Neurobiology of Epilepsy
NRSC 7614
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Goals and Objectives

At the conclusion of this lecture, participants will:

1) Understand the heterogeneity of “epilepsy”
2) Identify potential cellular mechanisms for epilepsy
3) Recognize associated common co-morbid symptoms associated with epilepsy
Epilepsy can be expressed in a multitude of ways

- **Cellular**
  - Ions and channels
  - Genes

- **Anatomy**
  - Cortex
  - Hippocampus

- **Electrical activity**
  - EEG

- **Seizures**
  - Types
  - Epilepsy syndromes

- **Patient**
  - Treatment
  - Co-morbidities

Cellular derangement in the brain leads to abnormal electrical activity.

Electrical activity is observed in the EEG.

Abnormal electrical activity results in dysfunctional motor and cognitive activity.

Patients suffer from the personal and social effects of seizures.
Definitions 1

• **Seizure:** episode of neurologic dysfunction leading to clinical changes in motor control, sensory perception, behavior or autonomic function.
  - A seizure is a sustained, pathologically synchronous activation of a neural network.

• **Epilepsy:** 2 or more unprovoked seizures.
Definitions 2

• **Neural Network**: collection of nerve cells which interact with one another, can vary in size from a subregion of the hippocampus to the entire neocortex.

• **Neuronal Synchrony**: when 2 or more neurons fire at the same time and their action potentials become additive.

• **Seizure Threshold**: the propensity for spontaneous seizure activity.

• **Epileptogenesis**: Process by which a normal neuronal population converts into a hyperexcitable network that sustains a seizure.
Definitions 3

EPILEPTOGENESIS

Initiating Injury

Cortical Dysplasia
Febrile seizure
Brain Injury

Latent period

Epilepsy

Spontaneous Seizures

Further Epileptic Damage

Cognitive Deficits
Mood Disorders
Further Seizure Susceptibility

Adapted from Stafstrom 2006
Classification:

Partial:
  - Complex (altered consciousness)
  - Simple (motor, sensory)

Generalized:
  - Primary generalized (e.g., Absence, myoclonic)
  - Secondarily generalized

Prolonged:
  - Status Epilepticus

http://www.mydr.com.au/content/images/categories/Epilepsy/Seizure_classification.gif
Clinical descriptions

• I passed out
• I fell down
• I felt weird

http://pediatricneurology.com/seizures_for_kids.htm
ADULTS
70% partial (focal)

Seizures
Cognitive impairment
Mood Disorders

Numbers: NEJM 359: 166-76
brain fig: http://pediatricneurology.com/seizures_for_kids.htm
Adapted from http://www.emedicine.com/neuro/images/Large/813813813NEU0692%2D02%2Ejpg
EPSPs
Na+ Influx
Ca++ Currents
Paroxysmal Depolarization

Seizure!!!!

IPSPs
K+ Efflux
Cl- Influx
Pumps
Low pH

Control
QUESTION

• What GENETIC and ENVIRONMENTAL (acquired) factors contribute to seizure threshold?
Genetic Epilepsies

- Genetic epilepsies refer to epilepsies caused by gene mutations.
- “Idiopathic epilepsies”

Mutations in **SCN1B**: allows passage of an increased sodium current, leading to greater depolarization during the action potential and increased tendency to fire repetitive bursts.

Mutations in **KCNQ2/KCNQ3**: encode potassium channels, associated with benign familial neonatal convulsions. These mutations decrease the potassium outflow underlying the longer-lasting "M current," are likely to cause a loss of spike-firing adaptation and therefore an increase in neuronal firing frequency.
GABAAR subunit genet mutations
Case: Temporal Lobe Epilepsy

A 16 yo girl

• presents with several complex partial seizures a day
• consisting of staring, fumbling movements of the left hand and head turning to left,
• followed at times by generalized tonic clonic convulsions lasting 1-2 minutes.
Temporal Lobe Epilepsy 1

- Most common type in adolescents and adults
  - 2-30 focal seizures/month.
  - Typically begin with aura, abnormal taste, smell, déjà vu, may secondarily generalize
- History of complicated febrile seizures, or other precipitating injuries (head trauma, intracerebral infections)
- Increased family history of epilepsy
- 20-30% intractable to anticonvulsant medications
- Intractable forms exist and may become impossible to control with medications
Temporal Lobe Epilepsy 2

• Progressive disease:
  – Decrease in hippocampal volume over years as a function of seizure number
  – Impaired memory function
TLE: EEG Findings

Mesial Temporal Sclerosis: Ictal EEG from R Temporal Lobe
Pramote Laoprasert, MD
Mesial Temporal Sclerosis R> L; Pramote Laoprasert, MD
Hippocampal sclerosis

- Selective loss of neurons in dentate hilus and hippocampal pyramidal-cell layer
- Gliosis accompanies loss of neurons, causing shrinkage and hardening of tissue
- Aka “mesial temporal sclerosis” because often accompanying neuronal loss in entorhinal cortex and amygdala.
Figure 4.
Histological specimens representative of coronal hippocampal slices stained by Nissl (left row) and neo-Timm (medium and right rows). The upper panels show a representative normal control hippocampal histology. The intermedium panels illustrate hippocampal histology of sporadic mesial temporal lobe epilepsy (MTLE) with mesial sclerosis (cellular loss and fascia dentata dispersion) showing intense mossy fiber sprouting in the inner molecular layer. The lower panels show a hippocampal specimen of case with familial form of MTLE where is observed the same pattern of cellular loss and fascia dentata dispersion, nevertheless with poor mossy fiber sprouting in the inner molecular layer. Arrows show the inner molecular layer.

