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Neurodegenerative Disorders Through the Lens of Optogenetics

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ABSTRACT

Neurodegenerative disorder, as the name suggests, encompasses progressive neuronal degeneration that renders patients with a lack of, or at the very least dysfunctional cognition, motor senses, and bodily functions. The progressive worsening of the condition in conjugation with the lack of therapeutic measures makes them very difficult to bear.

Optogenetics, as discussed below, offers an approach that has contributed to the research for a solution to neurological degeneration at two fronts. The tools in the disciple help us employ microbial opsins to gain pinpoint control over neuronal firing. Furthermore, the engagements after an inhibitory or stimulatory control have been gained over neural circuitry have been insightful in understanding the progression of neurological pathologies. The following review will delve into the therapies available for Alzheimer's Disease, Amyotrophic lateral sclerosis (ALS), Huntington's Disease, Multiple sclerosis (MS), and Parkinson's Disease and explore the research insights.

Keywords: Optogenetics, Neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Huntington's Chorea

INTRODUCTION

Microbial Opsins are the essence of the Optogenetic toolkits that allow for incredibly precise cellular control of mammalian systems. The opsin expressions can be deployed into the neuronal tissues using AAV vectors (Adeno-associated Viral Vectors) that grant us a fast execution with a profound expression due to the high infectivity of viral particles. *(Saksham et al., 2023, Sharma, 2023)*

Francis Crick addressed the concerns about manipulating neurons in isolation from cells around it, in mammalian tissues in his incredibly insightful literature, "Thinking about the Brain" *(Crick, 1979)*. Optogenetics has allowed for fast and specific excitation or inhibition in mammalian systems using light-based stimulation that propagates the movement of ions across membranes, producing the desired effect based on the wavelengths of light used. *(Fenno et al., 2011, Saksham et al., 2023, Sharma, 2023*) e.g. - Halorhodopsin would respond to yellow light illumination by conducting Cl^- ions into the cytoplasm. *(Fenno et al., 2011)*

We employ several methods to deliver opsins into the mammalian tissues like viral-mediated gene delivery, transgenic animals, and direct injection of plasmids. *(Sharma, 2023, Yizhar et al., 2011)*

In theory, the ability to control neuronal flow would prove to be a valuable asset when tackling neurodegenerative disorders. The

control would also grant us data of immense value in understanding neuronal firing and the progression of diseases and their precise pathophysiology. This review will delve into the latest developments in the field.

MATERIALS AND METHODS

The review has been drafted by researching and studying several types of research across journals that have been listed in the references.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is nowadays one of the major causes of dementia and the development of new diagnostic approaches has been going in advance during these years, including clinical features, relevant biomarkers, genetic risk and protective factors, and imaging. *(Scheltens et al., 2021, Masters et al., 2015)*

The most common explanation is the amyloid hypothesis, based on the imbalance of production and clearance of Aβ peptides, products of a regular metabolism, that leads to accumulating these peptides into a plaque in extracellular spaces and walls of blood vessels. *(Masters et al., 2015, Querfurth & LaFerla, 2010)* In the last few years, this hypothesis has been questioned due to the evidence against it, and recently a probabilistic model has been proposed that could help in the future to establish a standardized pathophysiology. *(Frisoni et al., 2021)*

AD has an estimated prevalence of 10–30% and an exponential rise of the incidence in people >65 years of age, based on the analysis made in four American states. *(Masters et al., 2015)*

At the moment there is no definitive treatment that can restore the damage caused by this neurodegenerative disease. Still, Acetyl-cholinesterase inhibitors (AChEI) and Memantine are two possible treatments related to increasing acetylcholine's availability and reducing toxicity antagonizing the NMDA receptor. *(Lane et al., 2017)*

Using Optogenetics to Understand and Treat AD

A study by Dr. Etter and their colleagues in 2019 worked on Alzheimer's disease mouse models. Adenoviral Vectors of serotype dj (hybrid capsids made using 8 AAV serotypes) were used to express channelrhodopsin-2 in the hippocampus, EF1α promoter These models were then subjected to slow gamma oscillations (30-60 Hz) which resulted in improved memory and reduced amyloid-beta Plaque levels in the brain. *(Etter et al., 2019)*

Another study in 2015 unilaterally transduced AAV vectors with SSFO enhanced Yellow fluorescent protein (EYFP) along with Calmodulin-dependent protein kinase IIα (CaM kinase IIα) promoters. The study aimed to employ optogenetics to activate specific neuronal pathways in APP (amyloid precursor protein) transgenic mice models of Alzeihmer's to understand the relation between synaptic activation and Aβ pathology. Chronic optogenetic activation was associated with an increased Aβ-plaque deposition. Furthermore, exacerbation of cognitive deficits was also associated with chronic optogenetic activation. Microglia were activated in response to that, suggesting that inflammation might play a role in exacerbating Aβ pathology. *(Yamamoto et al., 2015)* Similarly, a study in 2019 dealt with the activation of glutamate receptors in the hippocampus of mice models. The study used adeno-associated viral vectors carrying the promoter calmodulin-dependent protein kinase (CaMK) and the CHR2 gene which was injected into the bilateral dentate gyri. The results showed that the optogenetic stimulation improved memory performance and reduced Aβ pathology. *(Wang et al., 2019)*

