Automatic Focal Seizure Suppression System: An Application of Optogenetic Gene Silencing

To the Editor: There are many approaches for epilepsy control. Among them, electrical approaches like deep brain stimulation (DBS) had been helpful in some severe cases. Despite the advantages of DBS in controlling seizures, there are many side effects attributed to this invasive treatment method. These complications motivate new researches in the field to control epilepsy with fewer side effects. Photostimulation provides an appropriate alternative to electrode stimulation. Light beams can be easily and quickly manipulated to target neurons.[1] In photostimulation, neurons can be bidirectionally turned on and off with cell-type specificity, high temporal precision, and rapid reversibility. To satisfy these requirements, the microbial light-sensitive proteins Chlamydomonas reinhardtii Channelrhodopsin-2 (ChR2) and Natronomonas pharaonis (NpHR) have been introduced into neurons.[1,2] ChR2 can depolarize neural cells, whereas NpHR acts in opposite way and hyperpolarizes neurons. These two proteins can be activated with two distinctive lights, with more than a 100-nanometer wavelength difference. Hence, these proteins can act together in neurons and may modulate neuronal activity. Both proteins have fast temporal kinetics, making it possible to drive reliable trains of high-frequency action potentials in vivo.[3] Because NpHR remains active for many minutes when exposed to continuous light and deactivates quickly when light is turned off, it can be used in epilepsy.

We propose a new intelligent method of focal epileptic seizure suppression using synthetic biological circuits for the purpose of activating optogenetic tools precisely at the locus of the seizure. It can be expected that decreasing the hyper-activation of neurons or disturbing the pattern of seizure in its onset with high spatial-resolution can be useful in controlling the seizure. Our general idea is the following: If the promoter of any up-regulated gene in epileptic neurons is recognized, the appropriate vector can be designed for targeting the involved neurons. Then we can target the transport of NpHR to epileptic neurons so that the hyper-activated epileptic neurons can be suppressed before and after the onset of seizure; hence, it will be possible to control the seizure by use of yellow light. We have designed a three-step regulatory network:

1) Targeting and gene expression mechanism: We designed a network consisting of two vectors: the temporary vector (T) and the permanent vector (P). The T vector has the induced-promoter, and, at the onset of the seizure, it is expressed. In this vector, there is a separate promoter for fluorescent protein (X-promoter for XFP). The X-promoter is repressed by the induced-repressor in the P vector. The second part of the P vector has a down-regulated section, and its activation is based on the expression of activator protein. The P vector has an autofeedback or memory loop in it so it can be expressed permanently when the activator concentration is above a threshold. Our idea differs from previous studies in having a genetic driver circuit that detects the involved neurons in epilepsy and builds a permanent memory of NpHR gene expression.

2) Tracking epileptic neurons: it is now possible to find the local position of targeted epileptic neurons by processing the data of EEG or by other imaging systems, such as fMRI.[4,5] Using our proposed method, it is possible to track the exact position of epileptic neurons by watching the fluorescent XFP proteins.

3) Optogenetic automatic system of seizure suppression: An automatic seizure-suppression system may be designed, assuming that the focal area of our interest is small and accessible.[6] We would hope that this method might disturb the synchronization of epileptic neurons and decrease the hyperactivity of epileptic neurons. Our hypothesis needs to be implemented in animal studies in order to be validated. If so, it will be possible to control the involved neurons in the epileptic attack by yellow light interaction.

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