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Review

Optogenetic cell control in experimental models of neurological disorders

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HIGHLIGHTS

- Optogenetics probes are valuable tools in models of neurological disorders.
- Optogenetic cell control has relieved symptoms in models of neurological disorders.
- Optogenetic tools may be experimentally applied investigatively or therapeutically.

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ABSTRACT

The complexity of the brain, in which different neuronal cell types are interspersed and complexly interconnected, has posed a major obstacle in identifying pathophysiological mechanisms underlying prevalent neurological disorders. This is largely based in the inability of classical experimental approaches to target defined neural populations at sufficient temporal and spatial resolution. As a consequence, effective clinical therapies for prevalent neurological disorders are largely lacking.

Recently developed optogenetic probes are genetically expressed photosensitive ion channels and pumps that in principal overcome these limitations. Optogenetic probes allow millisecond resolution functional control over selected optogenetically transduced neuronal populations targeted based on promoter activity. This optical cell control scheme has already been applied to answer fundamental questions pertaining to neurological disorders by allowing researchers to experimentally intercept, or induce, pathophysiological neuronal signaling activity in a highly controlled manner.

Offering high temporal resolution control over neural activity at high cellular specificity, optogenetic tools constitute a game changer in research aiming at understanding pathophysiological signaling mechanisms in neurological disorders and in developing therapeutic strategies to correct these. In this regard, recent experimental work has provided new insights in underlying mechanisms, as well as preliminary proof-of-principle for optogenetic therapies, of several neurological disorders, including Parkinson's disease, epilepsy and progressive blindness.

This review synthesizes experimental work where optogenetic tools have been applied to explore pathologic neural network activity in models of neurological disorders.

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1. Optogenetic cell control

The inherent complexity of the neural circuits of the brain, and the lack of experimental tools to functionally dissect these, has hampered the delineation of pathophysiological mechanisms underlying prevalent neurological disorders, including Parkinson's disease (PD), epilepsy, and blindness resulting from retinal degeneration. Until recently, it has remained extremely difficult to experimentally isolate and investigate specific neuronal populations within a given brain structure, as any given cellular population exists interspersed among numerous additional neuronal and glial cell types.

Experimentally, spatially confined control over cell populations has been commonly achieved electrophysiologically *via* electrodes or chemically by focal injections of pharmacological agents, in a not too well defined area around the stimulus or injection center. Both of these approaches affect all cells in the volume of application, often leaving cause/effect interpretations ambiguous.

This targeting specificity problem extends beyond the experimental interrogation of normal and diseased neural circuits and pathways. Clinically, pharmaceutical drugs do not target specific cell types, but rather influences all cells expressing a certain membrane channel, receptor or pump. The same holds true for electrical deep brain stimulation (DBS), a therapy directed against PD, epilepsy and other neurological disorders, in which all cells and passing projections in a given tissue volume are unspecifically stimulated, even if only a subset are implicated in symptom relief [1].

Genetic introduction of optically controllable membrane proteins harboring the potential to control the cell membrane potential at millisecond resolution has recently overcome many aspects of the specificity problem [2–4]. Several relevant photosensitive ion channels and pumps have been isolated from algae and bacteria and modified to be functionally expressed in mammalian cells. The most widely applied of these are the complementary blue light (around 470 nm) activated depolarizing cation channel channelrhodopsin-2 (ChR2) derived from a green algae [2], and the orange light (around 590 nm) driven hyperpolarizing chloride pump halorhodopsin, NpHR, derived from a halobacteria [4]. Both of these now come in several modified versions, tuned for specific stimulation frequencies or spectral activation wavelengths [*e.g.* [5,6]].

Such optogenetic probes allow relatively strict functional control over well-defined neural populations in intact tissue, even where targeted cells are interspersed among multiple other cell types. Conceivably, any cell type that can be identified based on transcription promoter activity can be selectively transduced, by genetically introducing an optogenetic probe expressed under that given promoter. In addition to somatically targeted optical control, projections extending from transduced cells may be directly activated or inhibited along their way by local illumination, while not influencing the activity of neighboring non-transduced somas and processes [7].

