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## **The importance of using methods of selective modification of neuronal function in the pathogenesis and therapy of Parkinson's disease**

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**Abstract:**

**Introduction:** Parkinson's disease (PD) is one of the most common neurodegenerative diseases that mainly affects older people over 60 years of age. Since life expectancy is increasing not only in Europe but also around the world, the number of people suffering from PD will gradually increase.

**State of knowledge:** One of the newest techniques used to study the mechanisms of diseases of the nervous system, which allows monitoring the activity of neurons by modifying their functions, is optogenetics. This method involves controlling neuronal activity using light. The sensitivity of cells to light is achieved by introducing into the body the genes of ion channels from algae or bacteria, which are incorporated into the cell membrane and then become excited when exposed to light. Depending on the gene used, the activity of a nerve cell can be intensified or inhibited. An important advantage of the method is the possibility of using it in vivo and recording the results in real time.

**Summary:** This publication aims to present the basics of optogenetics and is a review of works related to its use in the study of PD pathomechanism. For this purpose, the PubMed and Google Scholar databases were verified using the following words: "Parkinson optogenetic", "optogenetic stimulation", "channelrhodopsin".

**Keywords:** Parkinson's disease, optogenetics, neurodegenerative diseases

## 1. Optogenetics – historical view

Broadly speaking, optogenetics is a new and dynamically developing branch of science dealing with the creation of light-sensitive cells. One of the first people to suggest the basis of optogenetics was Nobel Prize winner James Watson. During his lectures, he noticed the limitations of modern methods and proposed the creation of a technique involving the stimulation of only selected neurons, and a little later, during one of his lectures, he proposed using light for this purpose. [1]. Before James Watson proposed his concept of optogenetics, already in 1971, two researchers Oesterhelt and Stoerkenius discovered the bacteriorhodopsin protein in the membrane of the bacterium *Halobacterium halobium*, which acts as a green light-activated pump [2].

The bacteriorhodopsin discovered by the researchers belonged to the opsin group, i.e. glycoproteins that are part of photosensitive dyes that cause the flow of ions and the activation or inhibition of cells in response to light of a specific wavelength. The following years resulted in the discovery of further opsins, but for a long time these discoveries did not translate into research using living organisms. The breakthrough in their use came only in 2005, when a group of scientists led by ES. Boyden using a lentiviral vector induced the channelrhodopsin 2 gene (ChR2) in rat hippocampal neurons, obtaining control over them after stimulation with short pulses of blue light [3]. In the same year, Nagel and colleagues showed that the introduction and activation of ChR2 in the cells of the nematode *Caenorhabditis elegans* induces body contractions after the application of an opsin that activates blue light. Similar motor activity of the nematode was not observed in the control group [4].

The effects were so promising that subsequent research teams attempted to simultaneously induce inhibitory and excitatory opsin genes into *Caenorhabditis elegans* motor neurons, thus gaining control over the animal's activity [5]. The research described above has contributed to the development of optogenetics, which can be summarized as the induction of promoter-driven opsin genes into selected neuronal populations using a vector and their subsequent activation by exposure to light. Current trials to use this method focus on diseases of the central nervous system such as neuropathic pain, epilepsy, and neurodegenerative disorders (Alzheimer's disease, Huntington's disease, PD) [6,7,8,9]. What's more, optogenetics also allows modulation of heart rate, and blood pressure, thus proving the extremely wide-ranging use of opsins to control various organs with light [10].

## 2. Opsins – classification

The opsin group can be classified in several ways, e.g. considering their molecular structure, origin, functions, or chromophore type. Type 1 and Type II opsins are both integral membrane proteins involved in the detection of light. Type I opsins occur as a channel or pump in archaea, bacteria, and algae. Due to their structure and the way they function as an ion pump, they influence neuronal excitability much faster than type II opsins. Thanks to these properties, type 1 opsins are used to modulate cellular activity. Type II opsins are G protein-coupled receptors and react to light slower than type I. They occur in vertebrates and participate in the process of vision and regulation of circadian rhythms. Both types require retinal (a derivative of vitamin A) to function, which, when attached to opsin, creates rhodopsin. Rhodopsin is a photosensitive protein that, after absorbing a photon of light, changes its conformation, which results in a modification of the cell's membrane potential [11].

