**Epilepsy and Seizures**

**Epilepsy:**
Two or more unprovoked seizures that arise from abnormal electrical discharges in the brain

**Often Unknown Etiology:**
infections, tumors, trauma, toxins, metabolic disorders, cerebrovascular disorders, developmental abnormalities such as cortical dysplasia, genetic disorders

**Epileptogenesis** - Factors leading to the development of epilepsy (changes in gene expression/protein function, cell death, abnormal synaptic circuitry)
Seizure:

*a change in behavior caused by an abnormal synchronous electrical discharge in the brain*

Too much excitation or too little inhibition ➔ Excessive, random discharge of a group of neurons in the brain
Antiepileptic/anticonvulsant/antiseizure drugs

‘First Generation’ (pre 1993)

potassium bromide (1857-1930s)

Phenobarbital (1912)

Phenytoin (Dilantin) (1938)

Primidone (Mysoline)

Carbamazepine (Tegretol)

Benzodiazepines, e.g.

Ethosuximide (Zarontin)

Valproate (Depakote)

Clorazepate (Tranxene)

Clonazepam (Klonopin)

Clobazam (Frisium)
Antiepileptic/anticonvulsant/antiseizure drugs
‘Second Generation’ (since 1993)

- Felbamate (Felbatol)
- Gabapentin (Neurontin)
- Lamotrigine (Lamictal)
- Topiramate (Topamax)
- Tiagabine (Gabitril)
- Oxcarbazepine (Trileptal)
- Zonisamide (Zonegran)
- Vigabatrin (Sabril)
- Levetiracetam (Keppra)
Seizure classification

International Classification of Epileptic Seizures

I. Partial (focal, local) seizures
   seizure activity remains confined to local area

II. Generalized seizures
    bilaterally symmetrical and without local onset

III. Unclassified seizures
I Partial seizures

A. Simple partial seizures (consciousness not impaired)

1. with motor symptoms (changes in movement)
2. with somatosensory or special sensory symptoms (e.g. tingling, flashing lights)
3. with autonomic symptoms (e.g. heart rate)
4. with psychic symptoms (alteration of consciousness, e.g. hallucinations)
B. Complex partial seizures (impaired consciousness)
Also called temporal lobe epilepsy most often in the temporal or frontal lobes

1. Beginning as simple partial seizures and progressing to impairment of consciousness
2. Preceded by an aura
3. Impaired memory of ictal (during seizure) phase

C. Partial seizures evolving into secondarily generalized seizures
1. Becomes tonic-clonic type
2. Loss of consciousness
3. Preceded by an aura
II. Generalized seizures

A. Absence seizures (petit mal seizures)
   sudden interruption of consciousness, blank stare
   no aura

B. Myoclonic seizures (random discharges in motor cortex)

C. Tonic-clonic seizures (grand mal seizures)
   abrupt onset usually no aura
   no symptoms of partial or complex seizure
   tonic - contraction
   clonic - shaking
   postictal-flaccid and unconscious
EEG

Reading

Perception of fear

Altered consciousness

Left hemisphere

Right hemisphere
Epileptic syndromes

Idiopathic epilepsies

Idiopathic epilepsies with partial seizures
  e.g. frontal lobe, temporal lobe

Idiopathic epilepsies with generalized seizures
  many childhood epilepsy syndromes
  neonatal convulsions, benign myoclonic seizures,
  absence seizures

Symptomatic epilepsies - e.g. trauma, tumor
Status Epilepticus

Seizures occurring acutely in greater intensity, number, or length than usual

A prolonged seizure that lasts longer than 10 minutes or repeated seizures over the course of 30 minutes

Life threatening - emergency care should begin immediately

Treated with benzodiazepines: Diazepam or Lorazepam
Secondary generalized seizure
Primary generalized seizure
Partial seizure
Seizure focus
Thalamus
Progression of a Partial Seizure:

1. Initiation - increased electrical activity in a single cell
2. Synchronization of surrounding neurons
3. Spread to adjacent areas (aura)
4. Seizure begins when a group of neurons depolarize suddenly

**Paroxysmal depolarizing shift**

Leads to abnormal succession of action potentials

Surround inhibition normally should prevent synchronization
Focal epileptiform activity (partial seizures)

