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Seizing Control: From Current Treatments to Optogenetic Interventions in Epilepsy

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Abstract

The unpredictability and severity of seizures contribute to the debilitating nature of epilepsy. These factors also render the condition particularly challenging to treat, as an ideal treatment would need to detect and halt the pathological bursts of hyperactivity without disrupting normal brain activity. Optogenetic techniques offer promising tools to study and perhaps eventually treat this episodic disorder by controlling specific brain circuits in epileptic animals with great temporal precision. Here, we briefly review the current treatment options for patients with epilepsy. We then describe the many ways optogenetics has allowed us to untangle the microcircuits involved in seizure activity, and how it has, in some cases, changed our perception of previous theories of seizure generation. Control of seizures with light is no longer a dream, and has been achieved in numerous different animal models of epilepsy. Beyond its application as a seizure suppressor, we highlight another facet of optogenetics in epilepsy, namely the ability to create “on-demand” seizures, as a tool to systematically probe the dynamics of networks during seizure initiation and propagation. Finally, we look into the future to discuss the possibilities and challenges of translating optogenetic techniques to clinical use.

Keywords

epilepsy; optogenetics; clinical treatments; closed-loop systems; microcircuits

Introduction

Epilepsy: Epidemiology and Current Treatments

Epilepsy is a widespread neurological disorder, affecting 50 million people worldwide (World Health Organization 2015). The overall prevalence is approximately 0.5% in developed countries and 1% or higher in developing countries (Banerjee and others 2009; Hirtz and others 2007; Picot and others 2008; World Health Organization 2015). Overall,

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30% to 40% of patients are pharmacoresistant (Kwan and Sander 2004). Unfortunately, this high percentage of non-responding patients persists despite the advent of a large number of new antiepileptic drugs (AEDs) since the 1990s. Currently, there are more than 20 clinically utilized AEDs (Duncan and others 2006; Zaccara and Perucca 2014). Patients with chronic refractory epilepsy have at least a twofold increase in mortality when compared with non-epileptic age-matched controls (Mohanraj and others 2006). This is partially due to the risk of sudden death associated with epilepsy (SUDEP), which rises from 1 per 1000 patient-years in all patients with epilepsy to 6 per 1000 patient-years in patients with refractory epilepsy (Laxer and others 2014; Thurman and others 2014). Additionally, the cause of death is directly epilepsy-related in one-third of patients (Brodie and others 1997). Epileptic patients also have a high risk of psychological comorbidities, with nearly one-third of patients suffering from depression and/or anxiety (Kwon and Park 2014). Finally, persistent seizures drastically decrease the patient's quality of life, limiting their independence and preventing them from driving or holding many types of employment (Taylor and others 2011).

The currently available treatment options for epilepsy are summarized in Figure 1 and described below. The first-line treatment for epilepsy is AEDs, which can offer excellent seizure control for many patients. However, they only treat the symptoms but not the disease, that is, the seizures but not the epilepsy (Duncan and others 2006). Additional drawbacks are that drugs are not effective for all patients or seizure types, they are not specific to the seizure focus, they must be taken at all times (not just during a seizure), and they can have serious negative side effects. Another issue is that except for a few drugs directed at specific types of seizures, such as ethosuximide for absence seizures, the selection of an AED is not tailored to the patient's seizure semiology (Duncan and others 2006). Furthermore, once patients are diagnosed with pharmacoresistant epilepsy, they have a very low chance (<4% per year) of achieving seizure remission with the addition of new drugs (Choi and others 2008). Drug-drug interactions are common among AEDs and can cause problems with affecting the efficacy of other drugs, such as other AEDs, oral contraceptives, antibiotics, analgesics, antidepressants, antihypertensives, and chemotherapeutic drugs (Zaccara and Perucca 2014). Much research has been done to investigate why there is such a significant population of drug-resistant patients. Hypotheses of pharmacoresistance include a failure of the drug to reach its target, an alteration of the drug's target, and the possibility that the drug may not be acting on the true pathogenic target (Kwan and others 2011).

Surgical treatments are the second-line therapy for patients with drug-resistant epilepsy. One well-established surgical treatment is temporal lobectomy, which leads to an excellent chance of seizure freedom. A randomized controlled trial of temporal lobectomy versus medical management for patients with medically refractory temporal lobe epilepsy demonstrated that 58% of surgical patients were completely seizure-free after 1 year, compared with only 8% of pharmacologically treated patients (Wiebe and others 2001). Focused resections of other lesions such as cortical dysplasia, tubers in tuberous sclerosis, and low-grade tumors can also be very effective in treating epilepsy. Overall, surgical resection of epileptic lesions leads to very good results, with about 70% of patients being seizure free after surgery with an MRI-identified lesion (Téllez-Zenteno and others 2010).