Excitatory opsins cause depolarization of the cell membrane. This group includes channelrhodopsins: VChR1 (Channelrhodopsin-1), ChR2, step-acting SFOs (Step-Function Opsins) and ultrafast synthetic ChETA (created based on ChR2 and E123T point mutation) and ChIEF, (chimera ChR2 and ChR1) [3], [11].

ChR2 is one of the most widely used excitatory opsins in neuroscience research. It was originally discovered in the green algae *Chlamydomonas reinhardtii*. ChR2 is a light-gated cation channel that opens in response to blue light (~470 nm). When exposed to light, ChR2 allows influx of cations, predominantly sodium ions, leading to depolarization of the neuron and generation of action potentials. ChR2 has been used in a wide range of applications, including optogenetic manipulation of neural circuits to study behavior, sensory processing, learning and memory, and motor control. It has also been utilized in therapeutic approaches for neurological disorders such as PD and epilepsy [12].

In turn, VChR1 is a naturally occurring channelrhodopsin found in the green algae *Volvox carteri*. Like ChR2, VChR1 is a light-gated cation channel that opens in response to green and yellow light (~530 nm) and allows influx of cations, primarily sodium ions, leading to neuronal depolarization. VChR1 exhibits faster kinetics compared to ChR2, allowing for more rapid control of neuronal activity [11]. While ChR2 remains the most widely used excitatory opsin, VChR1 has gained attention for its faster kinetics and potential advantages in certain experimental paradigms requiring rapid neuronal activation. It is true that in the case of ChR2 and VChR1 there is a minimal degree of spectra overlap, but this problem has been eliminated by the possibility of using the recently discovered pair of Chronos and Chrimson opsins, in which stimulation of one of them does not affect the operation of the other [13].

ChR2 is subject to constant modifications because it is the basis for the creation of synthetic opsins. This is important because ChR2 is characterized by a rapid reduction in sensitivity to light stimuli and a return to maximum activity only after 25 seconds. One of the ChR2-based synthetic variants was created by mutating a single gene and replacing arginine with histidine at position 134. This resulted in increased cellular currents and slower shutdown, and this variant was named H134R [14], [15]. Synthetic opsins ChETA and ChIEF have also been created, and their action prevents the generation of additional action potentials after applying a single pulse. Yang and colleagues showed that selective induction and activation of ChETA opsin in glioma cells led to their excessive depolarization, apoptosis and, consequently, a reduction in tumor volume [16]. The opposite to the opsins described above is SFO, which was also created based on ChR2. The mutation, which involves replacing cysteine with threonine, serine, or alanine at position 128 of the chain, is intended to prolong the channel's activity even after the light is turned off. SFO activity can be turned off at any time by providing light with a wavelength corresponding to yellow. [11].

Another opsin belonging to SFO works for up to eight minutes, and on its basis SSFO (Stabilized SFO) was created, which functions for up to half an hour after the end of stimulation with a light stimulus [17]. Based on VChR1 and ChR1, it was possible to create a chimeric opsin C1V1, for which the peak of excitation is red shifted, which allows its simultaneous use with ChR2 and even more precise control of neuronal activity [18].

Researchers also managed to discover opsins that can be used to induce hyperpolarization and thus inhibit neuronal activity. Inhibitory opsins include primarily halorhodopsin (NpHR) and pumps causing the removal of protons outside the cell. NpHR was originally discovered in the extremophilic archaeon *Natronomonas pharaonis*, which thrives in high-salt environments such as soda lakes. When exposed to yellow or amber light (~590-600 nm), NpHR undergoes a conformational change, leading to the transport of chloride ions across the cell membrane. This results in hyperpolarization of the neuron, effectively inhibiting its activity. Optogenetic control using NpHR offers high temporal precision, allowing researchers to precisely modulate neuronal activity with millisecond-scale resolution. The inhibition induced by NpHR is reversible; once the light stimulation is removed, neuronal activity returns to baseline levels [11].

The expression of opsins in tissues can be verified using fluorescent dyes, e.g. tdTomato, mCherry, yellow fluorescent protein (YFP). Gene sequences encoding these pigments are delivered on the viral vector together with opsin [19]. YFP is a variant of green fluorescent protein (GFP) that emits yellow-green light (~527 nm) when excited by blue or ultraviolet light.