- Spike
- Slow wave
- Depolarizing shift (DS)
- Post-DS hyperpolarization

Interictal discharge

EEG

Membrane potential
Surround inhibition is critical for normal function of the CNS
Complex-partial / Temporal lobe epilepsy

- Usually caused by abnormal activity in temporal lobe/hippocampus + amygdala
- Classically preceded by aura
- Altered consciousness
- Impaired memory
- Can be drug resistant/pharmacoresistant
Hippocampus circuitry

Dentate gyrus

Perforant path

Entorhinal cortex

Mossy fibers

CA3

Schaffer collaterals

subiculum

CA1

Normal activity

cortex
Hippocampus circuitry

Dentate gyrus

Perforant path
Entorhinal cortex
subiculum

Mossy fibers
CA3
Schaffer collaterals

CA1

cortex

interictal activity (abnormal)
Hippocampus circuitry

Dentate gyrus

Perforant path

Entorhinal cortex

Mossy fibers

Mesial temporal sclerosis due to excitotoxic cell death

ictal activity (seizure)
Antiepileptic drugs

Three basic categories:

1. Enhance Na+ channel-mediated inhibition
2. Inhibit T-type calcium channels
3. Enhance GABA-mediated inhibition
Basic mechanisms: antiepileptic drugs (AED)

- Depends on type of epilepsy
- Managed with drugs - may try to locate focus of partial seizure (surgery?)
- Manipulation of ion channels:
  - cellular level (Na+ channel inactivation)
  - network level (GABA-mediated inhibition)
Drug choice by seizure type  Partial seizures

Drugs of choice:  Carbamazepine (Tegretol)
                 Phenytoin (Dilantin)
                 Valproate (Depakote)

Alternatives:  Lamotrigine (Lamictal)
                Gabapentin (Neurontin)
                Topiramate (Topamax)
                Tiagabine (Gabitril)
                Zonisamide (Zonegran)
                Oxcarbazepine (Trileptal)
                Levetiracetam (Keppra)
                Primidone (Mysoline)
                Felbamate (Felbatol)
                Phenobarbital
                Vigabatrin (Sabril)
Drug choice by seizure type:
Tonic-clonic (grand mal) seizures

Drugs of choice: Valproate (Depakote)
                Carbamazepine (Tegretol)
                Phenytoin (Dilantin)

Alternatives: Lamotrigine (Lamictal)
              Topiramate (Topamax)
              Zonisamide (Zonegran)
              Oxcarbazepine (Trileptal)
              Levetiracetam (Keppra)
              Primidone (Mysoline)
              Phenobarbital
              Felbamate (Felbatol)
Drugs that block voltage-dependent Na\(^+\) channels

Inhibit high frequency repetitive firing

**Carbamazepine** (Tegretol)
**Phenytoin** (Dilantin)
**Valproate** (Depakote)
**Lamotrigine** (Lamictal)
**Gabapentin** (Neurontin)
**Felbamate** (Felbatol)
**Topiramate** (Topamax)
**Oxcarbazepine** (Trileptal) [active metabolite HCBZ]
**Zonisamide** (Zonegran)
Voltage/frequency/use-dependent block

Drug stabilizes inactivated state
No drug

Low frequency

High frequency

Membrane potential inactivation

drug
Drugs that increase GABA levels in brain

Valproate (Depakote)
Gabapentin (Neurontin)
Tiagabine (Gabitril)
Vigabatrin (Sabril)
glutamic acid

GABA aminotransferase

succinate semialdehyde dehydrogenase

GABA transporter

GABA

gabapentin

tiagabine

valproate

valproate

GAT-1

vigabatrin

GABA

GABA

GABA

GABA

GABA
Interictal to Ictal transition

inhibitory synapses repetitively activated \rightarrow \text{decrease in efficacy.}

(might be desensitization of the GABA}_A_ receptor)

excitatory synapses repetitively activated \rightarrow \text{increase in efficacy}

Inhibitory surround breaks down
Cerebral cortex

GABAergic interneuron

Glutamatergic pyramidal neuron
Inhibitory surround

Excitatory center

Pyramidal cell (glutamatergic)

Inhibitory interneuron (GABAergic)

Excitatory synapse

Inhibitory synapse

Membrane potential

Inhibitory postsynaptic potential
Low interictal frequency  
No drug  
Excitatory center  
Drug (increased GABAergic activity)

