

Introduction

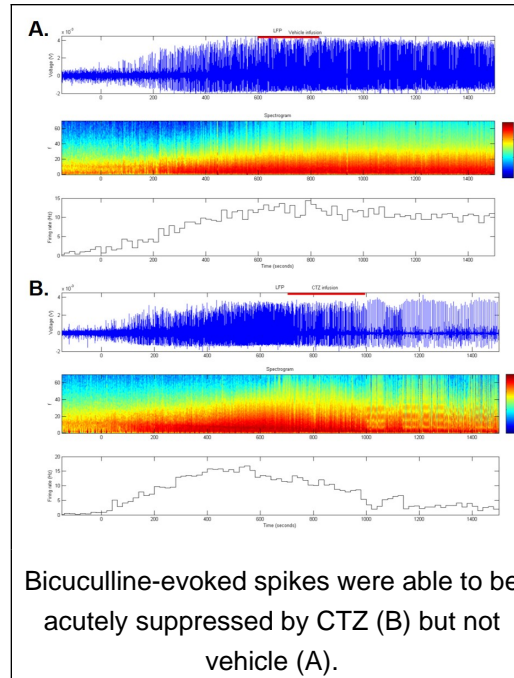
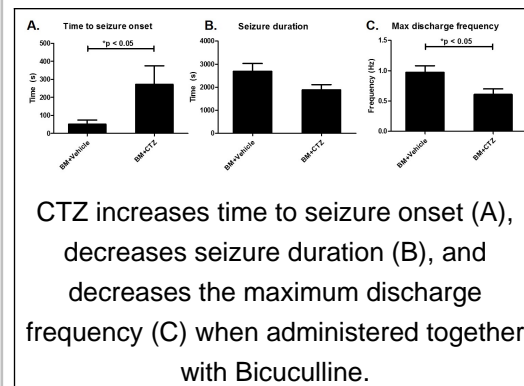
Optogenetics has shown great promise as a direct neuromodulatory therapy for halting seizure activity in various animal models of epilepsy. However, light delivery into the brain is still a major practical challenge that needs to be addressed before future clinical translation. Not only does light delivery into the brain require surgically implanted hardware that can be invasive, but it is also difficult to illuminate large or multiple structures due to light scatter and attenuation. We have bypassed the challenges of external light delivery by directly coupling a bioluminescent light source to an inhibitory opsin as a single fusion protein, which we term an inhibitory luminopsin (iLMO). iLMO2 was previously shown to inhibit neural activity in response to both external light illumination and a chemical substrate, coelenterazine (CTZ) [1]. In this study, we apply this tool in various animal models of epilepsy to suppress seizure activity in a hardware-independent fashion.

Methods

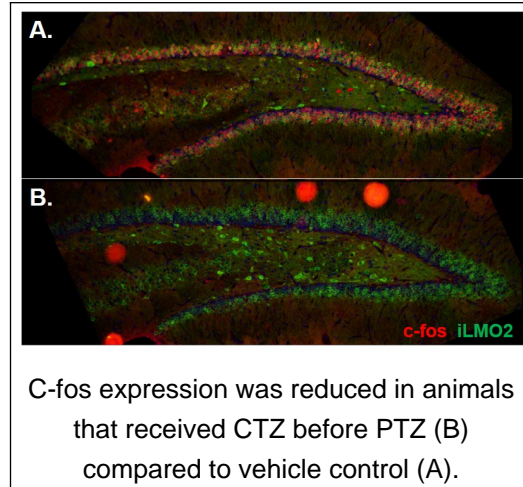
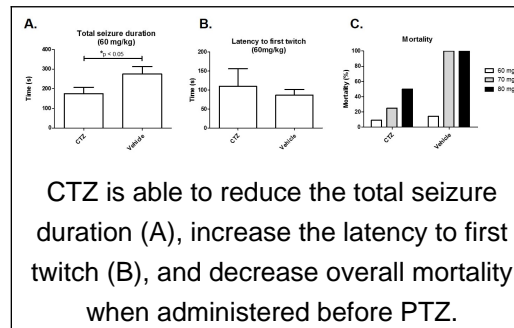
The ability of iLMO to suppress seizure activity was tested in the context of two acute models of epilepsy. Acute focal discharges were induced by injection of bicuculline into the dorsal hippocampus of rats while acute generalized seizures were induced by intraperitoneal injection of pentylenetetrazol (PTZ). The ability of iLMO2 to suppress epileptic discharges was tested by expressing iLMO2 in pyramidal cells of CA1 and CA3 and injecting CTZ mixed with bicuculline through a chronically implanted cannula-electrode. The ability of iLMO2 to suppress behavioral seizures was investigated by expressing iLMO2 in the granule cells of the dentate gyrus and/or the anterior nucleus of the thalamus and administering CTZ before an intraperitoneal injection of PTZ.

Results

iLMO activation in the hippocampus was shown to acutely suppress bicuculline-induced epileptic discharges, increase the time to seizure onset, and reduce the maximum discharge frequency.



Optogenetic inhibition of granule cells of the dentate gyrus and/or the anterior nucleus of the thalamus with iLMO2 was able to reduce the total seizure duration and mortality associated with systemic PTZ administration.



Conclusions

We have developed and applied a novel optogenetic probe that is capable of non-invasive, hardware-independent inhibition of neural activity that will add to the versatility, scalability, and practicality of utilizing optogenetic approaches for halting seizure activity in vivo.

Learning Objectives

Luminopsins are novel optogenetic tools that can be utilized for non-invasive control of seizure activity in vivo.

References

1. Tung, Jack K., Claire-Anne Gutekunst, and Robert E. Gross. "Inhibitory luminopsins: genetically-encoded bioluminescent opsins for versatile, scalable, and hardware-independent optogenetic inhibition." *Scientific reports* 5 (2015).

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