It is commonly used as a marker for visualizing protein localization, protein-protein interactions, and gene expression in live cells and tissues. tdTomato is a red fluorescent protein derived from DsRed (*Discosoma* sp. red fluorescent protein). It emits red-orange light (~581 nm) when excited by blue or green light. tdTomato is widely used as a fluorescent marker due to its bright fluorescence, high photostability, and minimal cytotoxicity. mCherry emits red light (~610 nm) when excited by blue or green light. Like tdTomato, mCherry is commonly used for labeling cellular structures, tracking protein localization, and studying gene expression dynamics [13].

### **3. Methods of introducing opsin genes and light delivery**

Inducing the expression of opsin genes in tissues involves delivering the genetic material encoding these opsins into the target cells or tissues in a controlled manner. One of the most popular ways of delivering genes is viral vectors such as adeno-associated virus (AAV), lentivirus, HSV-1 (herpes simplex virus) or rabies virus. These vectors can be designed to carry a given opsin gene, a promoter specific to target cells and a fluorescent protein and then injected directly into the target tissue or introduced into cells in culture. Viral vectors ensure high transduction efficiency and long-term expression of the opsin gene in target cells [11].

A commonly used promoter is choline acetyltransferase with affinity for cholinergic neurons or calcium-calmodulin-dependent kinase II $\alpha$  ( $\alpha$ CaMKII) [20], [21]. In the case of  $\alpha$ CaMKII, however, caution should be exercised in its application, as Miyashita et al. showed that its 80-day expression in combination with ChR2 may result in abnormalities in the structure of axons in the form of cylindrical and cup-shaped degenerations, which were not noticed after changing the promoter). Scientists also use many other promoters that target neuronal populations, such as synapsin, Thy1, VGAT (Vesicular GABA Transporter) or DAT (Dopamine Transporter) Promoter. [21], [22].

The biggest inconvenience in using viral vectors is their limited capacity, which reduces the possibility of using promoters of larger sizes and thus limits their delivery to selected cell populations. This problem has been solved by transgenic animals carrying Cre recombinase in the cells into which the opsin gene must be inserted. This system relies on the ability of the enzyme Cre recombinase to induce recombination between two DNA sequences known as "site-specific recombination sites", often referred to as "loxP sites". These sequences have a specific arrangement that allows for precise excision, insertion, or inversion of DNA fragments. The Cre recombinase originates from the bacteriophage P1 and exhibits high efficiency and specificity of action. Genes that we want to introduce or activate are delivered into the target

organism in the form of a construct containing loxP sequences at specific locations. Then, in the presence of Cre recombinase, recombination occurs between the loxP sequences, leading to specific genetic manipulations [23], [24].

The light that excites opsins is mainly generated by lasers or light-emitting diodes (LEDs). Both LED and laser implants provide precise control over the spatial and temporal pattern of light delivery to targeted brain regions or specific neuronal populations. This precision is essential for studying the functional connectivity of neural circuits and the role of specific neurons in healthy individuals and in models of various diseases. When tested in animal models, both methods are invasive, but if properly induced, they do not involve complications. LED implants in experiments involving optogenetic stimulation of the superficial layers of the cerebral cortex can be placed above the brain, but in the case of stimulation of deeper areas, their usefulness is limited because they generate heat that may contribute to tissue damage. LED implants and lasers can be integrated with electrophysiological recording techniques such as patch-clamp recordings or recordings using a multi-electrode array, enabling simultaneous manipulation, and monitoring of neuronal activity. They can also be combined with in vivo imaging techniques such as two-photon microscopy to visualize real-time neuronal dynamics during optogenetic experiments [14], [25].

ACTION TYPE	OPSIN	SOURCE
Stimulating	ChR2  VChr1  ChETA ChIEF SSFO	occurs in the cell membrane of the alga <i>Chlamydomonas reinhardtii</i>  occurs in the cell membrane of the algae <i>Volvox carteri</i>  was created based on ChR2 synthetic, long-lasting
Inhibitory	NpHR  Arch	occurs in the cell membrane of archaeobacteria <i>Natronomonas pharaonic</i>  occurs in the cell membrane of archaeobacteria <i>Halorubrum sodomense</i>

**Table 1.** Classification of opsins considering their origin and effect on cellular activity. Own study.

#### **4. Parkinson's disease - causes, epidemiology, symptoms**

PD is a complex neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra region of the brain. Epidemiologically, PD typically affects individuals over the age of 60, although cases can occur earlier, referred to as early-onset PD. The prevalence of PD increases with age, and it is estimated that about 1% of individuals over 60 years old are affected. The exact cause of PD remains largely unknown, but it is believed to result from a combination of genetic and environmental factors. Some genetic mutations have been linked to familial forms of PD, but these account for only a small percentage of cases. Environmental factors such as exposure to toxins like pesticides and certain metals have also been implicated in increasing the risk of developing PD [26], [27].