High interictal frequency  
Inhibitory surround 
No seizure  
seizure
Drugs that Increase activity of $\text{GABA}_A$ receptors

Barbiturates: Phenobarbital

Benzodiazepines
- Clorazepate (Tranxene)
- Clonazepam (Klonopin)
- Clobazam (Frisium)

Topiramate (Topamax) - not fully understood
Levetiracetam (Keppra) - not fully understood
Barbiturates
Increase
Efficacy of
GABA
Increase
duration
of opening

GABA

Benzodiazepenes
potentiate GABA
binding enhance
the affinity
Increase
frequency of
channel opening

Cl⁻
Treatment of *status epilepticus* is unique:

- Diazepam (Diastat)
- Lorazepam (Atavan)
Drug choice by seizure type:
Absence (petit mal) seizures

Drugs of choice:  Ethosuximide (Zarontin)
                 Valproate (Depakote)

Alternatives:    Lamotrigine (Lamictal)
                 Clonazepam (Klonopin)
                 Zonisamide (Zonegran)
Drug choice by seizure type

Atypical absence, myoclonic, atonic seizures

Drugs of choice:  **Valproate** (Depakote)

  **Lamotrigine** (Lamictal)

Alternatives:  Clonazepam (Klonopin)

  Topiramate (Topamax)

  Zonisamide (Zonegran)

  Felbamate (Felbatol)
Drugs that block T-type Ca$^{2+}$ channels

Ethosuximide (Zarontin)

Valproate (Depakote)

Zonisamide (Zonegran)

Clonazepam at reticular thalamic nucleus*may be a unique BDZ
EEG

Absence seizure

‘Spike and wave’ activity in typical absence seizure
Awake EEG

Slow wave sleep EEG

1 sec
cortex

nucleus reticularis thalami (NRT) GABAergic neurons

Ascending arousal system and sensory afferents

Thalamic relay nucleus
Slow-wave sleep

EEG

Thalamic firing extracellular

Bursts

Waking

EEG

Thalamic firing extracellular

Bursts

Single spikes

Thalamic firing intracellular

$Ca^{2+}$ $Na^+$

Bursts

Single spikes

$50 \text{ mV}$

$0.5 \text{ s}$

$100 \text{ ms}$
Thalamic neurons

**Awake**
Relay neurons “transmission mode” to cortex (single spikes on EEG)

**Sleep**
“Burst mode” sensory information is not transmitted to cortex (T-type calcium channel is active)

**Absence seizure**
Inappropriate activation of T-type channel in an awake state
Thalamic neuron has 2 firing modes:

- **Absence seizure or slow-wave sleep**
  - Oscillatory / burst mode

- **Awake**
  - Tonic (single spike) / transmission / relay mode

Depolarization caused by ascending arousal system and sensory afferents.

- At -58 mV: One burst
- At -65 mV: 2 sec
Thalamic neurons

Voltage-dependent $\text{Na}^+$ channels
Voltage-dependent $\text{K}^+$ channels

$\text{T-type Ca}^{2+}$ channels ($I_T$)
$I_h$ channels (hyperpolarization-activated cation channels)

$\text{Na}^+$-dependent action potentials (spikes)

Pacemaker activity; enables oscillatory mode
Thalamic neuron – oscillatory mode

Burst of Na\(^{+}\)-dependent action potentials

I\(_h\) opening

I\(_T\) opening

I\(_h\) closing

I\(_T\) closing

Pacemaker potential

Ca\(^{2+}\)-dependent action potential

-65 mV

I\(_T\) recovering

0.5 sec
Thalamic neurons

At ‘awake’ resting potential: T-type Ca\(^{2+}\) channels inactivated

Hyperpolarization by NRT neurons
\((\text{GABA}_A\text{ and GABA}_B\text{ receptors})\)

\(\downarrow\)

T-type channels recover (de-inactivate)

\(\downarrow\)

Oscillatory mode

(slow-wave sleep or absence seizure)
Activation of GABA\textsubscript{B} receptors causes \textbf{hyperpolarization}
Synchronized activity in Absence seizure

