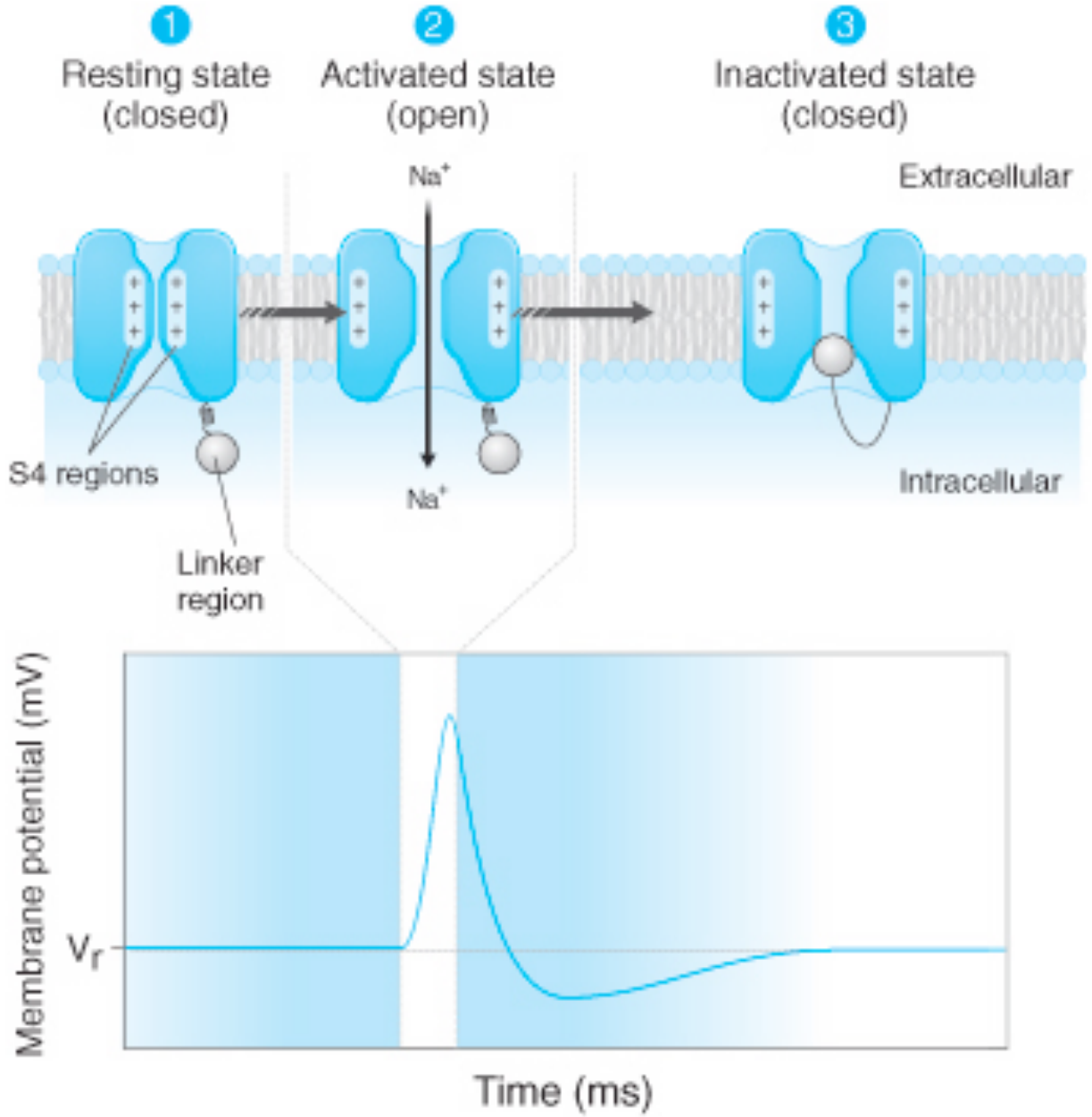
Antiepileptic agents

- 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

