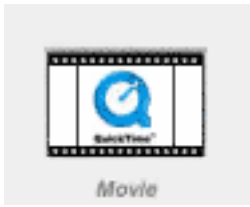
GABAA Receptor Activation Trigger Ictal Events in in Vitro/In vivo Animal Seizure Models and Human Neocortex

Michael Chang BMSc PhD Candidate; Joshua Dian; Suzie Dufour BSc, PhD; Homeira Moradi-Chameh; Lihua Wang MD, PhD; Thilo Womelsdorf; Taufik Valiante MD, PhD

Division of Fundamental Neurobiology, Toronto Western Research Institute, Toronto, ON

University Health Network
Toronto Western Research Institute



Introduction

There have been reports that excessive interneuronal activity is correlated to the generation of seizures [1,2,3].

Hypothesis: selective activation of interneurons can trigger seizures

Methods

Optogenetic mice expressing channelrhodopsin-2 (ChR2) on inhibitory interneurons were utilized. The temporal correaltion between seizures onset and light stimuli were visualized using circular histograms (as seen below)

Figure 1 | Opgenetic activation of interneurons

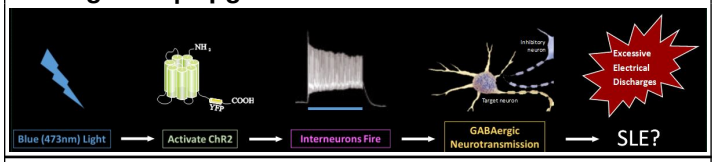
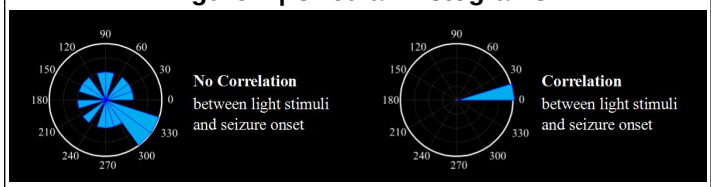
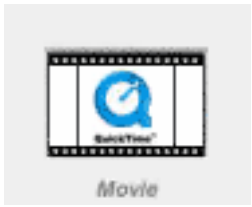


Figure 2 | Circular Histograms

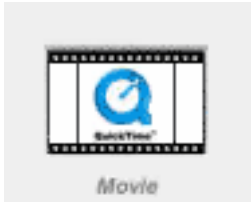


Visualization of seizure onset and light stimuli correlation



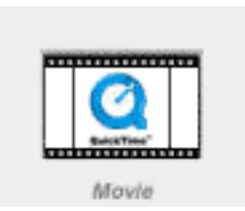
Results

We found that brief (30 ms) pulses of light unfailing evoked electrographic seizures in the *in vitro* and *in vivo* 4-AP seizure model. We found that these observations were portable to other regions of the brain and to other distinctly different seizure models. Moreover, these observations were translatable to human brain tissue.



Discussion

- The robust observation that optogenetic activation of interneurons lead to seizure onset in multiple seizure models suggests synchronous activation of interneurons may be a generic mechanism to trigger seizures.
- Whole-cell and perforated patch recordings from the 4-AP model suggest that it is not the GABAergic 'inhibition' itself, but the subsequent post-inhibitory rebound excitation that causes seizure initiation.
- Observations that brief pulses of GABA can trigger ictal events in human cortical tissue suggests that similar GABA-mediated mechanisms for seizure onset may be operative in human cortical tissue.
- Novel therapies that attempt to restore balance in the brain will need to consider the fact that excessive inhibition may paradoxically lead to seizure onset.



References

[1] Avoli M, de Curtis M (2011). Progress in neurobiology 95:104-132.

[2] Huberfeld G et a.l (2011). Nat Neurosci 14:627-634.

[3] Pavlov I, Kaila K, Kullmann DM, Miles R (2013). J Physiol 591:765-774.