Optogenetic stimulation can lead to the loss of Aβ plaques, helping our understanding of the pathology and progression of the disease. *(Wang et al., 2019, Yamamoto et al., 2015, Etter et al., 2019, Mirzayi et al., 2022)*

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, is a rare progressive neurodegenerative disorder that causes motor neurons to degenerate, resulting in muscle weakness and paralysis. *(Kiernan et al., 2011)*

ALS occurs in two forms: sporadic (90% of cases) and familial (10% of cases). The cause of sporadic ALS is unknown, though environmental factors may play a role. Familial ALS is inherited and linked to mutations in genes like SOD1, C9orf72, and FUS. These mutations lead to protein aggregation, oxidative stress, and motor neuron death. *(Hardiman et al., 2017)*

The hallmark pathology of ALS is the accumulation of abnormal proteins in motor neurons and the degeneration of these neurons, which control voluntary muscle movement. As the disease progresses, patients experience muscle wasting, stiffness, difficulty breathing and swallowing, and often require ventilation or feeding tubes. *(Traynor et al., 2003, Van Den Bos et al., 2019)* The incidence of ALS is 1-2 cases per 100,000 people per year. ALS is more common in men and usually develops between ages 40 and 70, though it can occur at other ages. ALS appears more common in those of European descent and military veterans. *(Talbott et al., 2016)*

The main treatment for ALS is riluzole, which modestly extends survival. Other treatments manage symptoms like muscle spasms, pain, depression, and difficulty speaking or moving. Physical and speech therapy also helps maintain function. *(Traynor et al., 2003)*

Optogenetic therapeutic approaches being researched in ALS-animal models

A recent study employed the use of Transgenic zebrafish models and using blue lights to stimulate the ChR2-expressing motor neurons. This resulted in creating muscle contractions in fish. The researchers were able to inject 8-OH-DPAT into the ChR2-expressing fish that abolished blue light-stimulated muscle contractions. *(Asakawa et al., 2021)*

Transgenic mice expressing ChR2 alongside a Thy-1 promoter were optogenetically stimulated. The stimulation to the primary motor cortex induced motor activity in mice. *(Bryson et al., 2016, Aravanis et al., 2007)*

Optogenetics presents an incredibly promising therapeutic approach that can prevent muscle wasting and the generation of muscle motor activities.

HUNTINGTON'S DISEASE

Huntington's disease is a rare, progressive neurodegenerative disease of autosomal dominant inheritance, characterized by chorea, dystonia, and cognitive and psychiatric disturbances in middle-aged adults while some cases with onset of 20 years are called Juvenile Huntington Disease. *(Walker, 2007, Finkbeiner, 2011)*

The mutation accumulates within neurons due to CAG trinucleotide repeat expansion in exon 1 of the huntingtin (HTT) gene on chromosome 4. The primary neuropathology is the spontaneous inhibitory synaptic activity in medium-sized spiny neurons (MSNs) in the corpus striatum with relative sparing of cholinergic and GABAergic interneurons. *(Cepeda et al., 2013, Holley et al., 2015b)* Anticipation is seen as the gene is passed from the paternal side to the offspring as sperms tend to show a high repeat variability in comparison to somatic tissues. *(McColgan & Tabrizi, 2018, Novak & Tabrizi, 2010, Barry et al., 2018)*

HD affects both sexes equally and has a prevalence of 10.6-13.7 individuals per 100,000 in Caucasians with a mean age of onset at 30-50 years and a much lower prevalence in populations of Japan, Hong Kong, and South Africa. *(McColgan & Tabrizi, 2018, Roos, 2010)*

Though there are no promising treatment modalities available to slow the disease progression, the main therapeutic goal is to alleviate the symptoms and improve the quality of life through a multidisciplinary approach. Motor symptoms like chorea are managed with atypical antipsychotics like

clozapine and olanzapine. Tetrabenazine, deutetrabenazine (VMAT-2 inhibitors) are the only highly efficacious drugs approved to treat chorea after a randomized control trial. *(McColgan & Tabrizi, 2018, Novak & Tabrizi, 2010)* Individuals with a known family history are offered genetic counseling and testing for prenatal diagnosis. (*Roos, 2010)* The inclusion of deep brain stimulation of the Globus Pallidus in HD is under trial.*(McColgan & Tabrizi, 2018)* Certain studies state that optogenetic stimulation of direct or indirect pathway neurons might improve movement. (*Barry et al., 2018)* Emerging targeted molecular therapies using Anti-sense oligonucleotides (ASOs), RNAi or small molecule splicing inhibitors are the most promising approaches at present.*(McColgan & Tabrizi, 2018)*

