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OPTOGENETICS- A BRIEF REVIEW

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ABSTRACT: Optogenetics (a branch of biotechnology) is a biological tool used in the field of neuroscience that encompasses a combination of techniques from optics and genetics to study the functioning of individual neurons in a living tissue. Spatio-temporal precision in neuronal control can be achieved using optogenetic actuators or reporters and sensors or indicators. The present review highlights the brief history of optogenetics, opsins- the functional unit in optogenetics, and the design of optogenetic experiments to study behaviour in normal function or disease models. The review also discusses the limitations of the technique and its applications in various behavioural and neuropsychiatric disorders such as anxiety, fear, depression, addiction, autism and Parkinsonism. Looking back at the rate of progress over the last few years, it is reasonable to predict and believe that the molecular techniques for optogenetics will continue to evolve rapidly and that the applications of these methods will continue to expand.

INTRODUCTION: Optogenetics is defined as a branch of biotechnology that involves genetic targeting of specific neurons or proteins with optical technology for imaging or control of targets with intact or living neural circuits. [1] Optogenetic actuators or reporters like channelrhodopsin, halorhodopsin and archaerhodopsin; and optogenetic sensors or indicators for calcium (Aequorin, Cameleon, GCaMP), Chloride (Clomeleon) or membrane voltage (mermaid) have been employed for precise neuronal control. [2]

Brief History: The early ideas were inspired by Charles S. Sherrington in 1940 who described the different stages of sleep- to- wake transition as neuronal activity with points of light. Later Crick in 1979 envisioned that light might be used to control and monitor the activity of genetically defined neuronal populations.

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The approaches for optogenetic control were developed and applied by Boris Zemelman and Gero Miesenbock at Sloan- Kettering Cancer center in New York; and Dirk Trauner, Richard Kramer and Ehud Isacoff at the University of California, Berkeley. [3, 4] The implementation of an optical measure of neuronal activity were studied by using organic (voltage sensitive organic dyes) to fluorescent proteins and finally to genetically encoded reporters. Fully genetically encoded fluorescent reporters were generated by fusing one or more fluorescent proteins (FPs) with various protein moieties offering sensitivity to signals such as transmembrane potential, ions (calcium, pH, chloride or zinc), neurotransmitters (glutamate) or second messenger molecules like cyclic nucleotides. [5] Susana Lima and Miesenbock in April 2005, reported the first use of genetically targeted P2X2 photostimulation to control the behaviour of animal. [6]

The hallmark approach of optogenetics therefore is introduction of fast light activated channels and enzymes (microbial opsins) that allow temporally precise manipulation of electrical and biochemical events within intact tissue or behaving animals.

Opsins: Opsins are membrane bound proteins that can incorporate small organic retinal molecules to become a light receptor. Microbial opsins used to investigate the function of neural systems are i) channelrhodopsins (ChR1, ChR2, VChR1 and SFOs) to excite neurons whereas ii) other microbial rhodopsins like halorhodopsin (NpHR), eNpHR2.0 and eNpHR3.0) archaerhodopsin (Arch), Leptosphaeria maculans fungal opsins (Mac) and enhanced bacteriorhodopsin (eBR) have been employed to inhibit neurons in freely moving animals. [7-9] Channelrhodopsins (ChR1, ChR2) were cloned from the species *Chlamydomonas reinhardtii* (green algae), VChR1 from *Volvox Carteri* [10] and MChR1 from *Mesostigma Viride*. [11] These opsins are permeable to cations [12, 13] and can thus mediate depolarising currents upon illumination with blue light (450-500 nm). Other microbial rhodopsins were known to exist in halophilic archaebacteria, [14] in bacteria [15] and in some eukaryotes [16].

Proteins like bacteriorhodopsins, proteorhodopsins and archaerhodopsins (from *Natronomonas pharaonis*) extrude protons from cytoplasm and generate a hyperpolarizing photocurrent to silence the neurons upon illumination with yellow light (532 nm). Some newer opsin variants include engineered channelrhodopsin variants - ChETA family and ChIEF [17-19] which are used to evoke ultra fast firing frequencies in fast spiking neurons; OptoXRs (Opsin receptor chimaeras in which the intracellular loops of rhodopsin are replaced with intracellular loops from other G-protein coupled receptors such as adrenergic receptors); the step function opsin (SFO) which delivers prolonged, bi-stable, subthreshold depolarization of membranes [20]; and C1V1 family that are significantly more potent than ChR2 and approximately fourfold more potent than Volvox channelrhodopsin 1 (VchR1) [21]. By fusing these opsins to specific G-Protein coupled receptors, it is possible to determine the concentration of intracellular messangers such as cAMP and IP3 in targeted cells within behaving animals.