At the molecular level, PD is characterized by the accumulation of abnormal protein aggregates, particularly alpha-synuclein, within neurons. These aggregates form structures called Lewy bodies, which are pathological hallmarks of the disease. The progressive loss of dopaminergic neurons in the substantia nigra leads to a deficiency of dopamine, a neurotransmitter involved in regulating movement and coordination [28], [29]. This dopamine deficiency results in the characteristic motor symptoms of PD, such as tremors, bradykinesia (slowness of movement), rigidity, and postural instability. In addition to the motor symptoms, PD can also involve non-motor symptoms, including cognitive impairment, mood disorders (such as depression and anxiety), sleep disturbances, autonomic dysfunction, and sensory symptoms [30], [31].

Many changes occur in the brain of a patient with PD. The most characteristic pathological feature of PD is the loss of dopaminergic neurons in the substantia nigra. The progressive loss of these neurons leads to decreased production of dopamine in the brain. During PD, protein aggregates containing alpha synuclein, called Lewy bodies, are also deposited in the brain. These aggregates disrupt normal cell function and contribute to neuronal dysfunction and death. [32]. Inflammation within the brain is believed to play a role in the progression of PD. Activated microglia, the immune cells of the brain, contribute to neuroinflammation and can exacerbate neuronal damage [33]. In addition to dopamine depletion, alterations in other neurotransmitter systems, such as serotonin and noradrenaline, have been observed in PD. These changes also can contribute to non-motor symptoms such as mood disorders and cognitive impairment.



## **5. Parkinson's disease – genetic predisposition**

Genetic mutations play a role in a subset of PD cases, known as familial or hereditary PD. While most Parkinson's cases are sporadic, meaning they occur without a clear family history, approximately 10-15% of cases have a familial component. Several genes have been identified that are associated with an increased risk of PD when mutated. Some of the most well-known genes implicated in familial PD [34], [35].

Mutations in the SNCA (alpha synuclein) gene lead to abnormal aggregation of alpha-synuclein protein, which forms Lewy bodies within neurons. This is the same protein implicated in the pathology of sporadic PD [36]. Mutations in the LRRK2 (Leucine-rich repeat kinase 2) gene are the most common genetic cause of familial PD. LRRK2 mutations can lead to dysfunction in cellular processes such as mitochondrial function and protein degradation pathways [37], [38]. Mutations in the PARKIN gene are associated with early-onset PD and are inherited in an autosomal recessive manner. The PARKIN protein is involved in the clearance of damaged mitochondria through a process called mitophagy. Mutations in PARKIN lead to impaired mitochondrial function and increased oxidative stress within neurons [39].

Mutations in the PINK1 gene (PTEN-induced putative kinase 1) are also associated with early-onset PD and are inherited in an autosomal recessive manner. PINK1 plays a role in mitochondrial quality control and is involved in the regulation of mitophagy [40]. Mutations in the DJ-1 gene are associated with early-onset PD and are inherited in an autosomal recessive manner. DJ-1 is thought to have various functions within cells, including protecting against oxidative stress and regulating mitochondrial function [41].

In addition to these genes, mutations in several other genes, including VPS35, ATP13A2, GBA, and others, have been linked to familial PD, albeit less frequently. While mutations in these genes are relatively rare and account for a small percentage of Parkinson's cases overall, studying them has provided valuable insights into the underlying mechanisms of the disease, including mitochondrial dysfunction, protein aggregation, and oxidative stress [42].

## **6. Parkinson's disease – animal models**

Animal models of PD play a crucial role in understanding the disease's pathophysiology, testing potential therapeutic interventions, and exploring new avenues for treatment development. Several animal models have been developed to mimic different aspects of PD, each with its advantages and limitations.

