



Shining Light on Epilepsy: Optical Approaches for Treating Seizures

Optical Control of Focal Epilepsy in vivo with Caged Gamma-Aminobutyric Acid.

Yang X, Rode DL, Peterka DS, Yuste R, Rothman SM. *Ann Neurol* 2012;71:68–75.

OBJECTIVE: There is enormous clinical potential in exploiting the spatial and temporal resolution of optical techniques to modulate pathophysiological neuronal activity, especially intractable focal epilepsy. We have recently utilized a new ruthenium-based caged compound, ruthenium-bipyridine-triphenylphosphine- γ -aminobutyric acid (RuBi-GABA), which releases GABA when exposed to blue light, to rapidly terminate paroxysmal activity in vitro and in vivo. **METHODS:** The convulsant 4-aminopyridine was used to induce interictal activity and seizures in rat neocortical slices and anesthetized rats. We examined the effect of blue light, generated by a small, light-emitting diode (LED), on the frequency and duration of ictal activity in the presence and absence of RuBi-GABA. **RESULTS:** Neither blue light alone, nor low concentrations of RuBi-GABA, affected interictal activity or baseline electrical activity in neocortical slices. However, brief, blue illumination of RuBi-GABA, using our LED, dramatically reduced extracellular spikes and bursts. More impressively, illumination of locally applied RuBi-GABA rapidly terminated in vivo seizures induced by topical application of 4-aminopyridine. The RuBi-GABA effect was blocked by the GABA antagonist picrotoxin, but not duplicated by direct application of GABA. **INTERPRETATION:** This is the first example of optical control of in vivo epilepsy, proving that there is sufficient cortical light penetration from an LED and diffusion of caged GABA to quickly terminate intense focal seizures. We are aware that many obstacles need to be overcome before this technique can be translated to patients, but at the moment, this represents a feasible method for harnessing optical techniques to fabricate an implantable device for the therapy of neocortical epilepsy.

Commentary

Resistance to therapy remains a major problem for patients with epilepsy. Despite the addition of many new drugs in recent years and the availability of more than 20 antiseizure medications overall, about 30% of patients with epilepsy are medically intractable (1). Some patients with medically refractory epilepsy benefit greatly from epilepsy surgery, including achievement of seizure freedom. However, many patients are not good candidates for epilepsy surgery due to the inability to localize the epileptogenic zone or risk of neurological deficits from surgical resection of “eloquent cortex.” Other proven non-medical treatments for epilepsy include a ketogenic diet and vagal nerve or deep brain stimulation, but these options may have significant adverse effects or limited efficacy. Thus, the search for better treatments for epilepsy continues, including novel therapeutic devices (2).

A major limitation of antiseizure medication is side effects. In theory, currently available medications could completely stop even the most intractable seizures if a high enough concentration of drug could be achieved in the brain. However, common

dose-limiting side effects of antiseizure medication—such as sedation, ataxia, and respiratory depression—prohibit such high concentrations from being utilized. In patients with intractable focal seizures, one approach to circumvent this problem is drug application locally, only to the site of seizure origin, leaving the rest of the brain and body unexposed to drugs and free of side effects (3). However, there are significant limitations and technical barriers to implementing a local drug-delivery system, including the invasiveness and timing of repetitive drug administration directly into the brain.

Yang and colleagues have taken a novel approach to rapidly deliver seizure medication to localized brain regions. Rather than applying an active drug to the brain directly, they used optical stimuli to rapidly convert an inactive prodrug already circulating in the tissue back into an active form. They had previously used a caged gamma-aminobutyric acid (GABA) analog, which is inactive in its parent form, but then releases active GABA when exposed to ultraviolet (UV) light. In previous studies, a UV light-emitting diode (LED) suppressed convulsant-induced epileptiform bursting activity in cultured neurons and hippocampal slices bathed in the caged GABA analog (4, 5).