Patients without a clear lesion can go through so-called phase I and phase II monitoring. Phase I consists of inpatient video-electroencephalography. If the electrographic and clinical features of the seizures localize to one side of the brain, the patient may be eligible for phase II monitoring, where either subdural or depth electrodes are surgically implanted. The patient then undergoes further video-electrocorticography (ECoG) analysis, and if a resectable seizure focus is identified, this is then surgically removed. A recent study showed that after 10 years of follow-up, 38% of such patients remained seizure free (Noe and others 2013). Although long-term seizure freedom of 38% of patients is much higher than can be achieved with medical management, this number demonstrates that there is still a real and urgent need for more efficacious treatments.

Surgical implantation of electrodes for stimulation offers another type of treatment for refractory epilepsy. Deep brain stimulation (DBS), which involves the delivery of electrical impulses through electrodes surgically implanted into subcortical regions of the brain, is well-known as a highly effective treatment for Parkinson's disease. DBS is also currently approved for treatment of epilepsy in Europe and Canada, and there is evidence that DBS has particularly beneficial outcomes for patients with temporal lobe epilepsy (Beudel and Brown 2015; Miocinovic and others 2013; Nune and others 2015). A randomized controlled trial of DBS in the anterior nucleus of the thalamus demonstrated significant seizure reduction in patients with refractory epilepsy (Fisher and others 2010). Vagal nerve stimulation is another surgical option for patients with non-lesional epilepsy or an unresectable seizure focus, and this technique offers about 50% seizure reduction. With this stimulation, small electrodes are wrapped around the left vagus nerve in the patient's neck, and these electrodes stimulate the vagus nerve in response to substantial increases in the patient's heart rate, which serves as a proxy for seizure activity (Nune and others 2015). Drawbacks to vagus nerve stimulation include an unknown mechanism of action, open-loop rather than closed-loop control, and lack of curative potential (Orosz and others 2014).

Over the past 10 years, several new neurosurgical technologies have emerged with applications for epilepsy. One very promising, newly approved treatment is responsive neurostimulation (RNS). This is a closed-loop system in which electrodes are implanted either deep into the brain or onto the surface of the brain. The attached device is then programmed to detect seizures, and delivers electrical stimulation to the implanted electrode upon detection of a seizure. The device has a built-in seizure detection algorithm, which is customizable to the patient's own seizures. The initial clinical trial showed promising results in terms of seizure control (Heck and others 2014), and follow-up studies are promising in terms of improved cognition (Loring and others 2015). This new and promising device represents a first step toward the goal of "no seizures, no side effects." Laser interstitial thermal therapy (LITT) is another new surgical option for refractory epilepsy. With this technique, a laser fiber is stereotactically implanted into the patient's pre-identified seizure focus, and then the tissue is heated to 90°C, using real-time thermal MRI to verify the tissue temperature and the zone of the lesion (Medvid and others 2015). This technique has been successfully used for the treatment of many types of lesional epilepsy, including hypothalamic hamartoma, mesial temporal sclerosis, focal cortical dysplasia, cortical tubers, insular lesions, and Rasmussen's encephalitis (Curry and others 2012; Esquenazi and others 2014; Hawasli and others 2013; Lewis and others 2015; Willie and others 2014). LITT

ablation of the hippocampus has also been used for mesial temporal sclerosis. A small study of this technique suggests that postoperative language function is better preserved with LITT than with temporal lobectomy (Drane and others 2015). Overall, although surgical techniques for epilepsy can offer excellent outcomes in select patients, drawbacks include the following: patient hesitation to undergo surgery, the need for an identified and accessible seizure focus, the fact that many of these techniques are destructive, the risk of surgical complications, and the fact that many patients are not candidates for these procedures. Therefore, given the fact that current surgical and medical techniques cannot adequately treat a substantial population of epilepsy patients, new treatments must be developed.

Optogenetics: Theory and Current Scientific Uses

Optogenetics has greatly evolved over the past decades since the first opsin (light-sensitive protein) was discovered in 1971 in *Halobacterium salinarum*, a single-celled archaeon that uses the opsin to pump protons out into the extracellular environment, thus creating a gradient that drives ATP synthesis (Oesterhelt and Stoeckenius 1971, 1973). The field of optogenetics was brought into the limelight in 2005 when the light-gated cation channel channelrhodopsin-2 (ChR2), from the unicellular green alga *Chlamydomonas reinhardtii*, was successfully expressed in cultured rat hippocampal neurons. With the expression of this protein, it became possible to activate transfected neurons on a millisecond timescale with simple photostimulation (Boyden and others 2005). Since these early breakthroughs, the field of optogenetics has exploded, and now encompasses a wide array of light-gated excitatory channels, inhibitory pumps and channels, and G-protein coupled receptors (Figure 2). Two additional opsins which are especially relevant to epilepsy are the chloride pump halorhodopsin (NpHR), identified in the archaeon *Natronomonas pharaonis*, and the proton pump archaeorhodopsin-3 (Arch) from the bacterium *Halorubrum sodomense* (Chow and others 2010; Yizhar and others 2011). The harnessing of natural opsins and engineering of novel opsins with desired kinetic properties, has led to unprecedented spatial and temporal control of neuronal activity.