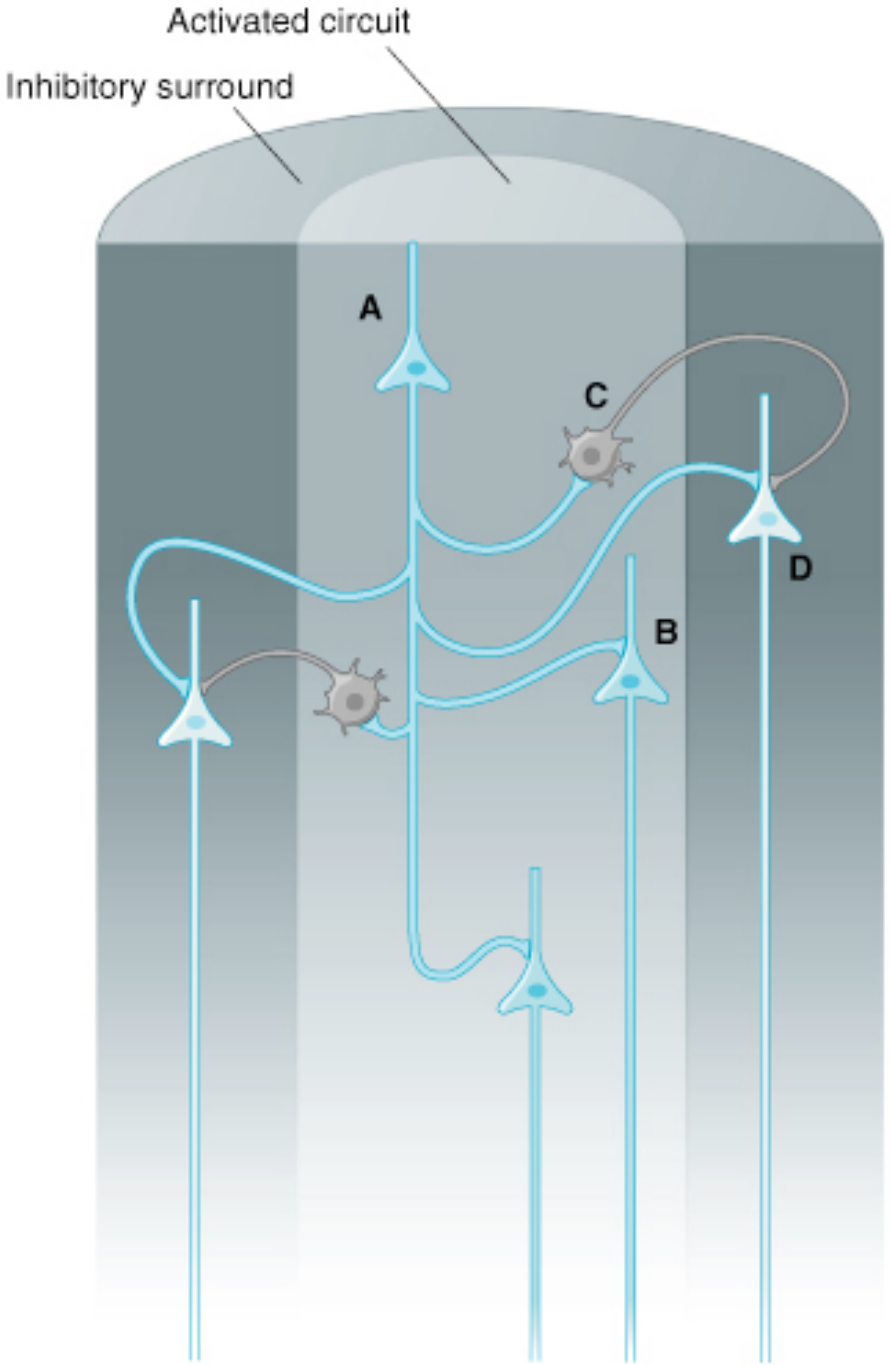
- Na+ channel activation for excitability
- Na+ channel inactivation
- K+ channel activation for hyperpolarization



