Epilepsy and Neural Engineering

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Overview

1. **Epilepsy**
   - definition
   - causes
   - current 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 in 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**
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
Generation of Seizures

Generalized Seizures

A Spike and wave activity in typical absence seizure

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
2 Secondary generalization
3 Seizure focus

B Primary generalized seizure

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

- Neurons → Recording Electrodes → Amplifier → A/D conversion → signal conditioning and processing, analysis → 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.
Diagnostics through Electrode Arrays

Electrocorticography (ECoG)

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
Developing treatments for Epilepsy
Stopping Seizures with Electrical Stimulation

**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
Stopping Seizures with Electrical Stimulation

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

LT1-16-AVG
LT1-17-AVG
LOT1-AVG
LOT2-AVG
LOT3-AVG
LOT4-AVG
LOT5-AVG
LOT6-AVG
LOT7-AVG
LOT8-AVG
AST1-AVG
AST2-AVG
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.

Cellular assays has been highly successful in new generation of drugs against some types of cancer.

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.
Questions?
Thank you!