Neurobiology of Epilepsy

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Molecular, Synaptic, and Cellular Effects of Seizures

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

Paroxysmal Depolarization Shift

• 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⁺/Ca²⁺)
  - 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

A. Intracellular recording
B. Extracellular recording

Paroxysmal depolarizing shift

Wong, 1984.

PDS – Ionic Conductance

A. Interictal PDS within seizure focus
B. Basic cortical circuit

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Pathophysiology of Interictal Spike

- Interictal discharge
  - Originating in temporal lobe
- Excitatory Center
- Inhibitory surround
- Basket cells
- Synaptic inhibition in Surrounding neurons
- DS Hyperpolarization


Epileptic Focus – Interplay Between Excitatory and Inhibitory Circuitry

Neurobiology of Absence Seizures

A

EEG

Neuron

GABA
c
T.Ca^{++}

GABA
c
T.Ca^{++}

GABA
c
T.Ca^{++}

1 sec

B

Cortex

Thalamus


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

Interactions Between NMDA Activation, Extracellular Space and Potassium Concentration

Effects of Seizure on Extracellular Space and Ionic Concentration

Pathophysiology of Interictal Spike

Interictal discharge
Originating in temporal lobe

Excitatory Center

Inhibitory surround

Basket cells

Pyramidal Cells

DS

Hyperpolarization

Synaptic inhibition in Surrounding neurons


Right Temporal Epileptiform Activity

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Interictal Epileptiform Activity

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
Transition From Interictal State to Ictus

A

Tonic Phase

Clonic Phase

B

Seizure Focus

Distant


Depth Electrode Recording of CPS Onset

Ictal Discharge in CPS

GABA Desensitization Leading to Inhibitory Failure
Neuronal Subtypes in Neocortex

Glutamate and GABA Synapses and Potential Sites of MOAs

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**Excessive Excitation**

**Breaking Down Inhibition**

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**Glutamate Neurotransmission**

Seizure-Induced Change in Neuron Function and Structure

Morphologic Changes Due To Excitotoxicity

Sloviter, 1983.
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


Hippocampal Reorganization

Holmes & Galea, 2002.
Mossy Fiber Synaptic Reorganization


Synaptic Reorganization Resulting in Hyperexcitability and Epilepsy

- Hyperexcitability is due to the loss of feedforward 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’

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Receptor Activation During Seizure

Tonic-Clonic Electrographic Paroxysm

- EEG
- Neuron
- AMPA
- GABA
- NMDA
- Non-T Ca^{2+}

Primary Epileptogenic Zone
Zone of Dissemination


Spread of Ictal Discharge

A. Partial seizure
1. Spread
Seizure focus

2. Secondary generalization
Seizure focus
Thalamus

B. Primary generalized seizure

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Neurobiology of Absence Seizures

A

EEG
Neuron

GABA GABA GABA GABA

T.Ca** T.Ca** T.Ca**

1 sec

B

Cortex

Thalamus

Example of Excitotoxicity in Hippocampus after Status Epilepticus

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EEG, MRI, PET Scan in Mesial Temporal Sclerosis

Engel, 1986.

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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.”

Gowers, 1881.
Pathophysiology of Epilepsy

Pathophysiology of Epilepsy

Ontogeny

Epileptogenesis

Brain insult

Latency

No Seizures

Recurrence Spontaneous Seizures

Progression

Initiation

Amplification

Termination

ICTOGENESIS

Epileptogenesis

Genetics

Critical modulators

Structural / Functional changes

Clinical Seizures

CHRONIC EPILEPSY

Refactory Epilepsy?

Neurobehavioral changes,
Cognitive impairment?

Latent Period

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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

Gowers, 1881.