Intrinsic limitations on neuronal activity

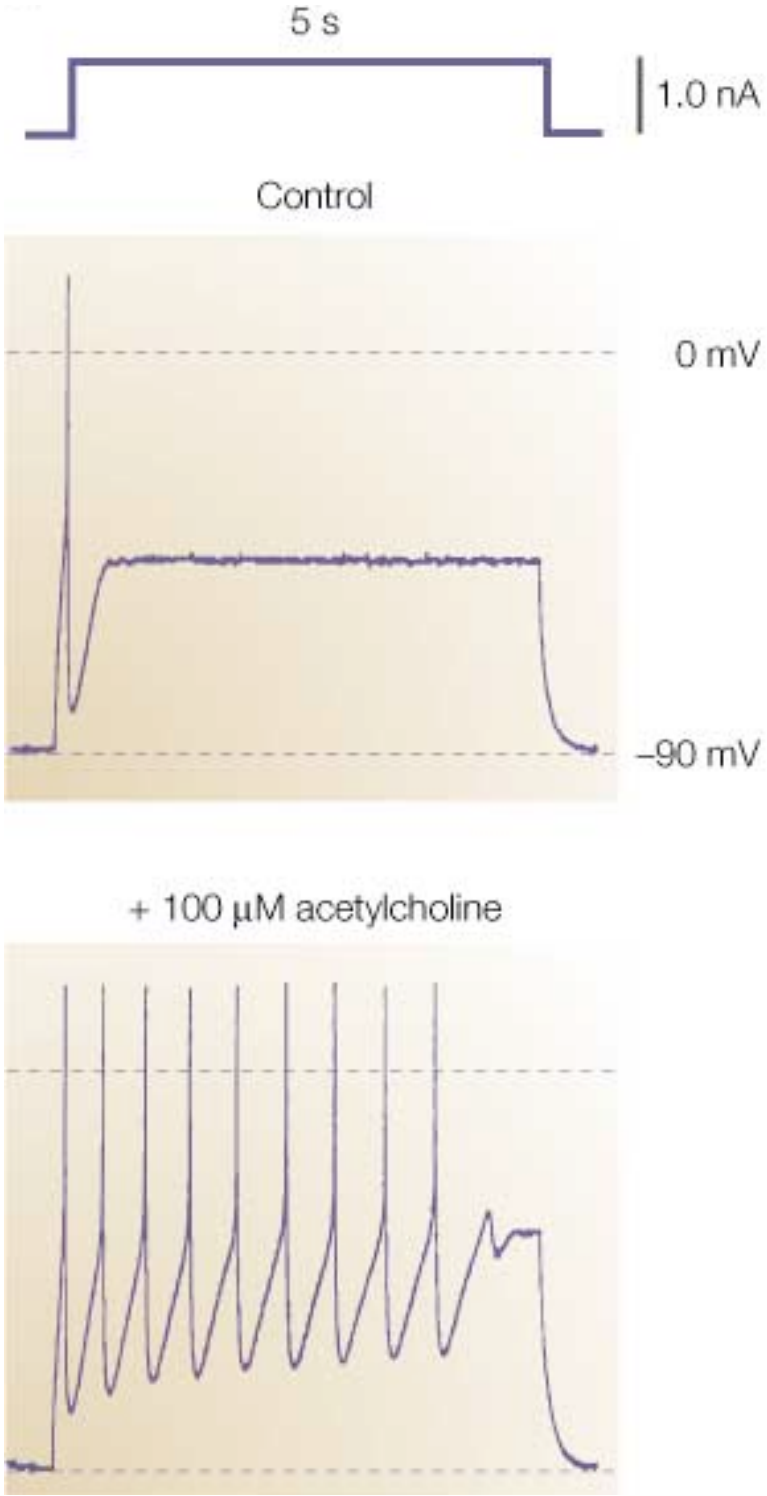
Controlling neuronal activity

- 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