However, the real power of optogenetics lies in the ability to express these opsins selectively and specifically in spatially or genetically targeted populations of neurons. This allows the activation or silencing of nearly any imaginable definable neuronal population. There is a large, and ever expanding, repertoire of viral vectors and transgenic animals available for opsin targeting. One common method is to package an opsin into a viral vector (such as lentivirus or adeno-associated virus) that includes a fluorescent protein and a cell-type specific promoter. The virus is then injected into a target area, and only the neurons with cell bodies near the injection site will take up the virus and express the opsin. Not all promoters are amenable to viral delivery, however, and some situations call for expression of the opsin in a larger area than accessible by viral injection. Therefore, transgenic mouse lines are also available. A common strategy is to use a Cre recombinase-loxP targeting strategy. In this situation, one set of mice expresses Cre under a specific promoter (e.g., in parvalbumin [PV]-expressing neurons). These are crossed with another set of mice which express an opsin in a Cre-dependent manner. The double mutants will express the opsin only under the control of the specific promoter. Further details of optogenetic targeting techniques as well

as the different opsins have been reviewed in detail elsewhere (Bernstein and Boyden 2011; Krook-Magnuson and Soltesz 2015; Paz and Huguenard 2015; Yizhar and others 2011).

Using Optogenetics to Control Epileptiform Events and to Dissect Critical Microcircuits in Epilepsy

One of the key advantages of optogenetic techniques in studying neurological disorders is that they are uniquely suited to dissect neuronal circuits. With optogenetic tools, researchers can selectively switch on or off specific elements of a circuit, one at a time, and thereby probe the effect of each element on total circuit function. In the context of epilepsy, this has been useful in examining the role of specific microcircuits in seizure dynamics, by permitting precise perturbation of neuronal subpopulations and investigating how it alters epileptiform activity.

The first study to demonstrate that epileptiform events could be controlled with optogenetic manipulation in vitro was published in 2009. NpHR was expressed in principal cells of hippocampal neurons, in organotypic slice culture. Optical silencing of either CA1 or CA3 pyramidal led to the suppression of stimulation-induced bursting in these slices (Tonnesen and others 2009). Shortly after, it was shown that epileptiform activity could also be controlled in awake, behaving animals. In the intrahippocampal kainic acid model of temporal lobe epilepsy, spontaneous seizures were suppressed optogenetically, by inhibiting hippocampal principal cells as well as by exciting a subset of interneurons (Krook-Magnuson and others 2013). Optogenetic inhibition of thalamocortical cells was able to suppress stroke-induced cortical seizures (Paz and others 2013), and suppression of the activity of principal cells in a model of tetanus toxin-induced neocortical seizures could also abort electrographic seizures (Wykes and others 2012).

These studies have been essential in demonstrating the potential for translational applications of optogenetics in seizure control. They have also set a basis for a wave of studies that have used similar experimental schemes to probe the contribution of various microcircuits to seizure activity and to test previously posited hypotheses in new ways. One such hypothesis, the dentate gate theory, proposes that the dentate gyrus normally acts as a “gate” to the rest of the hippocampus by shutting down incoming hyperexcitability before it can travel to the rest of the hippocampus. In epilepsy, however, it has been hypothesized that this gate breaks down and the normally quiescent granule cells are overexcited, thus allowing the spread of hyperexcitation throughout the hippocampus (Heinemann and others 1992; Lothman and others 1992). An experimental restoration of the dentate gate in vivo in epileptic mice was created by silencing selectively labeled granule cells with NpHR. Consistent with the hypothesis, on-demand gate restoration was able to stop seizures (Krook-Magnuson and others 2015).

Understanding the contribution of interneuronal subpopulations in epilepsy has also been a major research focus. An often-posed hypothesis is that, in epilepsy, interneurons are no longer able to shut down out-of-control excitation because GABA can become excitatory during seizures (Pavlov and Walker 2013; Staley 2004). Supporting this theory, selective optogenetic activation of PV-positive inter-neurons led to depolarizing—that is excitatory—

GABAergic events in CA3 pyramidal cells during in vitro low-magnesium-induced ictal events, due to a brief collapse in the Cl^- reversal potential. This contribution of PV cells to network excitability during ictal events was further validated by the fact that optical silencing of these cells led to decreased afterdischarges during the ictal event (Ellender and others 2014). Of note, as discussed below, only the activation of PV cells very near the seizure focus led to hyperexcitability (Sessolo and others 2015). Therefore, these results do not necessarily contradict reports of PV cell activation leading seizure cessation, but do emphasize the complexity of the role of interneurons in epilepsy.