Optogenetic therapeutic approaches being researched in Huntington's Disease - animal models

The following studies employed the use of R6/2 mice models that express the mutant form of the human huntingtin gene with an expanded CAG, along with Q175 mice models with a similar mutation but at a different location than in R6/2. Large cholinergic interneurons in the R6/2 mice models of Huntington's disease exhibited alterations in their firing patterns when compared with the normal cholinergic interneurons owing to the increase in GABA-ergic inputs to the interneurons. The optogenetics activation of these GABAergic inputs into the cholinergic interneurons has enabled us to mimic normalcy, as observed in those R6/2 mouse models. *(Holley et al., 2015c)*.

Another study also reported an increase in locomotor activity when the cholinergic interneurons in the striatum of R6/2 mice while inhibition of low threshold spiking (LTS) interneurons in the Q175 mice models gave the same results, indicating model-specificity. Inhibition of the LTS interneurons in the Q175 also resulted in a greater increase in locomotor activity in the HD models, indicating that interneurons have a regulating role in motor activity in the HD models. *(Cepeda et al., 2013b).* Research has also shown that optogenetic stimulation used to selectively activate the direct or indirect pathways in the striatum resulted in different effects in the R6/2 and Q175 mice, helping to understand the alterations in the direct and indirect pathways of the striatum that contribute to the various phenotypes that are observed in Huntington's Disease. *(Barry et al., 2018b).* The HD mice models were provided with Optogenetic stimulations of the striatal FSI (fast-spiking interneurons) which resulted in partial restoration of the motor deficits *(Cepeda et al., 2013c).*

MULTIPLE SCLEROSIS

MS is the most prevalent non-traumatic debilitating disease affecting young individuals *(Kobelt et al., 2017)*. The prevalence of MS and the socioeconomic toll of the condition are both rising globally. T-cell-mediated organ-specific autoimmune illness is how multiple sclerosis has traditionally been categorized. But the conventional T-cell autoimmune dogma is put to the test by the efficacy of B-cell targeted therapies. Pathophysiology Perivenular inflammatory lesions that result in demyelinating plaques are the pathological hallmark of MS. *(Karussis, 2014)* T-lymphocytes, predominantly MHC class I restricted CD8+ T-cells, are found in the inflammatory infiltrates, along with smaller amounts of B-cells and plasma cells.

Lower serum vitamin D levels, smoking, childhood obesity, and Epstein-Barr virus infection are likely to lead to disease progression *(Ascherio, 2013)*. With the sex ratio progressively rising to around 3:1 (F: M) *(Orton et al., 2006)* in most developed countries, multiple sclerosis is more prevalent in women.

The suppression of inflammation (and disease activity) must keep going during treatment. The closest thing to a potential cure for MS right now is the use of immune reconstitution medications, such as alemtuzumab and cladribine, which can be offered in small amounts to establish lasting

immunological effects. Patients suffering from particular vascular diseases or smoke are more susceptible. *(Handel et al., 2011)*

Optogenetic therapeutic approaches being researched in Multiple Sclerosis animal models

Electric stimulation is often employed to increase neuronal activity in MS to cause myelination and proliferation of oligodendrocytes but this electrical stimulation is non-specific and thus presents a list of complications and side effects. Channelrhodopsin 2 optogenetic stimulation of the PFC (prefrontal cortex) has been shown to increase the neuronal activity of the neurons in the discussion, thus increasing myelination (thickness being the aspect) and oligodendrocyte increase, offering pinpoint precision and specificity. *(Ordaz et al., 2017, Gibson et al., 2014)*

Research also suggests that Oligodendrocyte precursor cells (OPCs) could be optogenetically modulated to tackle MS, furthermore, astrocytes expressing ChR2 could be stimulated with light to reduce inflammation and increase the protection of neurons. *(Koussy & Jadavji, 2017)*

PARKINSON'S DISEASE

The disease was first described as "shaking palsy" by James Parkinson in 1817. PD, after Alzheimer's disease, is the most common neurodegenerative disorder. *(Yang et al., 2020)* Parkinson's disease (PD) consists of mainly two types: Primary (Idiopathic) PD which is the most common cause (80%), and Secondary Parkinsonism which includes normal-pressure hydrocephalus (NPH), vascular parkinsonism (VP), drug-induced parkinsonism (DIP), toxin-induced parkinsonism (TIP), chronic traumatic encephalopathy, brain tumors, juvenile parkinsonism (JP) and Parkinson-plus syndromes. The clinical features of PD are divided into two categories namely Primary Motor Symptoms which include resting tremors (pill-rolling), bradykinesia, rigidity (cog-wheel type), postural instability (balance problems) and non-motor symptoms which include loss of sense of smell, constipation, REM sleep behavior disorder and hypersomnolence, mood disorders, orthostatic hypotension all of which appear early during the course of the disease and other which appear later include cognitive impairment including dementia (30-80%), drooling and weight loss, fatigue and sexual problems like erectile dysfunction.

