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Neurobiology of Epileptogenesis

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Molecular, Synaptic, and Cellular Effects of Seizures

Intracellular
- Ca++
- Enzyme Activity

Extracellular
- Adenosine
- K+

Presynaptic Element (Axon Terminals)
- Glutamate Excitation

Postsynaptic Element (Receptors/Channels)
- GABA Inhibition
- Facilitation

Presynaptic-Postsynaptic Functional Unit
- PTP
- LTP

Glial Cells
- Necrosis
- Apoptosis

Neurons
- Neuron Loss

Network Milieu
- Excitation > Inhibition Imbalance

Cellular Milieu
- Disconnection Between Regions

Synaptic Milieu
- Synaptogenesis

Molecular Milieu
- Gene Expression
- Nerve Growth Factors
- Axon Proliferation, Growth

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

**Paroxysmal depolarization shift**

- $V_m$
- $V_{th}$
- $V_{rest}$
- $-70$ mV

**Time**

- Voltage dependent
- $K^+$ efflux
- $Ca^{2+}$ dependent

- 200 msec

Voltage dependent $Na^+$ influx

$Ca^{2+}$ influx

$K^+$ efflux
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

Intracellular recording

Extracellular recording

Paroxysmal depolarizing shift

A. Interictal PDS within seizure focus

B. Basic cortical circuit

Epileptic Focus – Interplay Between Excitatory and Inhibitory Circuitry

Neurobiology of Absence Seizures

A

EEG
Neuron

GABA
GABA
GABA
GABA

T-Ca++
T-Ca++
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.

Interactions Between NMDA Activation, Extracellular Space and Potassium Concentration

**NEURONAL FIRING DURING INTERICTAL BURSTS**

- **↓ Spike threshold**
- **↓ Burst AHP**
- **Depolarization**
- **↓ IPSP**
- **Cell swelling**
- **↓ EC space**
- **↑ Ephaptic coupling**

**RISE IN BASELINE [K+]**

**Larger [K+] transient during interictal burst**

**Seizure**
Effects of Seizure on Extracellular Space and Ionic Concentration

EEG

\[ [\text{Ca}^{++}]_o \]

\[ [\text{K}^+]_o \]

ECS

Glial Cell - Role in Generation and Spread of Seizures

- Impaired $K^+$ buffering due to reduced $g_{K(Ir)}$ in sclerotic epileptic hippocampus
- Enhanced expression of astroglial gap junction protein supports hypersynchronization
- Enhanced activation of metabotropic glutamate receptors with increased intracellular $Ca^{++}$

Astrocytic Ionic Regulatory Function
Pathophysiology of Interictal Spike

Interictal discharge
Originating in temporal lobe

Excitatory Center

Inhibitory surround

Basket cells

Pyramidal Cells

Synaptic inhibition in surrounding neurons

Hyperpolarization

Transition to Ictus

• Imbalance of excitation and inhibition
• Failure of inhibition:
  • Activity dependent disinhibition
  • 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

GABA Desensitization Leading to Inhibitory Failure
Excessive Excitation
Breaking Down Inhibition
Seizure-induced Change in Neuron Function and Structure

Example of Excitotoxicity in Hippocampus after Status Epilepticus
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, re-innervating themselves resulting in a recurrent positive feedback loop

Hippocampal 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’

A - Normal circuitry

B - Temporal lobe epilepsy

Receptor Activation During Seizure

Tonic-Clonic Electrographic Paroxysm

EEG

Neuron

- AMPA
- GABA
- NMDA
- Non-T Ca^{++}

Primary Epileptogenic Zone

Zone of Dissemination

Inflammation in Experimental Models

• In many animal models of epilepsy and acute seizures there is up-regulation of inflammation with microglial activation and increased expression of transcription factors and cytokines that help coordinate the inflammatory response
  • Toll-like receptor (TLR) family upregulated in microglia leading to transcriptional activation of cytokines, chemokines in the MHC class I and II
• This contributes to the seizure-related neuronal death and neuronal reorganization seen in hippocampal epilepsies

Breakdown of BBB

- In mice, CNS infection with LCMV results in seizures and death
- CD8+ T cells recognize LCMV infected cells, bind to them and kill them
- CD8+ T cells secrete chemokines, which trigger influx of myeloid cells and breakdown of BBB
- Depleting the myeloid cells delays seizures and death, suggesting a causal role of inflammation, breakdown of BBB, and fatal seizures

LCMV=lymphocytic choriomeningitis virus

Breakdown of BBB

• Pilocarpine model of experimental seizures and epilepsy
• Pilocarpine results in transient adherence between WBCs and endothelial cells of BBB resulting in a leaky BBB
• This permits albumin and other proteins to cross the BBB causing down regulation of astrocytic K+ channels, disrupting K+ homeostasis producing seizures and epilepsy. Seizures induce angiogenesis with porous BBB.
• Suppressing this interaction between WBC and endothelial cells and porous BBB prevented seizures and progression to epilepsy

Paraneoplastic/Autoimmune Encephalitis

• Clinical phenotype
• Myelitis, limbic or brainstem encephalitis
• Antibodies intracellular proteins
  – ie, anti-Hu, anti-Ma2, anti CRMPs encephalomyelitis
• Antibodies to synaptic proteins
  – ie, anti-NMDA, anti-AMPA, LG1 antibody, anti-GABA A,B, anti-Caspar2, anti-LGI1
• Treatment: Steroids, IVIG, PLEX, remove tumor. If no response rituximab, cyclophosphamide

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 WR. 1881.
Pathophysiology of Epilepsy

ONTOGENY

EPILEPTOGENESIS

Brain Insult

Latency

No Seizures

Recurrence Spontaneous Seizures

Progression

Initiation → Amplification (Time & Space) → Termination

ICTOGENESIS

Remission

Epileptogenesis

- Genetics
- Initiating Event
- Age
- Critical modulators
- Structural/Functional changes
- Clinical Seizures
- CHRONIC EPILEPSY
- Latent Period
- Refractory Epilepsy?
- Neurobehavioral changes, Cognitive impairment?
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

- Affects 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
In 1967, Goddard 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 days produced a permanent epileptic condition
EEG: Kindling; Day 1-6-14
Prolongation and Spread of the AD

Day 1

Day 6

Day 14
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.”

Gowers WR. 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

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, and perhaps zonisamide, topiramate, and perampanel blunt the epileptogenic process as judged by the kindling model.
- Prevents the development of epilepsy.
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 (ie, 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.