In addition to being a powerful approach for characterizing the role of various neuronal populations in seizure activity, optogenetic studies can also reveal detailed mechanistic information about circuit function and dysfunction, such as changes in synaptic transmission. In that respect, in a novel model of absence seizures, created by selectively deleting P/Q-type calcium channels in rhombic lip-derived neurons, optogenetic activation of cerebellar granule cells (GC) showed that the GC to Purkinje cell (PC) synaptic transmission was substantially reduced, implicating alterations to the GC to PC circuit in this type of seizure (Maejima and others 2013). In another model of absence seizures triggered by deletion of the GluA4 AMPA receptor, the thalamocortical circuit's normal oscillatory action is perturbed, leading to pathologic seizures rather than physiologic spindles. Specific optogenetic labeling of different synapses within the circuit was utilized not only to show pathologic problems in the thalamocortical circuit during seizures but also to help map out the synaptic pathway involved in normal oscillations (Paz and others 2011).

Finally, it is becoming clear that results obtained from optogenetic studies can have profound implications for future epilepsy treatments. For example, a set of recent studies showed that in temporal lobe epilepsy, seizures could be effectively stopped by optogenetically manipulating neurons in areas physically distant from the ictal focus. Targeting PV interneurons contralateral to the site of seizure initiation significantly curtailed seizure activity (Krook-Magnuson and others 2013), and intervening at a site even as remote as the cerebellum could effectively stop seizures originating in the hippocampus (Krook-Magnuson and others 2014). The cerebellum proved to be a powerful seizure “choke-point” in absence epilepsy as well (Kros and others 2015), and in the case of cortical seizures, long-range thalamic projections to the cortex could be targeted to interrupt both electrographic and generalized seizures (Paz and others 2013). These results highlight the feasibility of “remote seizure control,” which could be a useful clinical strategy in cases where the seizure focus is unknown, diffuse, or not surgically approachable. Additionally, optogenetic control of seizures is not limited to chronic epilepsy but has been shown to be effective in postponing status epilepticus following the injection of a convulsant. By optically inactivating halorhodopsin expressing pyramidal cells, the onset of acute electrographic and behavioral seizures induced by injection of lithium-pilocarpine into the hippocampus of living rats, could be successfully delayed (Sukhotinsky and others 2013).

Closed-Loop Optogenetic Intervention

The studies demonstrating the success of optogenetics in the control of seizures in vitro and in vivo have greatly advanced the field, and another important leap toward the translational

usefulness of optogenetic technology would be a fully automated system. This type of system would offer advantages over most current treatments of epilepsy. Namely, an on-demand automated system (referred to as “closed-loop”) would allow treatment to occur only during seizure initiation and at the location of a seizure focus, thus providing temporal and spatial specificity. Closed-loop optogenetic control involves a real-time readout of the neural activity recorded from electroencephalographic, electrocorticographic or electromyographic signals. Once a seizure is detected, the system immediately responds with the delivery of light to excite or inhibit the opsin-expressing cells and abort the seizure (Figure 3). In neurological disorders like epilepsy where abnormal activity occurs sporadically, such activity-guided intervention is extremely attractive as the optogenetic stimulation can be restricted to those precise moments when seizures occur, thus avoiding unnecessary perturbations during normal brain activity.

Various seizure detection systems for use with closed-loop optogenetics have been developed for studying rodent models of temporal lobe epilepsy and thalamocortical epilepsy (Armstrong and others 2013; Krook-Magnuson and others 2013; Paz and others 2013). Since seizures in temporal lobe epilepsy are notoriously heterogeneous in terms of their electrophysiological signatures, it has been crucial to implement detection systems that are highly flexible and tunable. Typically, multiple characteristics of the recorded electrical signal, such as spike rate, amplitude, and frequency band power ratios, are simultaneously analyzed to distinguish the occurrence of a seizure from normal activity (Armstrong and others 2013). Manual tuning of the detection thresholds and of the filter parameters is often necessary to ensure the low occurrence of false-positive or missed triggers. Once a seizure starts, a brief integration period (<2 seconds) is usually sufficient to detect the pathological activity and respond. Using closed-loop optogenetic techniques, it was possible to drastically decrease seizure duration ($57\% \pm 14\%$ reduction) in epileptic animals through inhibition of hippocampal excitatory cells (Krook-Magnuson and others 2013). Likewise, on-demand inhibition of thalamocortical cells in a stroke-induced model of focal cortical epilepsy has also been shown to be effective at suppressing spontaneous seizure activity (Paz and others 2013). Like the new surgical technique of RNS described above, these experimental models operated as a closed-loop system, but the advantage to an optogenetic system is that the optical fiber specifically activates a target set of neurons, whereas the RNS electrode activates all nearby neurons.

