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Editorial

Optogenetics and its Potential Role in the Treatment of Epilepsy

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Editorial

Optogenetics, as the term has been commonly used, refers to the technology to use light to control neuron or neuronal network that has been specially sensitized to light [1]. The peak activation wavelength of light is mostly between 400 to 650 nm [2]. It has been firstly introduced into neuroscience since 2005 [3]. It is an integration of opics and genetics to control the activity of special neurons in living tissue. For example microbial opsin genes can be introduced in to a specific targeted neuron or neuronal population, then the effects of those manipulations can be precisely measured in real-time. The key factor used in optogenetisc is light-sensitive protein, usually referred to opsin. We can achieve gain-or loss-of function of the targeted neuron or neuronal network using different microbial opsins.

According to the function of opsins, there are three major types. A type such as Channelrhodopsin 2 (ChR2) induces the targeted to be depolarization and enables action potential elicited to light pulses. B type such as halorhodopsin (NpHR) and proton pumps enable the targeted to be hyperpolarization to prevent the induction of action potentials. C type such as light-activated membrane-bound G protein-coupled (OptoXR) or soluble (bacterial cyclase) receptors that minic various signaling cascades. The cascade is usually G_q, G_s or G_i signaling.

Apart from A type of opsins, B type is used to light to silence electrical activity in targeted cells. Available B type such as NpHR that directly move ions to achieve silencing is inefficient. Only a single ion per photon across the cell membrane is pumped rather than many ions per photon are allowed to flow through a channel pore. Recently, a class of ChR, which is originally cation-conducting, has been converted into chloride-conducting anion channels [4]. The new class of ChR enables fast optical inhibition of action potentials and displays step-function kinetics for stable inhibition of targeted neuron. Moreover, it is more sensitive to light than NpHR. An approach that is more physiological, efficient, and sensitive optogenetic inhibition has come to us.

Nearly 1% of people worldwide (70 million) have epilepsy [5]. Epilepsy is a common neurological disorders characterized by epileptic seizures. Epilepsy cannot be cured, but seizures can be controlled with medication. The seizures are episodes that vary from brief or almost undetectable to a long period of vigorous shaking. Seizure is the clinical manifestation of a hyperexcitable network, in which the electrical balance underlying normal neuronal activity is pathologically altered.

There are many types of Anti-Epileptic Drugs (AEDs) to different targets. Generally speaking, there are ten classes of targets [6]. A. Voltage-gated ion channels, such as voltage-gated sodium channel, voltage-gated calcium channel, voltage-gated potassium channel, the Hyperpolarization-activated Cyclic Nucleotide-gated cation (HCN) channel, voltage-gated chloride channel. B. Ligand-gated ion channels, such as $GABA_A$ receptor, nicotinic cholinergic receptor, glycine receptor. C. Ionotropic glutamate receptors, such as NMDA receptor, AMPA receptor. D. Acid-sensing ion channels. E. G-Protein-Coupled Receptors (GPCRs). F. The metabotropic glutamate metabotropic receptors, such as $GABA_B$ receptor. G. Neurotransmitter transporters, such as plasma membrane GABA transporter, plasma membrane glutamate transporters, vesicular glutamate transporters. H. Presynaptic proteins which influence synaptic function, such as synaptic vesicle protein, synaptic anchoring proteins. I. Enzymes, such as GABA-transaminase, carbonic anhydrase, protein kinases and phosphatases. J. Gap junctions (connexins). So far the most important classes of targets for currently marketed AEDs are voltage-gated and ligand-gated ion channels. Other targets have been investigated, recently, it is reported that hydrogen sulfide aggravates Seizure-Like Events (SLEs) of rats *in vivo* and *in vitro*, which may be due to an increase in neuronal excitation [7]. Enzymes that control hydrogen sulfide biosynthesis are potential new targets for the treatment of epilepsy. Although lots of AEDs are available, effective symptomatic relief is achieved only in about two thirds of the patients [8]. Surgery, neurostimulation or dietary changes may be considered for seizures that do not respond to medication.

As hyperexcitable network is the key factor underline seizure generation, reducing the excitability of network is the goal for treating epilepsy. As mentioned above, the new class of ChR enables fast optical inhibition of action potentials. This new opsin is supposed to directly and completely terminate epileptic discharge by light pulses.

The vast majority of optogenetic study to today has been carried out in mouse or rats. Viral vector delivery, which introduced the opsin to cells, to the primate brain has been well established and used for limited forms of neuromodulation [9] . Two optogenetic works on primate have been performed, demonstrating for the first time that optogenetics can be used in rhesus macaques [10,11] . Given that mammalian optogenetics is just at the beginning, it still has a lot of progress made in non-human primate and toward human use. However, significant technical obstacles are still remained, requiring

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advances in opsin engineering, vector delivery, and light pulse among other fields. For example, the brain of rhesus is approximately 250 times larger than rat while the brain of human is approximately 10 times larger than rhesus [12]. Thorough safety studies will be required prior to any human use. Moreover, the safety of the expression of opsin and delivery devices of light will need to be tested. Just now, the histological data available from the non-human primate work described above are conducted for several months, in this short time frame, no large-scale neuronal damage is reported [10,11,13].

It is thoughtful that optogenetics with the new class of ChR will be used in the treatment of epilepsy in the foreseeable future.

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