. The ChR channel, when illuminated with blue light, allows passage of cations leading to cell depolarization. Halorhodopsin (NpHR) is a light-sensitive chloride pump that allows the inward transport of chloride when illuminated with yellow light [1]. Optogenetics has been used for studying neurodegenerative disorders like PD, Alzheimer's Disease (AD), Epilepsy, etc. Parkinson Disease (PD) is the second most common neurodegenerative disorder after Alzheimer's Disease and the most common existing movement disorder. PD occurrences have affected 5.8 million people, causing 329,000 deaths, WHO (2022). Most of the PD cases have been reported after the age 60. Early onset forms can have a genetic basis. Clinical features of PD include rest tremors, rigidity, bradykinesia, gait dysfunction, postural instability, freezing gait, dystonia, and dysphagia. Nonmotor symptoms include REM sleep disorder, cognitive issues, fatigue, hallucinations, etc [3]. Pathological features include loss of dopaminergic neurons in SNc, decreased striatal dopamine, and protein inclusions such as Lewy bodies. Underlying causes reported so far can be genetic such as coding mutations in the *LRRK2* gene and noncoding variation in the 5' region of the *LRRK2* locus [5], environmental factors; caffeine consumption, and pesticide exposure.

II. Role of Optogenetics in PD

In an experiment aimed to investigate the link between PFn and iSPNs, AAV carrying a Cre-off ChR2-enhanced yellow fluorescent protein (eYFP) expression construct was stereotaxically injected into PFn region of Grp-KH288 mice. It was observed that PFn evoked excitatory postsynaptic currents in iSPNs of Parkinsonian mice [1]. Vectors AAV5-CaMKII-eYFP, AAV5-CaMKII-HA-ChR2-IRES-eYFP, and AAV5- CaMKII-HA-eNpHR3.0-IRES-eYFP were delivered bilaterally in STN of Parkinsonian rodent models; eYFP, ChR2, and NpHR3.0 to study bilateral regulation of motor function in optogenetically manipulated STN. Results showed the magnitude of ambulatory distance traveled was in the order: NpHR3.0>eYFP> ChR2 during stimulation [1]. Optogenetics to understand α-synuclein aggregation in Parkinson's disease- The molecular basis of PD is linked

with misfolded α-synuclein aggregation. Light Inducible Protein Aggregation (LIPA) system has been used to study in vivo dopaminergic neuronal loss causing PD-like motor impairments and inducing α-synuclein inclusion formation [4]. Optogenetic manipulations in the 6-OHDA Model: 6-OHDA injected unilaterally into the medial forebrain bundle of a rat followed by selective optogenetic activation of dorsolateral striatum through AAV particles, results in dyskinesias in the 6-OHDA rat model [5].

III. Treatment

Opto-activation of M1 SST (Somatostatin) interneuron in unilateral 6-OHDA lesioned SST:: ChR2 mice was observed to successfully decrease their asymmetrical locomotor behavior. In the open field, Opto-activation of SST cells in 6-OHDA-lesioned SST::ChR2 mice decreased ipsilateral rotations [5]. High-Frequency Optical Stimulation (HFOS; 100 or 130 Hz; 4 ms pulses) in descending cortical projection of 6-OHDA mice with opsins reduced both hypokinesia and bradykinesia whereas low-frequency optogenetic stimulation (LFOS; 30 Hz; 4 ms pulse width) remained insignificant [6]. The effect could be potentially feasible in PD patients [5]. DBS with Optogenetics is one of the most effective treatments considered for PD [7]. The combination has been used by researchers to stimulate components of basal ganglia circuitry like GPe, GPi, and STN and exhibited distorted firing patterns and rates and β (13-30 Hz) band oscillations [7, 12]. In an experiment DBS and ChR2 stimulation on GPe to understand PD's inner mechanism. Researchers studied the results of single target stimulation; GPe, STN and GPi, and later combined target stimulation: STN + GPe, STN +GPi and GPe + GPi. Results showed that excitatory optogenetic stimulation of these targets can improve thalamic relay and GPe has been considered a potential target for clinical stimulation [15]. Excitatory optogenetic stimulation with high-frequency DBS of these three targets can decrease the thalamic errors in relaying cortical information to a certain extent and can be considered helpful in improving the Parkinsonian state [9, 17]. Another optogenetic DBS of the subthalamic nucleus (STN), chronos was used [11, 14]. The experiment showed significant results on motor behaviors in the unilaterally lesioned 6-OHDA model such as (i) reduced pathological circling behavior, (ii) relief from ipsilateral turning at high rates; (iii) corrected the bias for using unimpaired forepaw, (iv) both increasing and decreasing firing rates of STN and SNr neurons, also stronger reductions in neural beta band oscillatory activity observed in both STN and SNr during higher rate optical stimulation [11]. Levodopa treatment with Optogenetics is the gold standard treatment for PD, however chronic exposure to L-DOPA, 50-80% of patients are reported with levodopa-induced motor complications including enfeebling involuntary movements, called levodopa-induced dyskinesia (LID) within 5-10 years of treatment [10]. 'Peak Dose Dyskinesia' alleviation by cerebellar PC optogenetic stimulation has been undertaken to investigate whether optogenetic cerebellar (Purkinje cell) stimulation could attenuate LID when administered at the beginning of Levodopa treatment, [10] chose 6-OHDA-lesioned mice receiving daily cerebellar stimulation starting from the first day of levodopa administration (3 mg/kg) before developing dyskinesia [10]. This group exhibited only mild or no orolingual dyskinesia. Inhibition of a subset of D1-SPNs (DYSK-SPNs) Dyskinesia-specific spiny projecting neurons with NpHr in a mouse model of LID reduced involuntary movements caused due to L-DOPA administration [10]. Optogenetic Bioimplant for PD is yet to be utilized in vivo consisting of leaky optic fiber with a chronoamperometer made from pyrolytic carbon. oxidation of released dopamine on the fiber surface changes the electrical properties of the implant indicating neuronal activation [2].

Challenges of Using Optogenetics: Blue light used in optogenetic experiments cause phototoxicity as UV light causes phototoxicity due to high energy transfer [13, 16]. Insertion of foreign ion channels or pumps intocellular membranes can negatively affect intrinsic cellular machinery [2]. Often optogenetics-derived tools can't target a specific subset of a neuronal population but instead, indiscriminately drive all the cells within a genetically defined targeted population. Spike rate and phase are lost due to synchronous activation of all the cells of the target population. Despite clinical safety testing of viral vectors for PD patients, the long-term safety of foreign gene delivery through viral vectors remains questionable.

IV. Conclusion

Just like any other scientific tool optogenetics too has its side effects but the optimistic part is that most of its side effects can be mitigated by simple approaches. In the past few years, optogenetics has revolutionized PD treatment and its analysis be it the dissection of direct and indirect pathways, studying the initiation and sequences of actions, comprehending the α-synuclein aggregation, complementing DBS with specificity, or alleviating LID symptoms. Optogenetics offers a great possibility to study the pathology underlying PD causing motor deficits. Researchers have also demonstrated a completely non-invasive transcranial optogenetic approach for deep photoactivation of neurons, abolishing the need for surgical implants. To develop and optimize optogenetic brain stimulation (OBS) devices to treat PD, clinicians designed cell-type specific opsin expressed in an animal model of PD and established an OBS device that alleviates the side effects of DBS. They have also designed a model-based computational evolution approach, and optimized temporal patterns of stimulation to enhance the efficiency of OBS, with low power consumption. Hopefully, this would make an impact on PD treatment.

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