Clinical Implications of Optogenetic Studies

Optogenetic-based seizure control has not only been helpful in teasing apart important microcircuits involved in ictal activity, but it is also beginning to enhance our understanding of the therapeutic mechanisms underlying current clinical treatments such as electrical stimulation. It is unclear how clinically used electrical stimulation such as DBS and RNS interfere with ictogenesis, because of the fact that both of these techniques rely on global stimulation with nontransparent effects on individual cells or connections. Optogenetics can shed light on these mechanisms by allowing cell-specific stimulations in animal models, the effects of which can then be compared with those of the global stimulation generated by DBS. For example, in a 4-aminopyridine model of acute seizures, optogenetic stimulation of interneurons, at frequencies standardly used with DBS (Koubeissi and others 2013), was

sufficient to recapitulate the seizure suppressive effect observed when all neuronal cells were stimulated (Chiang and others 2014; Ladas and others 2015). Mechanistically, inhibitory cells appeared to initially induce a paradoxical excitatory bursting in pyramidal cells, which caused synchronization, and then ultimately suppression of pyramidal cell activity (Ladas and others 2015). These results emphasize the role of interneurons in network synchronization, and suggests that induction of the inhibitory network is a crucial aspect of DBS.

On-Demand Seizures: Characterizing Circuit Dynamics and Pinpointing Seizure Propagation Networks with Optogenetics

Beyond its use as a tool to control seizures, an unexpectedly powerful application of optogenetics is in the generation of “artificial,” light-inducible seizures. There are many ways to trigger seizures with optogenetic techniques. For example, patterned bursting in random networks of cultured ChR2-infected hippocampal neurons can be induced with pulsed optogenetic activation of the entire culture plate (El Hady and others 2013). Additionally, pulsed stimulation of ChR2-expressing cells in the rat hippocampus can lead to the successful induction of seizure-like afterdischarges (Osawa and others 2013).

However, if the ultimate goal is treatment of epilepsy, what is the utility of causing or triggering seizures? From a microcircuit standpoint, finding neurons that can provoke seizures or cause hyperexcitatory activity may reveal information about mechanisms of ictogenesis. This strategy was instrumental in demonstrating the hippocampal dentate gyrus’s place as a powerful node in the epileptic circuit, as excitation of granule cells increases seizure activity in mice (Krook-Magnuson and others 2015), as well as in revealing that seizures caused by optical activation of PV-positive interneurons may be partially due to a transient breakdown in GABAergic signaling (Ellender and others 2014), as described above.

In addition to pinpointing “guilty” elements in neuronal circuits, light-generated seizures have also been used as a way to create uniform seizures with well-defined initiation conditions. One of the most daunting challenges of epilepsy research lies in the heterogeneity and diversity of seizures and epilepsies. Even within a given epilepsy model, not all seizures are the same: seizures can differ in the location of initiation as well as in the subsequent microcircuit dynamics. In fact, studies using two-photon microscopy or microelectrode arrays have shown that, in experimental models as well as in human patients with epilepsy, such variability can occur even between sequential convulsive events within the same individual (Feldt Muldoon and others 2013; Keller and others 2010; Sabolek and others 2012; Truccolo and others 2011). For example, two-photon imaging of network dynamics was employed to examine the activity of neurons in the hippocampal granule cell layer during epileptiform events. It was found that for epileptic animals, clusters of spatially localized cells were simultaneously recruited during large-scale network events (Feldt Muldoon and others 2013). However, these synchronous neuronal clusters did not fire during each epileptiform event, and the clusters that were recruited varied from one event to another. This seizure-to-seizure variability can be a confounding factor when interpreting

experimental data, as seizures that appear similar may in fact involve different pathways and respond differently to optogenetic perturbations. Therefore, optogenetically generated seizures which begin with a predetermined population of neurons offer an attractive approach to the investigation of underlying mechanisms, since they would be expected to have more reproducible and stereotypic characteristics. These more tightly regulated, light-triggered seizures will be especially useful for investigating how and which networks are recruited during seizure initiation.

