

TITLE: Optical Control of Focal Epilepsy in Vivo with Caged GABA

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BACKGROUND:

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 previously demonstrated that a low concentration of a new caged GABA, ruthenium-bipyridine triphenylphosphine-GABA (Rubi-GABA), when illuminated by blue light, released sufficient GABA, to reduce seizure-like activity in brain slices. In a new set of experiments, we tested Rubi-GABA and a blue light emitting diode (LED) as a potential therapy for neocortical epilepsy in vivo.

METHODS:

Adult male Sprague-Dawley rats were anesthetized with isoflurane. We placed two screw electrodes symmetrically over each hemisphere and differentially recorded the electroencephalogram (EEG). After creating a 4 mm diameter cranial window over the left hemisphere, we carefully opened the dura and created a reservoir with dental cement around the cranial window to allow administration of artificial cerebrospinal fluid (ACSF) on the brain surface. The control and experimental group rats were pretreated by applying 200 μ l ACSF or ACSF containing 5 μ M Rubi-GABA, respectively, on the brain surface for one hour. We then induced focal neocortical seizures by switching to fresh pretreatment solution containing 500 μ M 4-aminopyridine (4-AP) for both groups. An LED (emission maxima of 470 nm) was glued to the end of a copper rod and placed just above the cranial window allowing unfocused light to directly illuminate the brain surface. A TTL pulse controlled the LED. The effect of one minute illumination (500 mA) at seizure onset was compared in the absence and presence of 5 μ M Rubi-GABA.

RESULTS:

LED illumination had no effect on seizure duration in the absence of Rubi-GABA. Seizure durations in the absence of Rubi-GABA, with and without light flashes, were 159 \pm 32 seconds and 160 \pm 58 seconds, respectively ($P > 0.05$; $N = 8$ rats). In the presence of 5 μ M Rubi-GABA without illumination, seizures were slightly, but insignificantly prolonged to 180 \pm 88 seconds ($P > 0.05$; $N = 8$ rats). However, the seizures were reduced to 41 \pm 24 seconds ($p < 0.01$; $N = 8$ rats) with illumination in the presence of 5 μ M Rubi-GABA.

CONCLUSIONS:

Illumination of Rubi-GABA with a blue LED uncages sufficient GABA to rapidly terminate severe experimental focal neocortical seizures. Because the Rubi-GABA is activated with visible light, there is greater tissue penetration and less photo-toxicity than with UV-sensitive caged compounds. We believe that it should be possible to integrate a small LED with a subarachnoid drug delivery pump and seizure detection algorithms to create an implantable device for the treatment of human epilepsy. The temporal and spatial resolution of optical techniques make this a potentially attractive approach for the therapy of focal epilepsy.