Mechanism of Status Epilepticus

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Seizure

- Initiation
- Recruitment
- Propagation
- Maintenance
- Termination
Seizure

- Initiation
- Recruitment
- Propagation
- Maintenance
- Termination – failure in Status Epilepticus
Paroxysmal Depolarization Shift

Intracellular and extracellular events of the paroxysmal depolarizing shift underlying the interictal epileptiform spike detected by surface EEG

Ayala et al., 1973
Sodium Channel

Untreated “epileptic neuron” Excess glutamate and aspartate release

Stimulus

Repeated influx of sodium ions

Excessive glutamate and aspartate release

Excessive stimulation leading to seizures
Interictal EEG spikes

Hippocampal CA3

• mutual excitation of pyramidal cells
• strong synapses (~1mV)
• intrinsic bursts
• ~1000 pyramidal cells needed for interictal spikes

Traub & Wong 1982, Science
What prolongs the hypersynchronous discharge beyond the 1\textsuperscript{st} second?

- Interictal discharges normally stopped by IPSPs / AHPs / synaptic vesicle depletion / presynaptic modulation…

- Slow excitatory processes, such as increased extracellular potassium ion concentrations which also cause negative DC shifts found in animal models and in appropriate clinical recordings.
Increase in the number of NMDA receptors with seizures

The increase in NMDA receptors leads to further excitation.
Recruitment

Origin and Spread of Seizures
Normal firing pattern of cortical neurons

Most of the brain/nerual oconnections are inhibitory
Basic Mechanisms Underlying Seizures

- Feedback and feed-forward inhibition, illustrated via cartoon and schematic of simplified hippocampal circuit.
Seizures due to Reverberatory Loops?
Longer Range Connections In Seizure Generator

Generalization

Midline Thalamic Nuclei

Amyg ← EC → HC

Cortex

Generalization

From Bertram
Glutamate Excito-toxicity from seizures
Prolonged or Repetitive Seizures Cause Neuronal Damage
Neuronal Specific Enolase

NSE and Duration of Seizures

NSE level (ng/mL)

Duration (hours)

<table>
<thead>
<tr>
<th>NSE level (ng/mL)</th>
<th>Duration (hours)</th>
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<tr>
<td>GCSE</td>
<td>Complex</td>
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<tr>
<td>14.1</td>
<td>23.9</td>
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<tr>
<td>4.9</td>
<td>16.2</td>
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(\(n=31\))

MRI Changes from Febrile Status

VanLandingham - feb status in 4 children

- Acute edema in hippocamp
- Atrophy subsequently

- Note average duration of status = 100 min!
Factors Modifying Neuronal Excitability

**Intrinsic**
- Ion channel type, number, and distribution
- Biochemical modification of receptors
- Activation of second-messenger systems
- Modulation of gene expression (e.g., for receptor proteins)

**Extrinsic**
- Changes in extracellular ion concentration
- Remodeling of synapse location or configuration by afferent input
- Modulation of transmitter metabolism or uptake by glial cells
Activation: excessive excitatory stimulation

Maintenance: failure of GABA mediated suppression &/or sustained glutamate stimulation
Disconnected Surgery

Corpus Callosumy

- Atonic Seizure
  “Drop Attack”

Subpial Transection

- Landau Kleffner Syndrome - Acquired Epileptic Aphasia
- Epilepsia Partialis Continua
Epileptogenesis

- Cell loss
- Gliosis
- Axonal sprouting
- Synaptic reorganization
- Neuronal neogenesis
- Alterations in neurotransmitter receptors
Mechanisms of Generating Hyperexcitable Networks

Neuroplasticity of seizures and epilepsy

• Excitatory axonal “sprouting”

• Loss of inhibitory neurons

• Loss of excitatory neurons “driving” inhibitory neurons
Schematic Illustration of a GABA<sub>A</sub> Receptor, with Its Binding Sites
$\text{GABA}_A$-Receptor - requires GABA to bind to allow Cl$^-$ in
The Central Inhibitory Synapse

- Astrocyte
  - Cholesterol
  - Pregnenolone
  - Neurosteroids

- GABAergic neuron
  - GABA receptors

Localization
- Synaptic: Phasic inhibition
  - Benzodiazepines
  - Barbiturates
  - Felbamate
  - Topiramate

- Extrasynaptic: Tonic inhibition
  - Neurosteroids, alcohol, general anesthetics

Benaroch EE. *Neurology.* 2007;68(8):612-614
Single Channel Chloride Current Evoked by GABA Is Enhanced by Diazepam and Phenobarbital

A. Control

B. GABA 2 uM

C. GABA 2 uM + diazepam 20 nM

D. GABA 2 uM + phenobarbital 500 uM

Diazepam resistance with increased duration of seizure

GABA(A) receptor internalization during seizures

GABA Receptor Internalization

NMDA Receptor Increase
HCN1 expression is repressed after epilepsy-provoking insults

HCN1: Hyperpolarization-activated cation non-selective 1: K channel
Multidrug Resistance Gene (MDR)

- MDR Gene encodes for P-glycoprotein is an efflux transporter - which contributes to the functionality of the blood brain barrier

- P-glycoprotein mediated drug extrusion may play a facilitory role in refractory epilepsy
STATUS EPILEPTICUS

• *Definition* (ILAE):

  30 minutes - based on primate models of status primate BP and oxygen supported but seizures still produce brain damage (Meldrum)

• *Working definition*: seizure lasting more than 5-10 min
Refractory status epilepticus (RSE)

has been defined as continuous seizures for **60–90 min** despite the administration of two to three anticonvulsant medications

Super Refractory Status Epilepticus

Seizures lasting over **24 hours**
Compensated

Decompensation
PLEDS

Periodic Lateralized Epileptiform Discharges

Subclinical Status
Burst Suppression
Hemodynamics

- **Sympathetic overdrive**
  - Massive catecholamine / autonomic discharge
  - Hypertension
  - Tachycardia
  - High CVP

- **Exhaustion**
  - Hypotension
  - Hypoperfusion

0 min 60 min

Status epilepticus
Cerebral blood flow - Cerebral O$_2$ requirement

- **Hyperdynamic phase**
  - CBF meets CMRO$_2$

- **Exhaustion phase**
  - CBF drops as hypotension sets in
  - Autoregulation exhausted
  - Neuronal damage ensues
Status epilepticus

Glucose duration

30 min

Hyperdynamic phase
- Hyperglycemia

Exhaustion phase
- Hypoglycemia develops
- Hypoglycemia appears earlier in presence of hypoxia
- Neuronal damage ensues

Status epilepticus
Schematic Representation of an Excitatory Synapse in the CNS and Putative Major Sites of Action of AEDs

Lacosamide is mechanistically distinct from other drugs that block voltage-gated sodium channels (specifically, it enhances slow inactivation of these channels).

Schematic Representation of an Inhibitory Synapse in the CNS and the Putative Major Sites of Action of AEDs

Seizure

- Initiation
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- Termination