Andrade-Valenca et al. Epilepsia 49(6) 1046-54, 2008
Experimental Models of Epilepsy

• Acute Brain Slices
  – Blockade of GABA-mediated inhibitory neurotransmission

• Organotypic and Cell cultures

• Animal Models Systemic Treatments
  – Application of Excitotoxins: Tetanus Toxin, Pilocarpine, Kainate Acid

• Animal Models Focal Treatments
  – Kindling

• Genetic epilepsy models.

• Computer models
Paroxysmal Depolarization Shift

- 1964
- Matsumoto and Ajmone Marsan
- Extracellular recordings of action potential of single cells
- Cat cerebral Cortex after topical application of penicillin.
- In-vitro correlate of interictal spike on EEG
R hippocampal EEG of rat 8 weeks prior, Status epilepticus using Kainate

In vitro CA3, naïve rat
Bains, Nature Neuroscience 2(8): 1999 Fig 1
Bains, Nature Neuroscience 2(8): 1999 Fig 5.
Epileptogenesis

Injury → Cell loss → Disinhibition → Synaptic plasticity → Spikes → Epilepsy

Staley, Hellier, Dudek, 2005
This is something that EVERY DOCTOR NEEDS TO KNOW

Most treatment of Status Epilepticus will **not** be made initially by a neurologist

Paramedic
Family Doc
ER Doc
IM Doc
Peds Doc
Status Epilepticus

• Seizures which repeat without an intervening lucid interval,
• Seizures lasting for **prolonged period of time (5min)**, and two seizures within 5min should be considered SE
• 50,000-200,000 cases occur annually in the United States. DeLorenzo et al (1996)

http://home.mdconsult.com/das/search/openres/62391844-2?searchId=516867814
SE: Causes in Adults

- chronic epilepsy (34%)
- remote symptomatic causes (24%)
- cerebrovascular accidents (22%)
- anoxia or hypoxia (10%)
- metabolic causes (10%)
- and alcohol and drug withdrawal (10%)

EEG: Status Epilepticus

http://www.medscape.com/content/2003/00/45/85/458594/art-sin458594.fig36.gif
GABA Receptors

Diagram of the GABA\textsubscript{A} receptor

From Olsen and Sapp, 1995
SUDEP is defined as a sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in a patient with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicological or anatomical cause of death.
 Syndromes with Epilepsy as a key feature 1

Tuberous sclerosis

Adenoma sebaceum  
Shagreen patch  
Ungual fibromas

http://www.uwo.ca/cns/resident/pocketbook/pictures/tuberousclinical.jpg

Figure 2. Central Nervous System Manifestations of TSC.
A fluid-attenuated inversion recovery sequence image shows multiple cortical tubers (Panel A, arrows). A subependymal giant-cell tumor (Panel B, arrow) is the cause of obstructive hydrocephalus. Immunohistochemical staining of a cortical tuber reveals giant cells (Panel C, arrows) labeled with antibodies against phosphorylated ribosomal S6 protein.
Syndromes with Epilepsy as a key feature 2

• The products of the TSC 1/2 genes, hamartin/tuberin, regulate a protein kinase mammalian target of rapamycin (mTOR), which acts to promote cell growth

• Mutations in TSC genes cause overactivity of mTOR and dysregulated cell growth, producing cortical dysplasias composed of giant cells.

• The mTOR inhibitor rapamycin was tested in a genetically engineered mouse model of TSC and found to improve survival and diminish seizures
CoMorbidities 1

• Conditions for which epileptic adults are at increased risk relative to the general population include depression, anxiety, sleep disturbances, cognitive impairment, and psychosis.

• Of the psychiatric disturbances, depression is the most common

CoMorbidities 2

• Cognitive impairments include problems with memory, verbal fluency, attention, executive function, and social perception.

Non Pharmacologic Treatments for Epilepsy

• Seizure Surgery
• Ketogenic Diet
• Vagus Nerve Stimulator
• Deep Brain Stimulation
Seizure Surgery
Types of Surgical Procedures

- Frontal lobectomy
- Anterior temporal lobectomy
- Amgdalohippocampectomy
- Central area resection
- Complete temporal lobectomy
- Functional Hemispherectomy
- Motor cortex
- Sensory Cortex
- Multiple subpial transection of sensory motor cortex
- Anterior 2/3 callosotomy
- Posterior 1/3 callosotomy
- Corpus callosum
Ketogenic Diet

Vagus Nerve Stimulation

www.epilepsyfoundation.org

Deep Brain Stimulation

http://www.neuropace.com/trials/overview.html
Bibliography

• *100 Questions & Answers About Epilepsy* by Anuradha Singh
Further Reading  (in your spare time)


• [www.aesnet.org](http://www.aesnet.org)
• [http://www.epilepsy.com/epilepsy_therapy_project](http://www.epilepsy.com/epilepsy_therapy_project)
• [http://www.cureepilepsy.org/home.asp](http://www.cureepilepsy.org/home.asp)
THE END