Epilepsy in a dish!

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Overview

• Basic neurobiology
  • Neuron structure and function
  • Electrical Signaling

• What is epilepsy?
  • Causes and symptoms
  • Epileptogenesis
  • Challenges in treatment

• What is *in-vitro* model of epilepsy in our lab?
  • Organotypic hippocampal cultures

• Current research in our lab
Action Potentials: Electrical Signaling in Brain
Epilepsy

- Recurrent and abnormal electrical signaling of the brain – Seizures

Posttraumatic epilepsy is particularly common among service members who experience head trauma.
Seizure Properties

• Seizure focus

• Propagation properties:
  1. Which regions of the brain are involved in each seizure?
  2. How quickly does the seizure travel?
  3. How long each seizure lasts?
  4. How, where and why the seizure initiates?
Post-traumatic Epilepsy and Challenges

• Following the injury molecular and cellular alterations lead to the development of epilepsy or epileptogenesis. However, the time required for these changes to produce seizures can range from weeks to years after initial insult and provides a potential therapeutic window.

• 30-35% of patients become resistant to the available anti-epileptic drugs (AEDs) which are anticonvulsants and are needed to be continuously administered. AEDs have not been shown to be preventive of the progression of the disorder.

• The difficulty in treating epilepsy either medically or surgically places great strains on patients and families, therefore significantly reducing the quality of life.
Epilepsy in a Dish!

- Organotypic cultures have been extensively used as a physiological model of the region of interest of the brain.
  - The cultures will preserve and maintain the architectural morphology of the region of interest and can survive for weeks.
  - The organotypic cultures provide a convenient platform for a wide array of investigative techniques.

Figure 1. Hippocampal Slice

Purves et al., 2001
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• Dissection procedure transform the healthy neuronal network to an abnormal circuitry. Transition from healthy network to an epileptic network happens *in-vitro*.

• Deafferentation results in axonal sprouting in an excessive fashion and possibly formation of a hyperexcitable network.

• These cultures will become spontaneously epileptic after approximately 7 days *in-vitro* (DIV) from a healthy animal (rat or mouse pups of age postnatal 4-11), thereby serving as chronic model of epilepsy.
Electrodes For Tracking Electrical Signaling

(a) EEG, ECoG, LFP Spikes

(b) Cortex, Platform Array, Microwires, Multisite Probe

Lago and Cester, Applied Science, 2017
1. Electrical Recordings

- Field potentials were recorded by placing tungsten micro-wires underneath the cultures.
- Seizures were defined as paroxysmal events happening in frequency of at least 2Hz and last for at least 10 seconds.

Figure 4. Sample of electrical recording
Co-Cultures on DIV18
Epileptic Activity Screening Techniques

2. Optical Recordings
   • jRGECO1a is a genetically encoded calcium indicator that is used to monitor calcium transients and optically measure epileptic activity

Grienberger and Konnerth, Neuron, 2012
Example of Optical Imaging
Optical and Electrical
Traumatic Brain Injury

- 40-50% chance of developing epilepsy post-trauma
- Injuries can occur with different mechanisms
- Mechanisms leading to epileptogenesis are not well described
- Different *in-vitro* models for TBI

Morrison et al., *Journal of Neurotrauma*, 1998
Weight Dropping TBI

• Mechanically Induced Focal Injury
  • At DIV2, a bar of weight 0.122g, is dropped on the cultures from a height of 2mm, at desired area.
  • Effects of trauma are assessed by propidium iodide staining.
  • Optical recordings are used to assess changes in epileptic activity, particularly the seizure onset and propagation to identify seizure focus.
DIV2 before Injury

4hrs post injury

3 days post injury

DIV5
NeuN staining

DIV11

Propidium Iodide Staining

NeuN – Confocal Stack

Ca^{2+} imaging
DIV11 _ Culture 1

1-DIV11 / Time =340s / FrameNo =3349
Thank you!