In their most recent study from *Annals of Neurology*, Yang and colleagues advanced this optical approach in at least two significant ways: First, instead of a UV-activated caged GABA analog, they utilized a new ruthenium-based caged



GABA (RuBi-GABA), which releases GABA upon exposure to visible blue light. Compared with UV light, blue light's longer wavelength and lower energy offer some advantages in allowing deeper penetration into tissue and less phototoxicity. More importantly, they demonstrate for the first time that illumination of caged-GABA inhibits seizures *in vivo*. While previous work had documented that this technique decreases interictal bursting activity in brain slices or cultured neurons, the current study demonstrates that shining a blue LED over the neocortex in rats preexposed to RuBi-GABA can rapidly terminate stereotypical electrographic seizures induced by 4-aminopyridine (4-AP). Administration of RuBi-GABA or blue light by itself had no effect on seizures. Remarkably, termination of the seizures occurs within seconds of flashing the blue light. By comparison, direct infusion of GABA over the cortex from a reservoir had no immediate effect but required several minutes to attenuate repetitive 4-AP-induced seizures.

This study provides proof of principle that optical activation of caged drugs is a feasible strategy for treating focal seizures. However, there are a number of caveats and technical issues that need to be considered before translating this novel therapeutic approach to patients with intractable epilepsy: First, the subset of epilepsy patients who are good candidates for this specialized therapy may be limited and needs to be defined carefully. For localized optical treatment, patients must have focal seizures—not generalized or multifocal—and, importantly, the specific location of seizure origin must be well defined. In patients with localization-related epilepsy, the ictal onset zone is not always precisely localized and may involve multiple points among a more widely distributed network. In cases where the ictal onset zone has been clearly identified, epilepsy surgery with resection of the epileptogenic focus is usually the favored option, offering the best chance of seizure freedom. Thus, the optical stimulation method would primarily be reserved for patients with well-localized seizures in which epilepsy surgery has unacceptable risks, such as when the seizure focus includes eloquent cortex.

Implementation of an optical control system for epilepsy will also involve significant technical challenges. The LED will need to be implanted within the vicinity of the seizure focus, and additional devices will be required to complete a complex integrated system—including a battery source and amplifier for the LED, electrodes and seizure-detection system to sense the seizures, and a long-term drug-administration system for the caged-GABA. LEDs can be integrated within flexible two-dimensional electrode arrays or matrixes near the seizure focus. However, innovative shapes and designs for this hardware may be needed to accommodate different situations, depending on the size and location of the seizure focus. In particular, while the rat studies involved seizures triggered near the surface of the cortex, the depth of light penetration within the brain from the cortical surface may be insufficient to reach some seizure foci within deep sulci. Similarly, a reservoir and pump for continuous delivery of the caged GABA to the seizure focus might involve multiple designs. Existing technology of implanted pumps for continuous drug administration into the subarachnoid space is an option, but it will need to be verified that the prodrug reaches the seizure focus in sufficient concentrations.

Despite these complicated issues and pitfalls, the general approach of designing and applying optical technologies for

novel therapeutic strategies in intractable epilepsy is promising and certain to result in other advances and benefits. Other photoactivated anticonvulsant drugs, such as GABA-potentiating neurosteroid analogs, are under development (6). In addition to optical activation of caged drugs, a related treatment strategy might involve optogenetics, an emerging technology with numerous research and translational applications (7). Optogenetic tools involve a variety of light-sensitive proteins, mostly derived from single-cell organisms that change their function in response to light. In the field of neuroscience, light-sensitive channel proteins that depolarize or hyperpolarize neurons are among the most useful. In particular, genetic transfection of light-sensitive halorhodopsin chloride pumps into mice allows light-activated hyperpolarization of hippocampal neurons and suppression of epileptiform activity in hippocampal slice cultures (8). Very recent, innovative studies demonstrate the ability of optogenetic methods to inhibit behavioral seizures in rats *in vivo* (9–11; also the subject of a future *Epilepsy Currents* article). Potential limitations of applying optogenetics to epilepsy in patients include technical difficulties of transfecting neurons *in vivo* and possible adverse effects of introducing foreign genetic material into the human brain. Nevertheless, recent studies using innovative optical methods indicate a bright future for shining light to treat epilepsy.

by Michael Wong, MD, PhD

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