An interesting study that took advantage of optogenetic seizure generation also utilized functional MRI to visualize network activity on a large scale (Weitz and others 2014). High-frequency optogenetic stimulation of excitatory cells in the intermediate hippocampus led to widespread propagation of activity to cortical and subcortical brain regions. On the other hand, when cells in the dorsal hippocampus were excited, the activity remained restricted to the hippocampus. Since the rodent dorsal hippocampus is equivalent to the human posterior hippocampus, this result has interesting clinical implications. In human temporal lobe epilepsy, prior studies have shown that the posterior hippocampus is much less epileptogenic and undergoes far less severe anatomical and neurochemical perturbations than other areas of the hippocampus (Babb and others 1984; Dam 1980; King and Marsan 1977; King and others 1997). These results also highlight that the combination of optogenetics and functional MRI represents a promising method for the investigation of large-scale functional networks and for mapping brain regions that are more susceptible or resistant to seizure propagation.

Microcircuits Affecting Seizure Dynamics or Seizure Dynamics Affecting Microcircuits?

Thanks to optogenetics, we are gaining a more complete picture of the circuit components involved in epileptic activity. However, it is also becoming increasingly clear that a static approach to circuit dissection might not be sufficient to develop a thorough understanding of the disorder. Seizures are inherently dynamic and so the effect of a given optogenetic perturbation does not depend solely on which connections are controlled, but also on the location of intervention with respect to the seizure focus as well as on the time of intervention with respect to ongoing brain processes.

One of the most notable illustrations of the need for awareness of the spatial context of an intervention concerns the role of interneurons in seizure activity. In a cortical slice model of focal epilepsy, exciting PV-positive interneurons had opposite effects on seizure activity depending on the proximity of the cells to the seizure focus. When PV interneurons at the seizure focus were stimulated, this induced a post-inhibitory rebound spiking in pyramidal cells, ultimately enhancing neuronal synchrony and promoting seizure generation. In contrast, activation of PV cells distant from the focus instead blocked ictal propagation and significantly shortened the seizure duration (Sessolo and others 2015). Therefore, stimulation of even the same type of GABAergic neurons can have antagonistic effects on epileptiform activity depending on the exact location of the stimulation in relation to the seizure focus.

Likewise, the temporal context of the light intervention with respect to the network dynamics has been shown to be important. For instance, optogenetic stimulation of GABAergic neurons in entorhinal cortical slices perfused with the pro-convulsant compound 4-aminopyridine was sufficient to elicit interictal spikes or preictal discharges that were followed by tonic-clonic seizure-like events (Yekhlief and others 2015). However, stimulation of the same neurons after the seizure had already begun did not alter the ongoing seizure activity. A recent report also revealed the outcome of activating principal cells is strongly correlated to the brain state prior to stimulation. Light delivery to ChR2-expressing cortical pyramidal cells was shown to trigger convulsive activity in a rodent model of absence seizures (Wagner and others 2015). Interestingly, seizures were not induced during every trial, and the occurrence of a seizure could be predicted by the power of the local field potential oscillations immediately prior to the stimulation. Increased local field potential power directly correlated with increased probability of seizure occurrence. This result corresponds well with the observation that in animal models as well as in humans, seizures occur mostly during certain behavioral states, such as drowsiness or light sleep. Additionally, it has been shown that the effectiveness of optogenetic intervention to terminate seizures can depend on the mouse's behavioral state (Ewell and others 2015).

Taken together, the results of these optogenetic studies clearly highlight the fact that the potential of a given targeted microcircuit for seizure control or induction is not a static property of the microcircuit itself, but is also a function of the state of network and the overall brain activity. In light of these results, it is expected that our understanding and treatment of epilepsy will greatly benefit from assays that combine optogenetics (as a way to engage or disengage specific neuronal populations) with technologies that can report on network dynamics during and in between seizures. Advances are being made in functional MRI (as discussed earlier) as well as in electrical recording capabilities. Studies using miniaturized electrocorticography arrays have demonstrated the ability to precisely record temporally and spatially discrete signals (Wang and others 2010; Richner and others 2014). A novel optrode has also been constructed, in which the electrode portion of the optrode is a multi-electrode array, which allows for seizure detection in a larger spatial area (Zhang and others 2009). This MEA-optrode construct was implanted into epileptic rats (Genetic Absence Epilepsy Rats from Strasbourg), which had been pre-treated to express ChR2 in neocortical neurons. The device was then successfully used to detect and stop spontaneous absence seizures in vivo. Another technique that exists but has not yet been used in the context of epilepsy is fiber photometry, which allows the recording of spatially and genetically well-defined neurons by measuring Ca^{2+} transients (Gunaydin and others 2014; Grosenick and others 2015).

Importantly, better understanding of the relationship between the network state and the effect of optogenetic manipulation of specific neuronal connections or populations will likely open doors for more efficient seizure control schemes. Closed-loop seizure control, for instance, could be improved by integrating information, in real-time, from recordings with a wider array of signals, such as fMRI or multi-electrode array recordings. Rather than simply applying light intervention based on a binary signal (seizure/no seizure), one could personalize the response to each seizure in an activity-guided manner.

