Physiological Markers of Pharmacoresistant Epilepsy
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Learning Objectives

• What are biomarkers of epileptogenesis and epileptogenicity?

• How can biomarkers be useful for the diagnosis and treatment of epilepsy?
THE CHALLENGE

• Biomarkers of pharmacoresistance would permit early identification for timely consideration of aggressive therapy such as surgery.

• Biomarkers of pharmacoresistance are essential for more cost-effective drug discovery and validation.

• There are no biomarkers of pharmacoresistance but these could evolve from active research to identify biomarkers of epileptogenesis and epileptogenicity.
BIOMARKERS AND BASIC MECHANISMS

• Elucidation of fundamental neuronal mechanisms underlying pharmacoresistance will provide insights into the development of biomarkers.

• Identification of biomarkers of pharmacoresistance will provide insights into fundamental neuronal mechanisms.

• There are undoubtedly multiple mechanisms responsible for pharmacoresistance; therefore, a single biomarker for pharmacoresistance per se is not likely to emerge. A profile of biomarkers may be necessary.
Dynamic changes that indicate the presence of an epileptogenic process with a sufficiently high degree of reliability to warrant intervention

- Biomarkers of epileptogenesis
- Biomarkers of epileptogenicity
MARKERS OF CLINICAL EPILEPSY

- Risk factors
- Precipitating factors
- Seizure prediction and detection
- Outcome measures
- Surrogate markers
- Biomarkers
TARGET MECHANISMS

- Cell loss (e.g., hippocampal atrophy)
- Axonal sprouting
- Synaptic reorganization
- Altered neuronal function (e.g., gene expression profiles, protein products)
- Neurogenesis
- Altered glial function and gliosis
- Inflammatory changes
- Angiogenesis
- Altered excitability and synchrony
POTENTIAL BIOMARKERS

• Hippocampal changes on MRI
• Interictal spike features, including fMRI
• Pathological high-frequency oscillations (pHFOs)
• Excitability – TMS
• AMT-PET imaging
• Gene expression profiles
HYP & LVF seizure onsets associated with unique patterns of damage

HYP or LVF seizure onsets associated with significant atrophy.

Atrophy in patients with HYP onset resembles classical hippocampal sclerosis.

Atypical pattern of atrophy associated with LVF onsets compared to HYP onsets.

Ogren et al. In press
Contralateral damage in patients with LVF seizure onsets

HYP onsets associated with isolated areas of damage, but overall not significantly different with respect to control subjects.

Significant contralateral atrophy in patients with LVF onsets.

Rat
Human

LAH

LEC

LEC

ROF

REC

REC

15 msec

5 mV

1 sec

100 msec

300 Hz

0.5 mV

1 sec

300 Hz

15 msec

100 msec
Alpha[C-11]methyl-L-tryptophan PET selectively identifies the epileptogenic tuber in a 7-year-old boy with tuberous sclerosis complex.

FLAIR MRI

![FLAIR MRI image]

FDG

![FDG image]

AMT

![AMT image]

EEG showed spike and wave activity in the right frontal region.

Asano, Chugani et al. 2000
PET Center/Pediatric Neurology,
Children’s Hospital of Michigan
Wayne State University
**Epileptogenesis**: The development and extension of tissue capable of generating spontaneous seizures. This includes:

- Development of an epileptic condition
- Progression after the condition is established

**Epileptogenicity**: Tissue capable of generating spontaneous behavioral seizures.
BIOMARKERS OF EPILEPTOGENESIS

- Identify the development of brain tissue capable of generating spontaneous epileptic seizures.
- Identify the progression of an epileptic condition after it has developed.
BIOMARKERS OF EPILEPTOGENICITY

- Identify the existence of brain tissue capable of generating spontaneous seizures.
- Measure the severity of an epileptic condition.
- Determine pharmacoresistance.
- Localize brain tissue capable of generating spontaneous seizures.
BIOMARKERS OF EPILEPSY DEVELOPMENT

• Predict epilepsy in patients with risk factors
  - genetic predisposition
  - prolonged febrile seizure
  - head trauma
  - intracranial infection
  - brain lesion
• Institute antiepileptic intervention
BIOMARKERS OF EPILEPSY PROGRESSION

• Diagnose progression in patients with epilepsy
• Early aggressive treatment is essential to prevent irreversible social and psychological disabling consequences of recurrent seizures
• Determine when to refer patients for surgical therapy
• Identify patients who might benefit from experimental treatments
BIOMARKERS OF THE EXISTENCE OF EPILEPSY

• Predict which people have epilepsy after a single seizure, in order to begin AED treatment immediately and not wait for a second seizure, which could cause injury or death.
• Diagnose epilepsy definitely in patients with equivocal events without the need for inpatient video-EEG monitoring.
• Confirm that a patient with epilepsy has been cured.
BIOMARKERS OF EPILEPSY SEVERITY

• Determine the efficacy of therapeutic interventions without the need to wait for another seizure to occur
  - test pre intervention
  - test post intervention
• Tailor individual pharmacotherapy
  - rapid drug screening to identify the best pharmacotherapy regimen for each individual patient
BIOMARKERS THAT LOCALIZE EPILEPTIC BRAIN TISSUE

- Localize the epileptogenic region for surgical resection without the need for expensive presurgical evaluation.
- Identify epileptogenic brain tissue for basic research on fundamental mechanisms of epilepsy.
BIOMARKERS OF PHARMACORESISTANCE

- Identify pharmacoresistance in individual patients without the need to conduct multiple drug trials
- Early aggressive treatment is essential to prevent irreversible social and psychological disabling consequences of recurrent seizures
- Determine when to refer patients for surgical therapy
- Identify patients who might benefit from experimental treatments
BIOMARKERS OF PHARMACORESISTANCE

• Facilitate clinical trials of interventions intended to prevent or treat pharmacoresistance
  - new antiepileptic drugs
  - rational polytherapy with rapid course change, e.g., I-SPY

• Create cost-effective rapid throughput animal models of pharmacoresistance to identify
  - antiepileptic compounds
  - antiepileptic devices