**Neurobiology of Epilepsy**

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**Basic Mechanisms of Seizures**

- Neuronal short-circuit - PDS  
  - Paroxysmal Depolarization Shift  
- Neuronal synchronization  
  - Gap junctions, ephaptic coupling, electrical fields, ionic concentrations  
- Transition from interictal to ictus  
  - Failure of inhibition, excessive excitation

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**Molecular, Synaptic, and Cellular Effects of Seizures**

- Paroxysmal Depolarization Shift (PDS) is described in both experimental animal models of epilepsy and in human tissue obtained in epilepsy surgery  
- Intracellular expression of epileptic spike  
- Well-characterized with micro-electrode studies
Paroxysmal Depolarization Shift

- Pathophysiology of PDS
  - Abnormal ionic conductance (Na+/Ca++)
  - Due to increased number of ionic channels
  - Excessive response to normal input
  - Due to excessive excitatory input
    - Giant EPSP (Excitatory post-synaptic potential)
  - Probably a combination of both

PDS Origin of Interictal Spike

PDS – Ionic Conductance
Pathophysiology of Interictal Spike

Epileptic Focus – Interplay Between Excitatory and Inhibitory Circuitry

Neurobiology of Absence Seizures

Neuronal Synchronization

- Poorly understood and difficult to study
- Synchronization is necessary to reach the critical mass of neurons to overwhelm normal surround inhibition for transition to ictus
- There are multiple mechanisms responsible for neuronal synchronization
Neuronal Synchronization

- Neuronal synchronization may occur at dendritic and axonal levels but not at cell body
- Gap junctions on these processes when blocked prevent fast ripple potentials that synchronize adjacent neurons
- Electrical field effects may synchronize adjacent neurons
- Alterations in extracellular space and ionic concentrations affect neuronal excitability and synchronization

Mechanisms of Synchronization

A - PDS

B - Absence

Engel et al. 1997

Interactions Between NMDA Activation, Extracellular Space and Potassium Concentration

Effects of Seizure on Extracellular Space and Ionic Concentration

Lothman 1993
**Pathophysiology of Interictal Spike**

Interictal discharge
Originating in temporal lobe

Excitatory Center
Inhibitory surround
Basket cells
Synaptic inhibition in Surrounding neurons
Hyperpolarization

Dichter, 1997

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**Right Temporal Epileptiform Activity**

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**Interictal Epileptiform Activity**

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**Transition to Ictus**

- Failure of inhibition
  - Loss of the after hyperpolarization (AHP)
  - Loss of surround inhibition
- Excessive glutamate stimulation
  - Positive feedback
- Recurrent excitatory feedback circuitry
Seizure Induced Change in Neuron Function and Structure

- GLUTAMATE
- NMDA
- AMPA
- Leak
- Ca+ influx
- Ca++
- PO4
- NO
- Free Radicals
- Arachidonic Acid
- Necrosis
- IEG
- Genome
- Cell Swelling
- Necrosis
- 2nd Messenger
- PLC, IP3, DAG, cAMP
- Programmed Cell Death (Apoptosis)
- Growth Factor Receptors
- Target Gene
- Functional Change
- Structural Change

Synaptic Reorganization Resulting in Hyperexcitability and Epilepsy

- Seizures result in neuronal death of the hilar dentate neurons
- The hilar dentate neuron is the target of the dentate granule mossy fiber axon
- These fibers seek new synaptic contacts, at times, reinnervating themselves resulting in a recurrent positive feedback loop

Morphologic Changes Due To Excitotoxicity

- A
- B
- C

Hippocampal Reorganization

- CA2
- CA3

Tauck & Nadler, 1985
Stuber et al, 1998
Holmes & Gates, 2009
Mossy Fiber Synaptic Reorganization

Synaptic Reorganization Resulting in Hyperexcitability and Epilepsy

- Hyperexcitability is due to the loss of feed forward inhibition due to loss of excitatory input to the inhibitory basket cell
- Loss of the inhibitory neurons feedback inhibition
- Probably all three mechanisms are involved

Changes in Synaptic Connectivity in Epilepsy

Hippocampal Epilepsy Dentate Gyrus as ‘Gatekeeper’
Receptor Activation During Seizure

Spread of Ictal Discharge

Depth Electrode Recording of CPS Onset

Neurobiology of Absence Seizures
Epilepsy and Other Chronic Convulsive Diseases

“Every fit, slight or severe, is in some degree the effect of those which precede it, the cause of those that follow it.”

Pathophysiology of Epilepsy

Epileptogenesis

- Genetics
- Initiating Event
- Critical Modulators
- Structural/Functional Changes
- Clinical Sequelae
- Chronic Epilepsy

Refractory Epilepsy?

Neurobehavioral Changes, Cognitive Impairment?