Populations of cells, or even fiber bundles, can thus be switched on/off at millisecond resolution, in a tissue volume defined by the cellular expression of the optogenetic protein and the availability of this tissue to be illuminated with light of a relevant wavelength [8]. Certainly, the latter restriction comes into play when considering the intact brain, where deeper nuclei are optogenetically targetable only after implantation of optical fibers to deliver light, each of which can effectively illuminate a volume of less than around 1 mm^3 due to scattering and absorption of photons in tissue [9]. Despite this limitation, the potential of optogenetic cell control in experimental studies relating to connectivity and excitability of defined neural populations is immense.

In addition to connectivity studies, circuit malfunctions underlying neurological disorders can be investigated in far more detail than with conventional pharmaceutical or electrophysiological means, as will be highlighted in this review.

Whereas the term optogenetics is commonly associated with ChR2, NpHR and other single component membrane associated opsins, there is an ever-increasing toolbox of complementary genetic and synthetic optochemical tools that allow neural cells to be controlled or monitored optically, the majority of which conceptually precede the currently popular rhodopsins. Among others, these include cis-trans isomerizable photo-sensitive receptor proteins and ligands, photo-releasable caged ligands (reviewed in Refs. [10,11]), as well as widely applied calcium sensitive fluorescent dyes and voltage sensitive dyes for monitoring membrane potential changes (reviewed in Ref. [12]). Though these tools have proven their aptness in experimental neurobiology, for coherency, this review focuses on studies applying rhodopsin based optogenetic probes.

1.1. Studying neurological disorders by optogenetics

To delineate pathophysiological signaling mechanisms underlying neurological disorders by means of optogenetics, experimenters can actively attempt to induce disease hallmarks on an electrophysiological or behavioral level, or try to intercept observed ongoing disease hallmarks optically. The specific experimental paradigm will then again depend on whether silencing or activating probes are used.

Bidirectionally controlling the excitability of targeted neural populations enables not only exciting experimental studies, but also conceivably clinical therapies for neurological disorders. The advantage over conventional chemical drugs is the millisecond onset of the probes, the ability to switch the probes off at millisecond resolution, and the before mentioned cellular specificity with which they can be applied. As described later, though, the translation from experimental models of neurological disorders into clinical trials is far from straightforward, and the clinical application of optogenetic tools to correct aberrant signaling is probably still a while ahead. However, it has been suggested that the use of optogenetics to uncover new pathways and circuits of the brain may in itself allow clinical translation in a nearer future, by allowing modulation of such pathways and circuits through conventional therapeutic tools [13].

Like experimental gene therapy, optogenetic cell control can be applied *in vivo* by direct injection of a gene vector into the target tissue, or *ex vivo*, by transducing cells cultured *in vitro* and since introducing these into the target tissue [14]. The latter provides means for combining cell therapy and optogenetics, which holds interesting perspectives for experimental models of stem cell based restorative neurology [15].

This review compiles current literature where optogenetic techniques are applied to understand or control neural circuits in experimental models of neurological disorders, including PD, epilepsy and retinal degeneration.

The three conditions included here are characterized, at least initially, by alterations in excitability of neurons in a relatively well-defined and confined area of the brain, and in their symptoms being clinically and experimentally relievable through electrostimulation approaches. Like electrode stimulations, optogenetic probes allows brain areas to be stimulated focally at high temporal resolution, though with the advantage of cell type specificity and the choice of strictly activating or silencing neurons. Optogenetic probes therefore potentially hold the key to unravel the mechanisms involved in pathophysiology, as well as the signaling mechanisms mediating symptomatic relief after electrostimulation. Consequently, the majority of optogenetic studies on