Design: There are basically five major steps in the design of optogenetic experiments to study behaviour in normal function or disease models- i) Selection of opsin best suited for the experiment ii) Selection of targeting stratergy by viral transduction methods or vectors to express opsin in target cells. The most commonly used viral vectors are lentivirus and adeno associated viruses for expression of opsin into the injection site. Herpes simplex virus or rabies virus are also used but present more toxicity.iii) Selection of light delivery methods- Illuminating deep brain areas requires the use of light guides such as optical fibers. Fibre optic light delivery can be implemented easily in freely behaving animals. [22-24] The numerical aperture, diameter and the mode of fibre will influence the spread of light. Fibre optics are designed for acute and chronic studies. iv) Selection of appropriate temporal parameters- Light stimulation parameters like duty cycle, pulse duration, frequency and intensity are selected for behavioural assays. v) Validation of experimental manipulation-Verification of the functioning of optogenetic tools are desired which is confirmed by using electrophysiology, immunohistochemistry, other pharmacological or behavioural assessments for data interpretation.[25].

Today's challenge for light microscopy consist in accessing deep structures (> 1 mm) and imaging neuronal activity in unrestrained animals, with long term goal of combining the two. By eliminating the need of dye loading step and allowing long term imaging, genetically encoded activity reporters have dramatically increased the attractiveness of such approaches. [26] One new requirement of optogenetics is the possibility of delivering light and recording electrical activity with the same implantable device. These "Optoelectrodes" (or optrodes) are useful to assess the efficiency of photostimulation and inhibition *in vivo*. Thus creation of a method to simultaneously perform optogenetic activation and achieve calcium imaging at a single cell or even dendritic spine resolution in a freely moving mammal would also be an enormous advance for the field.[25]

Limitations and Considerations: i.) Transfection methods- Transfection methods are focused on the construction of viral vectors and promoters for cell specific expression of the microbial rhodopsins. The virus approach is quick and efficient, whereas the construction of transgenic animals (rodents, fruit flies, zebrafish and *C. elegans*) are time consuming but have been proven to be ideal for a variety of different experiments in basic research.

Although viruses offer an effective and clinically applicable means for delivering the genes that encode these rhodopsins, it is still a laborious process to develop constructs that maximize the efficiency of gene delivery and expression. ii) Improvement of the optogenetic tools-Although the wild type ChR2 and NphR work quite well, the potential for toxicity at very high expression levels or long term expression is another limitation. There may be a limit to the level of opsin expressed by a given cell or else the cell health can be altered. It becomes necessary to perform controls under the same conditions as the experimental parameters. iii) Improvement of appropriate light sources- Better modes of light delivery will be required to improve the accuracy and efficiency of optogenetic strategies. The light emitted from optogenetic fibre may cause heating. Heating neurons may not only alter their activity but may be detrimental to cell health. [25]

Applications: Thus the field of optogenetics has paved way for scientific understanding on how specific cell types contribute to the function of biological tissues such as neural circuits in vivo. On the pre-clinical side it has been used to dissect neural circuits in animal models of symptoms that are relevant to a large number of neuropsychiatric disorders.

i) Optogenetics in behavioural studies- Optogenetic approaches have revolutionised the approaches in which the traditional behavioural assays are used. The elevated plus maze with optogenetics now allows within subject comparison of conditions (light on and light off) in single behavioural sessions. [27] Animals can be now allowed to freely explore the chambers in conditioned studies and different light stimulation parameters (duty cycle, pulse frequency, pulse duration and intensity) can be triggered depending on the animal's location, which allows for a finer measure of optical stimulation parameters in comparison to different drug doses which cannot be tested within a single session. This allows multi- day tests to be condensed into a single session.

