CHAPTER 3

Epilepsy

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Epilepsy

- Epilepsy is the commonest neurologic disorder with therapeutic indications, prevalence of 0.5-1%
- Understanding the pathophysiology of epilepsy is important in rational therapy
Seizures and Epilepsy

- Seizure is a sudden time limited involuntary alteration of behavior with or without loss of consciousness accompanied by an abnormal electrical discharge.
- Epilepsy is a disorder of the CNS whose symptoms are seizures.
Seizures and Epilepsy

- Reactive seizures: occurring in normal nonepileptic tissue
- Epileptic seizures occurring in chronically epileptic tissue
- Epileptogenesis: sequence of events that converts normal neuronal networks into hyperexcitable networks
Seizures

- **Partial Seizures**
  - Simple Partial
  - Complex Partial

- **Generalized Seizures**
  - Absence
  - Atypical Absence
  - Tonic
  - Clonic
  - Tonic-Clonic
  - Atonic
  - Myoclonic
  - Mixed Forms
A Partial seizure
1 Spread

Seizure focus

2 Secondary generalization

Seizure focus

Thalamus

B Primary generalized seizure
Neuronal Excitability

- Basic mechanism of neuronal excitability is the action potential...net positive inward ion flux
Neuronal Excitability

- Hyperexcitable state
  - Increased excitatory neurotransmission
  - Decreased inhibitory neurotransmission
  - Alteration in voltage gated ionic channels
  - Intra/extracellular ionic alterations in favor of excitation
Neuronal Excitability

- Neuronal circuits
  - Axonal conduction
  - Synaptic transmission
- Both of these processes employ ionic channels
  - Voltage gated channels
  - Ligand gated channels
Voltage Gated Channels

- **Depolarizing conductances**
  - Excitatory
  - Inward sodium and Ca currents

- **Hyperpolarizing conductances**
  - Inhibitory
  - Primarily mediated by potassium channels
Ligand Gated Synaptic Transmission

- **Excitatory transmission**
  - Glutamate (NMDA) the principal excitatory neurotransmitter

- **Inhibitory transmission**
  - GABA the principal inhibitory neurotransmitter
Glutamate

- The brain’s major excitatory neurotransmitter

- Two groups of glutamate receptors
  - Ionotropic: fast synaptic transmission. NMDA, AMPA, kinate. Gated Ca and Na channels
  - Metabotropic: slow synaptic transmission. Modulation of second messengers, e.g. Inositol, cAMP
GABA

- The major inhibitory neurotransmitter in the CNS
  - GABA A: presynaptic, mediated by Cl channels
  - GABA B: postsynaptic, mediated by K currents
Neuronal Excitation

- Both Glutamate and GABA require active reuptake to be cleared from the synaptic left.
- Factors that interfere with transporter function also activate or suppress epileptiform activity.
Cellular Mechanisms of Seizure Generation

- **Excitation:**
  - Ionic: inward currents of Na, Ca
  - Neurotransmitter: Glutamate, Aspartate

- **Inhibition:**
  - Ionic: inward Cl, outward K
  - Neurotransmitter: GABA
Hyperexcitability: Intrinsic Factors

- Ion channel type, number and distribution
- Biochemical modification of receptors
- Activation of second messenger systems
- Modulation of gene expression
Hyperexcitability: Extrinsic Factors

- Changes in extracellular ionic concentrations
- Remodeling of synaptic location
- Modulation of transmitter metabolism or uptake
Excitation

Basically inward flux of Na and Ca, and outward flux of K

- **Endogenous factors:**
  - Genetic predisposition

- **Environmental factors:**
  - Trauma or ischemia
  
  ...convert non-bursting neurons to potentially epileptogenic populations
Epileptogenesis

The process by which normal healthy tissue is transformed into a relatively permanent epileptic state

1. Hyperexcitability: The tendency of a neuron to discharge repetitively to a stimulus that normally causes a single action potential

2. Abnormal synchronization: The property of a population of neurons to discharge together independently.
Synchronization

