Antiepileptic agents

Excessive excitability of neurons in the CNS

- Abnormal function of ion channels
- Spread through neural networks

Abnormal neural activity leads to abnormal motor activity

Suppression of neural activity and it spread
Controlling neuronal activity

- Na+ channel activation for excitability
- Na+ channel inactivation
- K+ channel activation for hyperpolarization

Intrinsic limitations on neuronal activity
Controlling neuronal activity

- The role of neural networks in limiting the spread of activity
- Inhibitory (GABA) signals to surrounding neurons
- Surround inhibition
- The role of surround inhibition in preventing seizures
Generation of seizures

A focus - a group of neurons with synchronous, high frequency discharge
Pathophysiology of seizures

Synchronization of surrounding neurons

Loss of “Surround Inhibition”

- Decrease in GABA-mediated inhibition
- Repetitive firing increases extracellular K+
- Depolarization induced opening of NMDA channels — accumulation of Ca²⁺ in terminals
Generation of seizures

- A focus - a group of neurons with synchronous, high frequency discharge

- Causes - genetic defects, hypoxia at birth, head trauma, tumor

- Dysfunction of ion channels - Channelopathies

- Loss of ‘Surround Inhibition’

- Spread of discharge from the focus to other areas of brain

- The nature of seizure depends on the location of the focus and connections of the neurons
Types of seizures

Partial or local seizures - starting at a focus, with limited spread, e.g., in a single limb

Generalized seizures - widespread seizure activity involving both hemispheres
Partial seizures

Starting at a focus - limited spread

Simple partial - symptoms depend on location of abnormal activity in the brain - Examples:

- Involuntary, rapid movement (motor cortex)
- Paresthesias (sensory cortex)
- Flashing lights (visual cortex)

Complex partial - confused behavior and impairment of consciousness

Partial with secondary generalization
Generalized seizures

Tonic-clonic seizures (Grand Mal): muscle rigidity followed by synchronous muscle jerks

Myoclonic seizures: sudden muscle contractions
Generalized seizures

Absence seizures (Petit Mal): Very frequent but brief (10-30 s) episodes of loss of consciousness

Atonic seizures: sudden loss of muscle tone

Febrile seizures: fever-associated seizures in children (6 months - 5 years)

Status epilepticus: seizure activity that persists for a long time
Secondary generalization of partial seizures

For sufficiently strong focal activity - spread to neighboring regions of the cortex

Spread between hemispheres via Corpus Callosum

Thalamocortical projections for spread to various regions of the brain
Action of antiepileptic drugs

- Suppression of neuronal discharge within the focus
- Suppression of propagation of seizure activity
**Suppression of sodium influx**

These drugs suppress sodium influx through voltage-gated Na⁺ channels, reducing excitability.

Closed, open and inactivated states

![Diagram of sodium channel states](image)

- **Resting state (closed)**
  - S4 regions
  - Linker region

- **Activated state (open)**
  - Na⁺ influx

- **Inactivated state (closed)**
  - Extracellular
  - Intracellular
Enhanced Na\(^+\) channel inactivation

Some antiseizure drugs (shown in blue text) prolong the inactivation of the Na\(^+\) channels, thereby reducing the ability of neurons to fire at high frequencies. Note that the inactivated channel itself appears to remain open, but is blocked by the inactivation gate (I). A, activation gate.
Prolongation of Na+ channel inactivation

Quick recovery from inactivation in normal neurons

Prolongation of inactivated state by drugs

Resultant suppression of high frequency discharge

Phenytoin, carbamazepine, valproate, lamotrigine
Effect on neuronal excitability


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Suppression of Ca2+ influx

- Voltage-gated Ca2+ channels, influx, excitability
- Voltage-gated T-type Ca2+ channels in absence seizures
- Inhibition of voltage-gated T-type Ca2+ channels by drugs
- Resultant suppression of high frequency discharge
- Valproate, ethosuximide
Some antiseizure drugs (shown in blue text) reduce the flow of Ca$^{2+}$ through T-type Ca$^{2+}$ channels (see Chapter 12), thus reducing the pacemaker current that underlies the thalamic rhythm in spikes and waves seen in generalized absence seizures.
**Potentiation of GABA action**

GABA as an inhibitory neurotransmitter

**Inhibitory synapse**

- **Presynaptic neuron**
- **Action potential**
- **Ca^{2+}**
- **GABA release**

**Postsynaptic membrane**

- **Cl^-**

Diagram showing the interaction of GABA with the membrane, leading to hyperpolarization and inhibition.
Potentiation of GABA action

GABA as an inhibitory neurotransmitter

Increased GABA action by binding directly to GABA receptors - benzodiazepines and barbiturates

Increased GABA action by prolonging presence of GABA in the synapse - tiagabine

Increased GABA action by inhibiting the enzyme that degrades GABA - vigabatrin
Enhanced GABA synaptic transmission
Objectives of the lecture on Abnormal Electric Activity and Antiepileptic Drugs are to understand:

- the role of abnormal electric activity in generating epileptic phenomena
- the role of ion channels and receptors in generating and spreading abnormal electric activity
- the role played by inhibitory neural circuits in preventing the spread of abnormal neuronal activity
- various types of seizures
- approaches to suppress abnormal electric activity and its spread through neural networks
- antiepileptic drugs and the mechanisms underlying their action