ii) Circuitry of fear and anxiety disorders – A specific population of amygdala synapses has been identified using optogenetic tools that can rapidly and reversibly modulate anxiety levels in freely moving mammals. [27, 28] Selective optogenetic stimulation- of excitatory basolateral amygdala (BLA) cells with axons that project to the central nucleus of amygdala (CeA) with a channelrhodopsin and halorhodopsin produced an anxiolytic and anxiogenic effect respectively. Optogenetic tools have allowed researchers to selectively target and study glutaminergic lateral amygdala neurons which also contains GABA ergic interneurons and glutaminergic pyramidal neurons in the CA1 region of the hippocampus which are crucial for processing fear and expressing remote fear memories respectively. [29]

iii) Circuitry of addiction- It has long been known that nucleus accumbens (NAc) is critically involved in both reward processing and other addiction related behaviours. [30-33] Cholinergic interneurons expressing choline acetyltransferase (ChAT) in NAc modulate the activity of medium spiny neurons (MSNs) which modulates the ability of the animal to develop cocaine- conditioned place preference. Activating MSN- D1R expressing neurons enhances cocaine CPP and activating MSN- D2R expressing neurons suppresses cocaine CPP. [34] GABAergic neurons in the ventral tegmental area (VTA) are identified as new targets for addiction research because opiods act to reduce GABAergic suppression of VTA dopamine neurons. [35]

iv) Circuitry of depression- Optogenetic techniques have been used to target cell bodies of prefrontal cortex areas which projects to many neural pathways like corticolimbic, dorsal raphae, hippocampal, amygdala, striatal and mesolimbic dopamine circuits. Illumination of these areas expressing ChR2 showed an anti-depressant like response in mice. [36-37]

v) Circuitry of autism and schizophrenia- Although animal models of schizophrenia are still being optimized, one specific abnormality in psychiatric disease is the reduced number and functionality of neocortical parvalbumin neurons and therefore optogenetic approaches to the circuitry have included targeting these neurons. [38] The complexity and variability of symptoms in autism has been proposed due to the imbalance in cellular excitation and inhibition. [39]

This idea was tested using optogenetic tools by enabling the expression of SSFO which produces subthreshold membrane potential changes that lasts for many minutes in glutaminergic prefrontal cortical neurons that allowed the level of cortical excitation to be elevated. [40- 44]

vi.) Circuitry of neurological disorders such as parkinson's disease and epilepsy-Optogenetic control of afferent fibres in substantia nigra (STN) was shown to have profound therapeutic effects on motor behaviours in hemi-parkinsonian rat model. [45] Optogenetic stimulation in a corticothalamic circuit resulted in generation of aberrant oscillations similar to seizure activity.[46]

Optogenetics has several other applications. Optogenetic activation of cones rescued blindness due to neuronal loss.[47] Activation of neurons using optogenetic tools in the retrotrapezoid nucleus-parafacial respiratory group induced active respiration and regulated the rhythm of respiration. [48] This technique also improved neuropsychiatric sleep disorders.[49] On atrial cardiomyocytes optogenetics was used in atrial fibrillation to end spiral wave arrhythmias with light. [50] Optogenetic stimulation of spiral ganglion in deaf mice restored auditory activity. [51] Optogenetic activation of olfactory sensory neurons was found to be critical for demonstrating timing in odor processing [52] and for mechanisms of neuromodulatory mediated olfactory guided behaviours (aggression and mating). [53]

DISCUSSION AND CONCLUSION: The present review focusses on optogenetics- a neuromodulation technique, opsins- the functional unit in optogenetics, its history and its design. The technique's applications in various behavioural and neuropsychiatric disorders such as anxiety, fear, depression, addiction, autism and parkinsonism have also been explained. The precision of optogenetics has provided major experimental leverage [54] and has led insights into neural circuit function and dysfunction. Although the impact of these investigations has already been substantial, there remains much work to do like the application of optogenetics to non-human primates is still in its infancy and many disease states and symptom clusters remain unexplored. [55-57] It is reasonable to speculate that a very specific neural circuit dysfunction such as imbalance in excitation and inhibition could be casually involved in multiple psychiatric diseases including anxiety, depression, addiction, schizophrenia and autism. In particular given the high rate of co-morbidity among the various mental illnesses and the shared symptom logy between individual diseases, identification of such themes and unifying theories by optogenetic or by other means is one of the most pressing needs and exciting avenues of research into neurological and psychiatric diseases.

In 2010, Optogenetics was chosen as the "Method of the Year" across all fields of science and engineering by the interdisciplinary research journal *Nature Methods* and was also highlighted in the articles on " Breakthroughs of the Decade" in the academic research journal *Science.* Although just more than a decade old, optogenetics is already responsible for enormous progress in neuropsychiatric disorders, and its future is undoubtedly bright. After all exploration of the unknown lies in the very nature of basic research.

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