Epilepsy and Neural Engineering

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Overview

1. Epilepsy
   • Definition
   • Causes
   • Therapeutic strategies

2. Mechanism under Epilepsy
   • Neural circuits
   • Development of epilepsy

3. Epilepsy and Neural Engineering
   • Interfacing brain with electrical system
   • Accelerate drug discovery with brain-on-chip technology
Epilepsy

Neurological disorder, defined as repeated occurrence of unprovoked seizures

Age-specific incidence of epilepsy

Causes of epilepsy
Posttraumatic Epilepsy -- PTE

- Incidence after civilian head injury - **17%**
- Incidence after military head injury - **53%**
  (Vietnam veterans)

Prevalence of posttraumatic epilepsy

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 drugs
- Drugs are not curative and 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

A common mechanism:
Neural circuit malformation causes hyperexcitability
-- epileptic circuit
Neuronal Circuit

Excitatory neurons (A, B) – release excitatory neurotransmitter, cause other neurons to activate
Inhibitory neurons (C-H) – release inhibitory neurotransmitter, cause other neurons to de-activate
Basic cortical circuit

Red: pyramidal neuron – excitatory
Grey: interneurons – inhibitory
Classification:

- **Partial seizure** begins in one brain area and affects only part of the brain.
- **Generalized seizure** involves the entire brain.
Partial Seizure

Partial seizures originate within a small group of neurons known as a **Seizure Focus**.
Partial Seizure

Abnormality is confined in seizure focus by surrounding inhibitory interneurons.

If surround inhibition breakdown, abnormal activity spread out and will induce epilepsy.
Generalized Seizure

A Spike and wave activity in typical absence seizure

EEG from a patient with typical absence seizures
Generalized Seizure

Generalized seizures evolve from thalamocortical circuits
Seizure Propagation

A Partial seizure
1 Spread
Seizure focus

1
3

2 Secondary generalization
2

Thalamus

4

B Primary generalized seizure
A Clinical Case -- Temporal lobe epilepsy

A. before seizure

B. aura: feeling of fear

C. altered consciousness

seizure focus
A Clinical Case -- Surgical treatment of epilepsy
Interfacing brain with electrical system:

- better diagnostics through electrode arrays
- stopping seizures with electrical stimulation
- faster drug development with brain-on-chip
Neural activity can be detected with electrodes
Interfacing Brain with Electrical System

Neurons $\rightarrow$ Recording Electrodes $\rightarrow$ Amplifier $\rightarrow$ A/D conversion $\rightarrow$ signal conditioning and processing, analysis $\leftarrow$ D/A conversion $\leftarrow$ Amplifier $\leftarrow$ Stimulating Electrodes $\leftarrow$ Neurons, nerves, muscles
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
Electroencephalography (EEG)

- Most widely used, noninvasive
- Low spatial resolution
- Cannot determine deep brain activity
Electrocorticography (ECoG)

- Spatial resolution ~ 1cm
- Valuable diagnostic tool for presurgical planning
Recording of seizures with flexible electrode array
Intracortical Local Field Potential (LFP)

High spatial resolution even down to individual neurons
Stopping Seizure with Electrical Stimulation

Vagus Nerve Stimulation

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

ECoG lead

Intracortical lead
Responsive neurostimulator system

- Detect Seizure
- EcoG lead Record Activity
- Intracortical lead Deliver Stimulation to Seizure Focus
- Stop Seizure

![Image of EEG tracings showing spontaneous seizure, electrical stimulation, and seizure stop]
Drug Discovery

- 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
  - Ex Vivo Studies
- In Vivo Studies
  - Animal Models of Disease States
  - Behavioural Studies
  - Functional Imaging
  - Clinical Trials & Therapeutics

Drugs Discovery takes more than 10 years, costs over 1 billion dollars
Disease Model for Epilepsy

**Cellular model**
- fast screening of compounds
- highly successful in development of drugs against some types of cancer

No simple cellular assay that can be used to assess drug efficacy in epilepsy which require the presence of a **functioning neuronal network**

**Animal model** requires time-consuming and expensive surgical procedures for electrode implantation to monitor epilepsy from the brain
In Vitro Model of Epilepsy

**Organotypic hippocampal cultures**

Hippocampus is often the place where seizures originate in vivo.
Neural organization of hippocampus

On 30 DIV, Excitatory and inhibitory neurons are preserved
Epilepsy-on-Chip for high-throughput drug screening

Microfluidic MEA chip
Chronic recording reveals the development of epilepsy
Drug test

Phenytoin exerted acute, reversible anticonvulsivie effects on this in vitro model, which is the same as in epileptic patients.
Epilepsy-on-chip model is promising for high-throughput antiepileptic drug discovery
Question?
Thank you!