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>Mossy fiber sprouting</th>
<th>Chronic hyperexcitability</th>
<th>Latent period</th>
<th>Spontaneous seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kindling</td>
<td>Present</td>
<td>Present</td>
<td>Yes</td>
<td>No*</td>
<td>No</td>
</tr>
<tr>
<td>Status Epilepticus (i.e. kainic acid, pilocarpine, Li+ - pilocarpine, PPS†, SAS‡)</td>
<td>Marked</td>
<td>Marked</td>
<td>Yes</td>
<td>Days-weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical undercut</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>FeCl₂</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fluid percussion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Neonatal hypoxia</td>
<td>No</td>
<td>Minimal</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Neonatal hyperthermia</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Spontaneous seizures do develop with prolonged kindling stimulation
†Perforant path stimulation
‡Sustained amygdala stimulation

White, 2002.
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 afterdischarge (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 Stimulations
Kindling Effect

The kindling effect is a process where repeated subclinical stimulations lead to an increase in the frequency and severity of epileptic seizures. Once an animal is fully kindled, it will require a single subclinical stimulation to produce a motor convulsion, indicating that it has learned and retained how to have a seizure.

Every animal species tested demonstrated the kindling effect, from frogs to baboons. This permanent epileptic condition can be induced if the animal is left alone and not stimulated for up to a year. A single subclinical stimulation can then produce a motor convulsion.

**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, bicucilline, penicillin, metrazol, and cocaine.
- Any convulsant that can produce an afterdischarge (AD) at subclinical doses demonstrates the kindling effect with regular repeated exposures.


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<table>
<thead>
<tr>
<th>Kindling Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Not all brain regions kindle with the same ease</td>
</tr>
<tr>
<td>- In rat, mouse, cat, monkey and baboon</td>
</tr>
<tr>
<td>- Amygdala, hippocampus, pyriform cortex, and anterior neocortex are easily kindled</td>
</tr>
<tr>
<td>- Superior colliculus, cerebellum, and reticular formation cannot be kindled</td>
</tr>
<tr>
<td>- This suggests that the necessary neuronal machinery must be present for kindling to occur</td>
</tr>
<tr>
<td>- Areas of cortex that ‘learn’ are those that are kindled</td>
</tr>
</tbody>
</table>

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


Modification of Synapse with Kindling
“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.”

Gowers, 1901.

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
Antiepileptogenic Properties of Levetiracetam to Counteract the Development of Amygdala Kindling in Rats

Values given are the mean seizure severity score observed in each group during kindling development.
Adapted from Löscher, et al. 1998. With permission.

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
### AEDs That May Modify Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Development of kindling (prolongation of AD)</th>
<th>Spontaneous seizures</th>
<th>Fully kindled seizures (AD duration)</th>
<th>Seizure-induced damage (pretreatment)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>↓ or ↑</td>
<td>↓</td>
<td>↓</td>
<td>↓ or ↓ or ↑</td>
</tr>
<tr>
<td>Clobazam</td>
<td>↓</td>
<td>n.d.</td>
<td>↓</td>
<td>n.d.</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>↓</td>
<td>n.d.</td>
<td>↓</td>
<td>n.d.</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓ or ↑</td>
</tr>
<tr>
<td>Felbamate</td>
<td>n.d.</td>
<td>n.d.</td>
<td>↓</td>
<td>n.d.</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>n.d.</td>
<td>n.d.</td>
<td>↓ or ↓</td>
<td>n.d.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>↓ or ↓ or ↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>n.d.</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>↓ or ↑</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>↓</td>
<td>n.d.</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>↓ or ↑</td>
<td>n.d.</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Primidone</td>
<td>n.d.</td>
<td>n.d.</td>
<td>↓ or ↓</td>
<td>↓ or ↓</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>↓</td>
<td>n.d.</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Topiramate</td>
<td>↓</td>
<td>n.d.</td>
<td>↓ or ↓</td>
<td>n.d.</td>
</tr>
<tr>
<td>Valproate</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>n.d.</td>
<td>n.d.</td>
<td>↓ or ↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

AD = after discharge; AED = antiepileptic drug; n.d. = no data available; SE = status epilepticus; ↑ = no effect; ↓ = delay in kindling development or reduction in seizure duration; † = facilitation in kindling development.

*Seizure refers to status epilepticus, Pitkanen & Sutula, 2002.

SEE APPENDIX II FOR LARGER PRINT VERSION

### AED Effect on Neuroprotection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ischemia-induced damage</th>
<th>SE-induced damage</th>
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<tr>
<td>Carbamazepine</td>
<td>↓ or ↓</td>
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<td>↓</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>n.d.</td>
<td>n.d.</td>
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</table>

SEE APPENDIX III FOR LARGER PRINT VERSION

Pitkanen & Sutula, 2002.
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