- Recurrent excitatory synapses
- Electronic coupling by gap junction
- Electrical field and ephaptic effects
- Changes in extracellular ion concentrations

Different kinds of seizures are probably related to different combinations of the above
## Roles of channels and receptors in normal and epileptic firing

<table>
<thead>
<tr>
<th>Channel or receptor</th>
<th>Role in normal neuronal function</th>
<th>Possible role in epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voltage-gated Na(^+) channel</td>
<td>Sub-threshold EPSP; action potential upstroke</td>
<td>Repetitive action potential firing</td>
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<tr>
<td>Voltage-gated K(^+) channel</td>
<td>Action potential down-stroke</td>
<td>Abnormal action potential repolarization</td>
</tr>
<tr>
<td>Ca(^{2+})-dependent K(^+) channel</td>
<td>AHP following action potential; sets refractory period</td>
<td>Limits repetitive firing</td>
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<tr>
<td>Voltage-gated Ca(^{2+}) channel</td>
<td>Transmitter release; carries depolarizing charge from dendrites to soma</td>
<td>Excess transmitter release; activates pathophysiological intracellular processes</td>
</tr>
<tr>
<td>Non-NMDA receptor (ie, AMPA)</td>
<td>Fast EPSP</td>
<td>Initiates PDS</td>
</tr>
<tr>
<td>NMDA receptor</td>
<td>Prolonged, slow EPSP</td>
<td>Maintains PDS; Ca(^{2+}) activates pathophysiological intracellular processes</td>
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<tr>
<td>GABA(_A) receptor</td>
<td>IPSP</td>
<td>Limits excitation</td>
</tr>
<tr>
<td>GABA(_B) receptor</td>
<td>Prolonged IPSP</td>
<td>Limits excitation</td>
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<tr>
<td>Electrical synapses</td>
<td>Ultra-fast excitatory transmission</td>
<td>Synchronization of neuronal firing</td>
</tr>
<tr>
<td>Na(^+)-K(^+) pump</td>
<td>Restores ionic balance</td>
<td>Prevents K(^+)-induced depolarization</td>
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Examples of specific pathophysiological defects leading to epilepsy

<table>
<thead>
<tr>
<th>Level of brain function</th>
<th>Condition</th>
<th>Pathophysiologic mechanism</th>
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<tbody>
<tr>
<td>Neuronal network</td>
<td>Cerebral dysgenesis, post-traumatic scar, mesial temporal sclerosis (in TLE)</td>
<td>Altered neuronal circuits: Formation of aberrant excitatory connections (&quot;sprouting&quot;)</td>
</tr>
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<td></td>
<td>Down syndrome and possibly other syndromes with mental retardation and seizures</td>
<td>Abnormal structure of dendrites and dendritic spines: Altered current flow in neuron</td>
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<tr>
<td>Neuron structure</td>
<td>Pyridoxine (vitamin B\textsubscript{6}) dependency</td>
<td>Decreased GABA synthesis: B\textsubscript{6}, a co-factor for GAD</td>
</tr>
<tr>
<td>Neurotransmitter</td>
<td>Angelman syndrome, juvenile myoclonic epilepsy</td>
<td>Abnormal GABA receptor subunit(s)</td>
</tr>
<tr>
<td>synthesis</td>
<td>Non-ketotic hyperglycinemia</td>
<td>Excess glycine leads to activation of NMDA receptors</td>
</tr>
<tr>
<td>Neurotransmitter</td>
<td>Neonatal seizures</td>
<td>Many possible mechanisms, including the depolarizing action of GABA early in development</td>
</tr>
<tr>
<td>receptors: Inhibitory</td>
<td></td>
<td>Potassium channel mutations: Impaired repolarization</td>
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<td>Neurotransmitter</td>
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<td>receptors: Excitatory</td>
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<td>Synapse development</td>
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<td>Ion channels</td>
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<td>channelopathies</td>
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Pathophysiology of Epilepsy