Cortical neuron

Thalamic neuron

1 sec
<table>
<thead>
<tr>
<th>Drug effect</th>
<th>Suppress absence seizures</th>
<th>Exacerbate absence seizures (make them worse)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block T-type $\text{Ca}^{2+}$ channels</td>
<td>Ethosuximide</td>
<td>Valproate</td>
</tr>
<tr>
<td></td>
<td>Valproate</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Activate $\text{GABA}_A$ receptors</td>
<td>Clonazepam</td>
<td>Barbiturates</td>
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<tr>
<td>Increase GABA levels</td>
<td>Valproate</td>
<td>Tiagabine</td>
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<td></td>
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<td>Vigabatrin</td>
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<tr>
<td></td>
<td>Generalized Tonic-clonic</td>
<td>Partial</td>
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<td>--------------------------</td>
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<td>---------------------------------------------</td>
</tr>
<tr>
<td>Block Na(^+) channels</td>
<td>val, car, pht, lam, top, zon, oxc, fel</td>
<td>car, pht, val lam, gab, top zon, oxc, fel</td>
</tr>
<tr>
<td>Block T-type Ca(^{2+})</td>
<td>val, zon</td>
<td>val, zon</td>
</tr>
<tr>
<td>Activate GABA(_A)</td>
<td>barb</td>
<td>barb, bzd, top, lev</td>
</tr>
<tr>
<td>Increase GABA levels</td>
<td>val</td>
<td>val, gab, tia, vig</td>
</tr>
</tbody>
</table>
Drug treatment of seizures

Modes of action

Block $\text{Na}^+$ channels

Block T-type $\text{Ca}^{2+}$ channels

Enhance $\text{GABA}_A$ receptor activity

Increase $\text{GABA}$ synthesis

block $\text{GABA}$ degradation

block $\text{GABA}$ reuptake

Increase $\text{GABA}$ levels

Inhibit glutamate receptors?

Block L-type $\text{Ca}^{2+}$ channels?

Multiple actions, e.g. valproate
Glutamate

Postsynaptic neuron

Presynaptic terminal

Ca\(^{2+}\) channel (not T-type)

GABA?, FEL, LAM, HCBZ

Na\(^+\) channel

TOP

NMDA receptor

AMPA/kainate receptor

FEL

Ca\(^{2+}\), Na\(^+\) channel

CAR, PHT, VAL, LAM, GABA, TOP, ZON, OXC, FEL

Glutamate

Na\(^+\), Ca\(^{2+}\) channel

Postsynaptic neuron

FEL

NMDA receptor

AMPA/kainate receptor

TOP
Epileptogenesis

Changes in gene expression or protein function

NMDA receptors
   Altered subunit expression in epileptic cortex

AMPA receptors
   Increased expression in epileptic cortex

GABA$_A$ receptors
   Decreased expression in epileptic cortex

‘A-type’ K$^+$ channels
   Lost in epileptic hippocampus

Genetics – nACh receptor
Loss of ‘A-type’ $K^+$ channels
Axonal sprouting
SUMMARY

Epilepsy is characterized by recurrent seizures

Epilepsy has many different causes

Seizures are due to abnormal electrical activity in the brain

There are different types of seizure

Status epilepticus is life threatening
We can make some rationalizations about relationships between mode of drug action and seizure type.

Voltage/frequency/use-dependent block of voltage-gated Na\(^+\) channels suppresses high frequency firing in tonic-clonic and partial seizures.
Main points (continued)

Interictal discharges are abnormal (may be contained in a focus no symptomatic pathology but seen on EEG)

An increase in interictal activity may lead to a seizure by breaking down the inhibitory surround.

Drugs that increase GABAergic transmission may suppress partial seizures by enhancing the inhibitory surround.
Synchronized thalamocortical rhythms occur in slow-wave sleep and absence seizures.

Hyperpolarization of thalamic neurons allows the T-type Ca\(^{2+}\) channels to recover from inactivation.

T-type Ca\(^{2+}\) channels are required for the oscillatory mode of the thalamus.

Drugs that block T-type Ca\(^{2+}\) channels can suppress absence seizures.

Drugs that increase GABA levels can exacerbate absence seizures.
Epileptogenesis is a poorly understood process in which an initial event leads to the development of epilepsy.

We don’t have any drugs that prevent epileptogenesis.

Available antiepileptics only control seizures.