There is a depletion of pigmented dopaminergic neurons in substantia nigra pars compacta resulting in a decrease in dopamine levels which in turn leads to loss of inhibitory control of the subthalamus and ultimately less activation of the cerebral cortex. Microscopically, intracytoplasmic proteinaceous inclusions known as Lewy bodies that primarily contain the protein alpha-synuclein are easily seen in pigmented neurons. They are also found in the basal ganglia, brainstem, and cortex and increase with disease progression.

The incidence of PD is influenced by multiple factors including population, age, geographical location, prevalence of genetic and environmental risk, and protective markers. *(De Lau & Breteler, 2006)* The annual incidence is about 108- 212/ 1,00,000 among ages 65 and older and 47- 77/ 1,00,00 among ages 45 and older and the overall prevalence rate is 572/1,00,000. *(Van Den Eeden et al., 2003)* The incidence of PD increases with age above 65 years and is higher among males. *(Driver et al., 2009)* First-degree relatives with PD have a 2-3 times increased risk of developing the disorder. The male: female ratio for incident PD increases with age.

We pursue optimal management that begins at diagnosis and requires a multidisciplinary, coordinated approach. *(Bloem et al., 2021)* This mainly comprises pharmacological and Non-Pharmacological treatment. Pharmacological treatment includes antiparkinsonian agents, neuroprotective agents, drug therapy for treating associated symptoms, and surgery. Non-pharmacological treatment includes diet and

exercise, speech therapy, and physical and psychological rehabilitation.

Optogenetic therapeutic approaches in PD

In a study in 2009, optogenetic stimulation of the Subthalamic nucleus was restricted using the ChR2, motor deficits did not ameliorate *(Gradinaru et al., 2009)*, on the contrary when the cortex was optogenetically stimulated using the same opsin, ChR2, restricting them to the cortical neurons that project straight into the subthalamic nucleus help in improving the motor deficits and restore healthy neural activity within the subthalamic nucleus and the cortex. *(Holley et al., 2015, Sanders & Jaeger, 2016).* Optogenetic interventions could be further employed to restore dopamine production and release in the striatum as seen by stimulating engineered dopaminergic neurons in PD rat models. Furthermore, PD pathophysiology was explored by observing improvements in motor functions when cholinergic interneurons in the striatum were inhibited selectively in PD rat models. *(Chen et al., 2015).* In a recent study, the M2 cortex (secondary motor cortex) was infected with an AAV vector carrying the ChR2 with the promoter being the CaMK II in the PD rat models. Optogenetic activation of the M2 resulted in the locomotion of the animals, suggesting that activating the M2 cortex could potentially offer control over the clinical symptoms of PD. *(Magno et al., 2019)*

CONCLUSION & DISCUSSIONS

The acuity of light-based stimulation with the temporal precision of optogenetics has been harnessed to pursue cures for neurological disorders in animal models, ranging from anxiety and depression to impact injuries, and severe strokes and neurodegenerative disorders.

As discussed above, several of these models exhibit ameliorated functional properties following optogenetic stimulation. The functional improvements often are associated with neurotrophic factors being released or the formation of microcircuits *(Ordaz et al., 2017).* The discipline has been employed to both replace the degenerated sensations using optogenetic actuators, as well as deploying on-site signals to counter the degeneration of neural tissues. *(Kleinlogel et al., 2020, Ingles-Prieto et al., 2021, Janovjak & Kleinlogel, 2022).*

Thus, several key areas have been explored through optogenetics to gain a deeper understanding of pathophysiological manifestations of neurodegenerative disorders, understanding their response to individual neuronal circuitry and thus deciphering the progression of disorders with respect to the said circuits. That enables us to pursue a multi-disciplinary approach, considering optogenetics would work in tandem with several existing therapies. *(Vann, 2016, Saksham et al., 2023)*

We must also acknowledge the alternative non-invasive therapeutic approaches being provided by the developments in Giant magnetoresistive biosensors (GMRs) *(Murzin et al., 2020, Vann, 2016).* Regardless of that, optogenetics does offer solutions for neurological conditions, especially neurodegenerative disorders, beyond the immediately available approaches.

Declaration by Authors

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