Latent Period
Basic Mechanisms of Epilepsy

- “Seizures beget seizures”
- Kindling model of epilepsy
  - Model of partial epilepsy as well as neuronal learning
  - Chronic epilepsy is maladaptive learning
- Prevent rather than treat intractable epilepsy

Anticonvulsant Agents

- Identified by maximal electroshock or metrazol models
- Stop expression or spread of seizures
- Na⁺ channel/GABA mechanism of action
- Little effect on interictal spiking
- No effect on epileptogenesis (development of seizures) as judged by the kindling model of epilepsy

Antiepileptogenic Agent

- Effects the development with variable effects on the expression of seizures
- Interferes with the development of kindling
- Suppresses interictal spiking
- Action via glutamate mechanisms/Ca++
- Protects neuronal circuits from the deleterious effects of epileptic discharges

Animal Models of Epileptogenesis

<table>
<thead>
<tr>
<th>Model</th>
<th>Neuronal degeneration</th>
<th>Mosely fiber sprouting</th>
<th>Chronic hyperexcitability</th>
<th>Latent period</th>
<th>Spontaneous seizures</th>
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<tbody>
<tr>
<td>Kindling</td>
<td>Present</td>
<td>Present</td>
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<td>No*</td>
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<tr>
<td>Status epileptic i.e., tonic audiogenic, Li⁺-phenytoin, PPT (SATE)</td>
<td>Marked</td>
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</table>

*Spontaneous seizures do develop with prolonged kindling stimulation
$Sustained amygdala stimulation
Kindling Model of Epilepsy

- Goddard in 1967 reported on a new phenomenon he called kindling
  - Electrical stimulation in the rat amygdala that initially produced no clinical change in the animals’ behavior but did produce an after discharge (AD) if repeated daily
  - 10-14 d produced a permanent epileptic condition

Kindling Model

- With daily subclinical stimulations the AD lengthened and spread producing over subsequent days
  - Partial seizure
  - Complex partial seizure
  - Partial seizure with secondarily generalized motor convulsion

EEG: Kindling; Day 1-6-14
Prolongation and Spread of the AD

Progression of Seizure Stage With Daily Stimulation
**Kindling Effect**

**Kindling Model**

- This epileptic condition is permanent
- If the animal once fully kindled is left alone and not stimulated for up to a year, a single subclinical stimulation will produce a motor convulsion
- The animal has learned and retained how to have a seizure
- Every animal species tested demonstrated the kindling effect (frog to baboon)

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**Kindling Model**

- Early studies used electrical stimulation to produce kindling but it was soon found that the kindling effect was seen with repeated exposures of chemical convulsants at subclinical doses such as carbachol, bicuculline, penicillin, metrazol, and cocaine
- Any convulsant that can produce an after discharge (AD) at subclinical doses demonstrate the kindling effect with regular repeated exposures

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**Kindling Model**

- Not all brain regions kindle with the same ease
- In rat, mouse, cat, monkey and baboon
  - Amygdala, hippocampus, pyriform cortex, and anterior neocortex are easily kindled
  - Superior colliculus, cerebellum, and reticular formation can not be kindled
- This suggests that the necessary neuronal machinery must be present for kindling to occur
- Areas of cortex that ‘learn’ are those that are kindled

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[Image: Kindling Effect chart, Kindling Model text blocks]
Kindling Model

- Widespread effects on neurotransmitters, receptors, neuronal processes and gene expression
- Potentiation EPSP in stimulated pathway
- Long term potentiation (LTP) occurs early in the kindling process
- This allows better coupling between EPSP and neuronal output

“...This residual disposition to repetition of the same activity is the physical basis of memory, of muscular training, of all cerebral education and it is the basis of the morbid education of the brain which underlies epilepsy.”

Modification of Synapse with Kindling

Kindling Model

- Only model to allow a quantitative analysis of epileptogenesis and its prevention with AEDs
- Study the effect of AED on AD length and the number of electrical stimulations to reach a certain seizure stage
- Model for SPS, CPS, and CPS with secondary generalization
**AEDs Effect on Epileptogenesis**

- Sodium channel blockers treat kindled seizure but do not inhibit the kindling process
- Sodium channel blockers (DPH, CBZ) offer no prophylaxis in the development of epilepsy
- Valproate, levetiracetam, perhaps zonisamide, and topiramate blunt the epileptogenic process as judged by the kindling model
- ? Prevents the development of epilepsy

**Example of Excitotoxicity in Hippocampus after Status Epilepticus**

**Conclusions**

- Understanding the basic mechanisms of seizures allows increased understanding of the MOA of our AEDS and offers additional treatment targets in the treatment of seizures (i.e. gap junction blockers)
- Understanding basic mechanisms of epilepsy offers novel treatment options that may prevent the development of intractable epilepsy and its cognitive and behavioral sequelae