PD symptoms can be induced in animals by administering a toxin. These models involve the administration of neurotoxins that selectively target dopaminergic neurons, leading to their

degeneration and resulting in Parkinson's-like symptoms. The most widely used toxin for this purpose is 6-hydroxydopamine (6-OHDA), which is injected into specific brain regions, such as the substantia nigra or striatum, to induce lesions [43]. Another toxin, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), can also induce Parkinson's-like symptoms in animals by interfering with mitochondrial function and causing dopaminergic cell death [44].

Genetic models involve genetic manipulation to induce Parkinson's-like pathology in animals. For example, transgenic mice expressing human mutant forms of alpha-synuclein, such as the A53T or A30P mutations, develop Lewy body-like inclusions and progressive neurodegeneration resembling PD. Other genetic models involve knockout, or overexpression of genes associated with familial forms of PD, such as LRRK2, PARKIN, or PINK1, to study their role in disease pathogenesis [45].

Viral vectors can be used to deliver genes or toxins selectively to specific brain regions, allowing researchers to induce Parkinson's-like pathology in animals with spatial and temporal control. For example, adeno-associated viruses (AAVs) can be used to overexpress alpha-synuclein or other proteins implicated in PD in specific brain regions, leading to neurodegeneration and motor deficits. Chronic inflammation is believed to contribute to the progression of PD. Animal models involving the administration of inflammatory agents, such as lipopolysaccharide (LPS) or cytokines, can induce neuroinflammation and exacerbate dopaminergic cell loss, mimicking aspects of PD pathology [46].

In addition to targeting dopaminergic neurons, some animal models aim to replicate the broader neurodegenerative processes observed in PD. For example, models involving the administration of proteasome inhibitors or mitochondrial toxins can induce widespread neurodegeneration and motor deficits resembling PD [47]. Each of these animal models has its advantages and limitations, and researchers often use a combination of models to address different aspects of PD pathology and test potential therapeutic interventions. While animal models cannot fully recapitulate the complexity of PD seen in humans, they provide valuable tools for studying disease mechanisms and evaluating novel treatment strategies before translation to clinical trials.

## **7. The use of optogenetics in the diagnosis and therapy of Parkinson's disease**

Optogenetics allows researchers to precisely manipulate the activity of specific neuronal populations in the brain. By expressing opsins, such as ChR2 or NpHR, in distinct cell types within the basal ganglia circuitry implicated in PD, researchers can dissect the functional roles of these neurons in motor control. This approach has helped identify key circuits involved in the

pathophysiology of PD and has elucidated the aberrant neuronal activity patterns underlying motor symptoms [48]. Deep brain stimulation is a clinically established therapy for PD that involves the surgical implantation of electrodes into specific brain regions, such as the subthalamic nucleus (STN) or globus pallidus interna (GPi), followed by the delivery of electrical pulses to modulate neuronal activity [49]. Optogenetics offers a means to mimic and refine DBS effects in animal models by selectively activating or inhibiting neurons within the targeted brain regions. This approach allows researchers to optimize stimulation parameters and identify optimal targets for therapeutic intervention.

Closed loop optogenetic systems, where neuronal activity is monitored in real-time and used to dynamically adjust optogenetic stimulation, hold promise for precise and adaptive therapeutic interventions in PD. By integrating neural recording techniques with optogenetics, researchers can develop closed-loop systems capable of detecting pathological activity patterns associated with PD and delivering targeted optogenetic modulation to restore normal circuit function [50], [51]. Optogenetic approaches have also been explored for their potential in promoting neuroprotection and neurodegeneration in PD. By targeting specific neuronal populations implicated in disease progression, researchers aim to modulate cellular signaling pathways involved in neuronal survival, synaptic plasticity, and neurogenesis. Additionally, opsins can be used to manipulate local neurotransmitter release and neurotrophic factor expression to promote neuronal health, repair damaged circuits and improves motor deficits [52].

## **8. Conclusions**

While these potential applications of optogenetics in PD diagnosis and therapy hold promise, it's important to note that significant challenges and ethical considerations remain. Optogenetic techniques would need to be further refined and validated for safe and effective use in humans, and clinical trials would be required to evaluate their feasibility, efficacy, and long-term safety profiles. Additionally, ethical considerations related to invasive procedures and genetic manipulation of the human brain would need to be carefully addressed. Nonetheless, ongoing advancements in optogenetic technology and our understanding of PD offer hope for future innovations in diagnosis and therapy.

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**Authors contribution**

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