Future Directions

The final common goal for all epilepsy research is not just to understand the circuits involved or to stop seizures in mice, but to apply these lessons to humans in order to treat epilepsy patients, especially the thirty percent who are refractory to AEDs. The obvious “holy grail” of translating optogenetic techniques into humans would be a closed-loop implantable system using on-demand light stimulation to stop seizures. Under ideal circumstances, the seizure would be aborted while only still electrographic, that is, without any behavioral manifestations. Overall, the system setup would be similar to DBS or RNS and could be envisaged to work in the following manner: An optrode would be permanently implanted into the patient’s brain at his or her specific seizure focus. The optrode could either be inserted into the brain for a deeply located focus or placed subdurally for a cortical focus. The optrode lead would then be tunneled under the skin and connected to a power source/light source, which could be implanted either in the skull (like RNS) or under the skin in a subclavicular location (like DBS and vagus nerve stimulation). The seizure-detecting microchip would likely be housed with the power source and light source. The electrode portion of the optrode would detect the beginning of the seizure and then the light would be activated through the optical fiber portion of the optrode at a particular frequency and duration to stop the progression of the seizure. Ideally, like RNS, this human closed-loop optogenetic system would be customizable as far as seizure detection parameters and light activation parameters (Figure 4).

Unfortunately, there are major hurdles that lie between where we are today (closed-loop system in rodents) and the finish line. Technical challenges abound, and there are several questions regarding feasibility that remain to be addressed. First of all, given that the volume of the human brain is over one thousand times larger than the mouse brain, will the volume of tissue that can be illuminated by an optical fiber be sufficient to stop an entire human epileptic network? If a large volume of tissue is successfully activated, will this end up heating and damaging the neurons (Pavlov and others 2013)? In order for the system to be fully implantable, a laser or LED must be engineered, along with an associated power source, which is small and lightweight enough to be implantable. The power source will have to have sufficient power to last a few years before replacement, or be rechargeable through the skin. The optical fiber will have to be flexible enough to hold up to the patient’s head and neck movement without breaking. The optrode will have to be non-immunogenic.

Scientific challenges remain as well. To induce opsin expression in the human brain, genetically based Cre recombinase-loxP systems will not be usable. Two other possibilities do exist with current technology to induce opsin expression in human neurons: viral vectors to induce opsin expression under specific promoters, and injection of pre-transfected neuronal stem cells. Will either of these techniques be safe and successful with human tissue? Will institutional review boards approve the injection of mutational viruses or engineered stem cells into human patients with a non-fatal disease? If a viral method is chosen, will transfection be stable over decades of the patient’s life (Fisher 2012)? Current closed-loop technologies trigger a stereotyped activation of the light fiber to stop seizures, but do not contain a mechanism to detect whether the seizure has ended. In a human

application, it may be necessary to add in a “seizure-end” detection algorithm to ensure that the seizure has indeed stopped.

There are some answers from recent studies which suggest that the answer to at least some of the above questions is “yes.” Small trials have demonstrated the safety of both AAV and lentiviral vectors in human Parkinson’s patients (Bartus and others 2013; Palfi and others 2014). NpHR has been successfully expressed via a lentiviral vector in postmortem human photoreceptor cells, but we are not aware of any studies with successful expression of opsins in human neurons (Busskamp and others 2010). Recent studies have demonstrated the feasibility of functional expression of various opsins in macaque cortex, with appropriate electrophysiological responses, stable expression over months, and a labeled volume of 1 mm³ per injection (Diester and others 2011; Han and others 2009). Demonstrating a behavioral effect of optogenetic activation of neurons seems to be more challenging in primates. However, it has been shown that by activating the frontal eye fields or visual cortex of macaques with ChR2, functional saccades could be induced or altered (Gerits and others 2012; Jazayeri and others 2012). Other promising advances include the fabrication of MRI-compatible carbon fiber optrodes, which would improve the clinical utility in human subjects (Duffy and others 2015). Computer modeling studies in meso-scale model of the human cortex also demonstrated feasibility of using optogenetic control to suppress seizures (Selvaraj and others 2014).