- Neurons transition from normal firing pattern to interictal bursts to an ictal stage
- Mesial temporal lobe epilepsy the most prevalent focal epilepsy
  - Hippocampal pyramidal cells the most studied cells in the CNS
The Hippocampal Model

- Major source of input the entorhinal cortex by way of perforant path to the dentate gyrus
- Dentate gyrus by way of mossy fibers connects to CA3
- CA3 connects to CA1 through Schaffer collateral pathway
The Hippocampal Model

- In sections from epileptic areas, neurons from specific regions (CA1) are lost or damaged.
- Synaptic reorganization (mossy fiber sprouting) causes recurrent hyperexcitability.
- Variety of brain insults can lead to the phenomena of mossy fiber sprouting:
  - Trauma, hypoxia, infections, stroke, …
The Hippocampal Model

- Excitatory axonal sprouting
- Loss of inhibitory interneurons
- Loss of excitatory interneurons “driving” inhibitory neurons
Electroencephalography-EEG

- Graphical depiction of cortical electrical activity recorded from the scalp
- High temporal resolution but poor spatial resolution
- The most important electrophysiological test for the evaluation of epilepsy
Physiological Basis of the EEG

- Extracellular dipole generated by excitatory post-synaptic potential at apical dendrite of pyramidal cell
Physiologic Basis of EEG

- Brain electrical activity can be recorded
  - Pyramidal cells all have the same polarity and orientation
  - Many cells are synchronously activated
Physiological Basis of the EEG (cont.)

- Electrical field generated by similarly oriented pyramidal cells in cortex (layer 5) and detected by scalp electrode.
EEG Applications

- Seizures/epilepsy
- Altered consciousness
- Sleep
- Focal and diffuse alteration in brain function
Electroencephalography (EEG)

- Recording the electrical activity of the brain, mostly from the scalp
- Frequency of waveforms
  - Delta — 0 to 4 Hz
  - Theta — 4 to 8 Hz
  - Alpha — 8 to 12 Hz
  - Beta — More than 12 Hz
- Particularly helpful in the analysis of seizures and epilepsy
EEG Frequencies

A) Fast activity
B) Mixed activity
C) Mixed activity
D) Alpha activity (8 to \( \leq 13 \) Hz)
E) Theta activity (4 to under 8 Hz)
F) Mixed delta and theta activity
G) Predominant delta activity (<4 Hz)

Not shown: Beta activity (>13 Hz)
EEG: Interictal Spike

- Hallmark of focal seizures is the interictal spike on EEG
- Cellular correlate of EEG spike is the paroxysmal depolarization shift (PDS)
- A PDS is an event occurring in a single neuron
  - Initial depolarization initiated by AMPA, then maintained by NMDA receptors
The “Interictal Spike and 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
Focal Epileptic Discharges
Primary Generalized Epilepsy

- Absence epilepsy
  - Generalized spike and wave discharges on EEG reflect phase locked oscillations between excitation and inhibition in thalamocortical networks
  - aberrations of oscillatory rhythms that are normally generated during sleep by circuits connecting the cortex and thalamus

- Generalized tonic clonic seizures
Absence Seizures

- GABAergic neurons of the nucleus reticularis thalami as pacemakers...the thalamocortical loop
- Activation of transient Ca channels (T channels) and GABA B mediated hyperpolarization...3-4 Hz oscillations
- Ethosuximide suppresses the T-current
Absence Seizures
EEG: Absence Seizure
Termination of seizures

- Mechanisms unclear, but may include voltage-, calcium-, or neurotransmitter-dependent potassium channels
Chronic Models of Epileptogenesis

- Certain forms of epilepsy are caused by particular events
  - 50% of brain injury patients develop epilepsy after a silent period
  - epileptogenic process involves a gradual transformation of the neural network over time
Chronic Epileptogenesis

- Kindling: repeated administration of electrical stimulus or convulsant drugs
  - Initially each stimulus evokes a progressively longer afterdischarge and a more intense seizure
  - Once fully kindled, each successive stimulus evokes a stimulation-induced clinical seizure, and in some instances, spontaneous seizures