Epilepsy and Neural Engineering

Jing Liu
Overview

1. Epilepsy
   • definition
   • causes
   • current research situation

2. Mechanism under Epilepsy
   • neural circuits
   • generation of epilepsy

3. Developing Treatments for Epilepsy
   • diagnostics
   • electrical stimulation
   • faster drug development
Epilepsy

-- repeated occurrence of unprovoked seizures

Age-specific incidence of epilepsy

Causes of epilepsy
Posttraumatic Epilepsy-PTE

- Incidence after military head injury is up to 53% of patients (Vietnam veterans)
- Incidence after civilian head injury - 17%

Raymont V et al. Neurology 2010;75:224-229

Facts about Epilepsy

- 1 – 3% of general population suffers from epilepsy (5-6 million people in US)
- In 70% of cases, epilepsy is controlled by antiepileptic medication
- Medications are not curative
- Anticonvulsants have side-effects
- In 30% of cases, epilepsy is not controlled by medication, or becomes drug-resistant. These patients may have to undergo surgery
Mechanism under Epilepsy/Seizure

Classification:

1. A partial seizure begins in one brain area. It affects only part of the brain.
2. A primary generalized seizure involves the entire brain.
Mechanism under epilepsy

Neuronal Circuit

Excitatory neurons (A and B) – release excitatory neurotransmitter, cause other cells to activate

Inhibitory neurons (C-H) – release inhibitory neurotransmitter, cause other cells to de-activate
Mechanism under epilepsy
Neuronal Circuit

Basic cortical circuit
Generation of Seizures

Partial seizure

Partial Seizures Originate Within a Small Group of Neurons Known as a **Seizure Focus**

Interictal activity
Generation of Seizures

Partial seizure

Interplay between excitation and inhibition in seizure focus

Seizure begins to spread beyond the original focus if surround inhibition breakdown
EEG from a 12-year-old patient with typical absence seizures
Generalized Seizures Evolve From Thalamocortical Circuits
Mechanism under epilepsy

The pathways of seizure propagation

A Partial seizure
1 Spread
Seizure focus

B Primary generalized seizure

2 Secondary generalization
Seizure focus

4 Thalamus
A Clinical Case--Temporal lobe epilepsy

A. before seizure

B. aura: feeling of fear

C. alteration of consciousness, screaming
A Clinical Case--Surgical treatment of epilepsy
Developing treatments for Epilepsy
Interfacing Brain with Electrical System

- better diagnostics through electrode arrays
- stopping seizures with electrical stimulation
- faster drug development with brain-on-a-chip
Developing treatments for Epilepsy
Interfacing Brain with Electrical System

Diagram:
- Neurons → Recording Electrodes → Amplifier → A/D conversion → Amplifier → D/A conversion → Stimulating Electrodes
- Neurons, nerves, muscles
Developing treatments for Epilepsy
Diagnostics through Electrode Arrays

Electroencephalography (EEG)
from the scalp, non-invasive

Electrocorticography (ECoG)
from the surface of the cortex, invasive

Intracortical
Local Field Potentials (LFP)
within cortical tissue, invasive
Diagnostics through Electrode Arrays

Electroencephalography (EEG)
Diagnostics through Electrode Arrays

Electrocorticography (ECoG)

Surface of the brain is not even, and activity in sulci is inaccessible to surface electrodes
Seizures appear as spiral waves of activity on the cortex.
Diagnostics through Electrode Arrays

Local Field Potential (LFP)

LFP traces from the superficial and deep layers of the motor cortex in an anaesthetized cat and an intracellular trace from a layer 5 pyramidal neuron.
Vagus Nerve Stimulation

- Vagus nerve: enervates heart, larynx, lungs and intestines. Carries sensory information back to the brain.
- Mechanism of action: not understood, but may involve activation of the thalamus and/or release of neurotransmitter norepinephrine interfere epilepsy
Vagus Nerve Stimulation

Left vagus nerve is used for stimulation because the right vagus nerve affects the heart rate.
Responsive neurostimulator system

Responsive neurostimulator system (US manufacturer Neuropace)
Stopping Seizures with Electrical Stimulation

Responsive neurostimulator system

- Record Activity
- Detect Seizure
- Deliver Stimulation to Seizure Focus
- Stop Seizure

Figure 1.

Spontaneous Seizure  
Electrical Stimulation  
Seizure Stops
Developing treatments for Epilepsy
Faster drug development with Brain-on-a-Chip

Drug Discovery Process

- **Target Selection**: Cellular & Genetic Targets, Genomics, Proteomics, Bioinformatics
- **Lead Discovery**: Synthesis & Isolation, Combinatorial Chemistry, Assay Development, High-throughput Screening
- **Medicinal Chemistry**: Library Development, Structure-Activity Studies, In Silico Screening, Chemical Synthesis
- **In Vitro Studies**: Drug Affinity & Selectivity, Cellular Disease Models, Mechanism of Action, Lead Candidate Refinement
- **In Vivo Studies**: Animal Models of Disease States, Behavioural Studies, Functional Imaging, Ex Vivo Studies
- **Clinical Trials & Therapeutics**

Whole process takes more than 10 years, costs over 1 billion dollars
Faster drug development with Brain-on-a-Chip

However, there is no simple cellular assay that can be used to assess drug effectiveness in epilepsy which require the presence of a functioning neuronal network.

Animal model require time-consuming and expensive surgical procedures for electrode implantation to monitor neuronal activity.
Faster drug development with Brain-on-a-Chip

Organotypic Brain Slice Culture
Faster drug development with Brain-on-a-Chip
Organotypic Brain Slice Culture

Hippocampus
- Neatly organized neural structure
- Crucial in development of epilepsy

Hippocampal regions CA1, CA3, and dentate gyrus (DG) remain well-preserved and densely packed with neurons

Nissl staining of a DIV 28 culture
Faster drug development with Brain-on-a-Chip
Organotypic Brain Slice Culture

DIV 30 Neural organization of hippocampus. **Excitatory** and **inhibitory** neurons are preserved
Faster drug development with Brain-on-a-Chip
Epilepsy on a Chip

Custom MEA with four organotypic hippocampal cultures
Faster drug development with Brain-on-a-Chip

Epilepsy on a Chip
Faster drug development with Brain-on-a-Chip

Epilepsy on a Chip

Phenytoin exerted acute, reversible anticonvulsive effects in a model of post-traumatic seizures in vitro, which is the same in epileptic patients.
Rapid experiment rate with **epilepsy-on-a-chip** allowed us to evaluate > 150 drugs for antiepileptic effects, with some unexpected candidates emerging.
Questions?
Thank you!