Although injecting stem cells into human brain that could then be activated by light to stop seizures might seem like futuristic technology, it might not be so farfetched. It has been shown that implanted embryonic medial ganglionic eminence (MGE) cells into the hippocampus of pilocarpine-treated epileptic mice develop into functional inhibitory interneurons, and that this treatment greatly reduces the seizure frequency in these animals (Hunt and others 2013). In pilocarpine-induced temporal lobe epilepsy in mice, ChR2-expressing MGE cells were successfully transplanted into the dentate gyrus. Mice receiving these transplants had fewer seizures, and light-induced IPSCs were recorded in native dentate granule cells (Henderson and others 2014). In another study, long-term self-renewing neuroepithelial stem cells (ItNES) were successfully generated from human fibroblasts and then injected into the hippocampus of nude rats. By stimulating ChR2-labeled rat neurons, this group was able to evoke EPSPs in the human ItNES-derived neurons (Avaliani and others 2014). To move this into a translational application, one would want to have the human stem cell-derived neurons express ChR2. In this way, it might be feasible to inject human ChR2-expressing stem cells that would develop into GABAergic neurons into the seizure focus. An optrode would be implanted simultaneously. Once the stem cells have matured into functional neurons, the optrode would be used in a closed-loop fashion to detect the seizure and then optogenetically activate a large quantity of GABAergic neurons, thereby shutting down the seizure before any behavioral manifestation occurs. This would be a clever way to get the ChR2 cells into human brain without having to use a viral vector (Figure 4).

It is possible that, because of all these technical and ethical hurdles, optogenetics will not be directly translated into human clinical use. However, this does not diminish the importance or relevance of using optogenetic techniques to study seizures in animal models. As

discussed above, optogenetics presents a unique tool for determining what changes can lead to dysfunctional networks. Understanding more about the mechanisms of epileptogenesis, seizure initiation, and pathologic seizure circuitry could open up avenues to develop other treatments for epilepsy. For example, if a particular interneuronal subtype can be manipulated to stop seizures, perhaps a biologic drug could be developed to similarly modulate these neurons in humans. If clinically relevant models of epilepsy are studied and a stimulation target is found that can stop the seizure, perhaps an RNS electrode could be placed into that target. Finally, if seizure models are studied which are based on human genetic epilepsies, perhaps new drug targets may be found as well.

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Figure 1.

Currently used treatments for epilepsy in human patients. Medical and surgical treatments for epilepsy are shown with schematic diagrams. Major pros (+) and cons (-) of each type of treatment are noted.

Figure 2.

Optogenetic tools for light-mediated control of neuronal activity with high temporal precision. (A) Following light activation, the cation channel of channelrhodopsin-2 (ChR2) opens to allow passive movement of Na^+ , Ca^{2+} , K^+ , and H^+ ions down their respective electrochemical gradients (top) causing neurons to depolarize and fire action potentials (bottom, blue bar signifies time of light activation). (B) Halorhodopsin (NpHR) pumps Cl^- into the cell (top) following light stimulation. At standard chloride concentrations, this results in hyperpolarization and a decrease in neuronal firing (bottom, orange bar signifies time of light activation). (C) When activated, archaerhodopsin (Arch/ArchT) pumps H^+ out into the extracellular environment (top), thus suppressing cell firing and causing hyperpolarization (bottom, green bar signifies time of light activation). Note that Arch/ArchT may thus be particularly useful in epilepsy as it is not dependent on the reversal potential for chloride.

Figure 3.

Closed-loop optogenetic seizure intervention in epileptic mouse models. An optrode (optical fiber + electrode) is implanted into the brain. Electrocorticographic (ECoG) activity from the rodent brain is recorded in real time. (A) At the resting state, no seizure is detected, and the optical fiber is not illuminated. (B) When the animal begins to seize, the hyperactivity and hypersynchrony is detected by the recording software (green arrow), and a predetermined pulse of light is delivered via the optical fiber to modulate the firing activity of opsin-expressing neurons and thereby stop the seizure. (C) The seizure terminates (red arrow), and the light is turned off.

Figure 4.

A theoretical model of closed-loop optogenetic seizure control in humans. (A) The first step would be localization of the seizure focus. This could be performed via standard phase II monitoring (see text), but in the future this step could possibly be avoided in some patients if long-distance targets, or targets based on seizure semiology or genetics are identified. (B) The next step is to deliver the optogenetic vector to the seizure focus. This could be accomplished with a viral vector carrying an opsin gene, which would then transfect the patient's own neurons, or by pretransfecting neurons (or neuronal precursors) with opsins, which would then functionally integrate into the patient's brain. (C) An optrode construct (gray denotes electrodes for recording, orange denotes optical fibers) is implanted in the brain at the seizure focus or remote target. The electrical leads and optical fibers are tunneled under the skin to the "control box" which is implanted in a subclavicular location. This control box would contain a seizure-detecting microchip, a power source, and a light source. Its function would be to detect seizures quickly and then turn on the light source to activate or silence specific neurons, thereby stopping the seizure. As noted in the figure, ethical concerns with such a system include the safety of injecting optogenetic viral vectors or transfected neuronal precursors into the human brain. Technical challenges include being able to optogenetically activate a sufficient volume of tissue to cause a physiological response, the stability of optogenetic expression in neurons over decades of the patient's life, manufacturing a compact and lightweight light source, customizing seizure detection algorithms, and avoiding tissue heating with light activation.