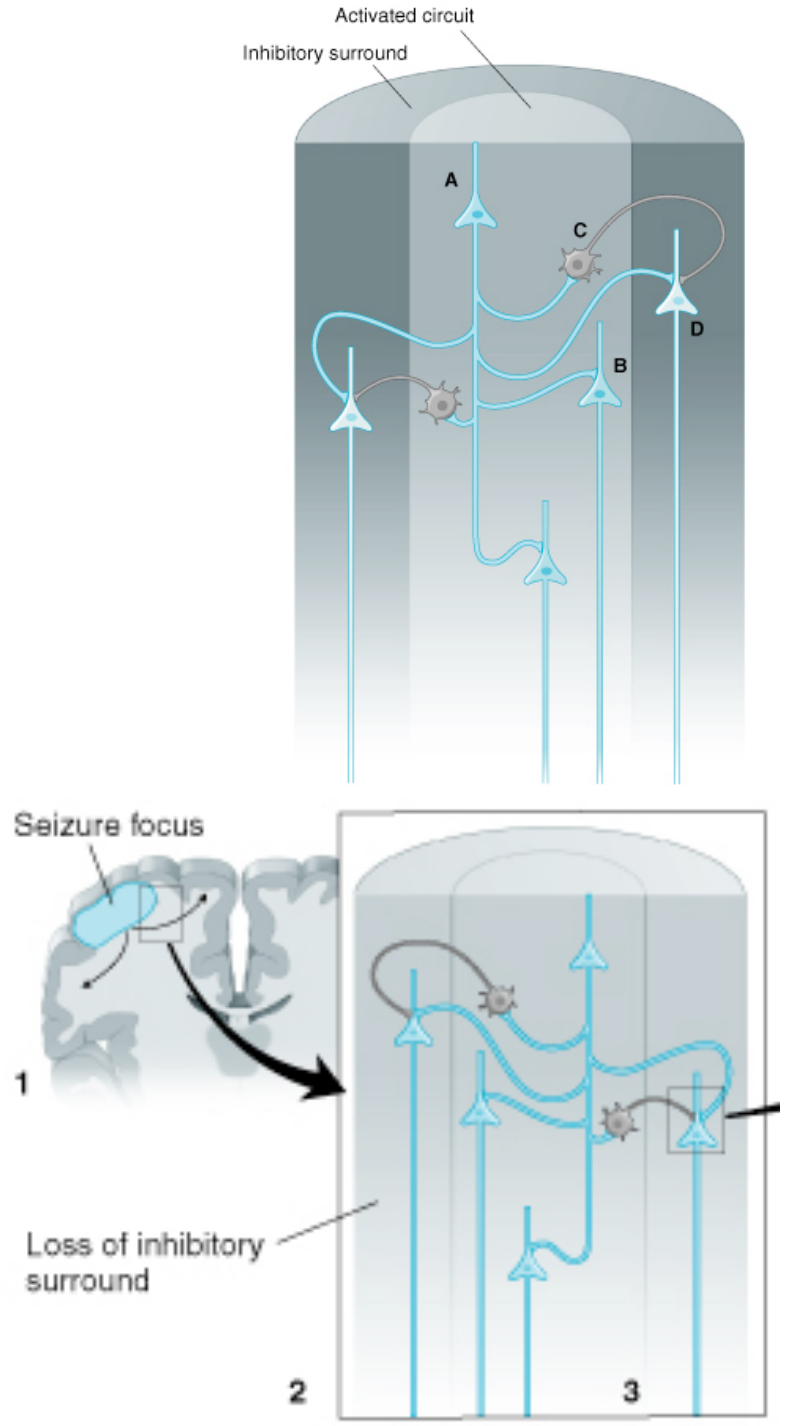
Generation of seizures

- 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

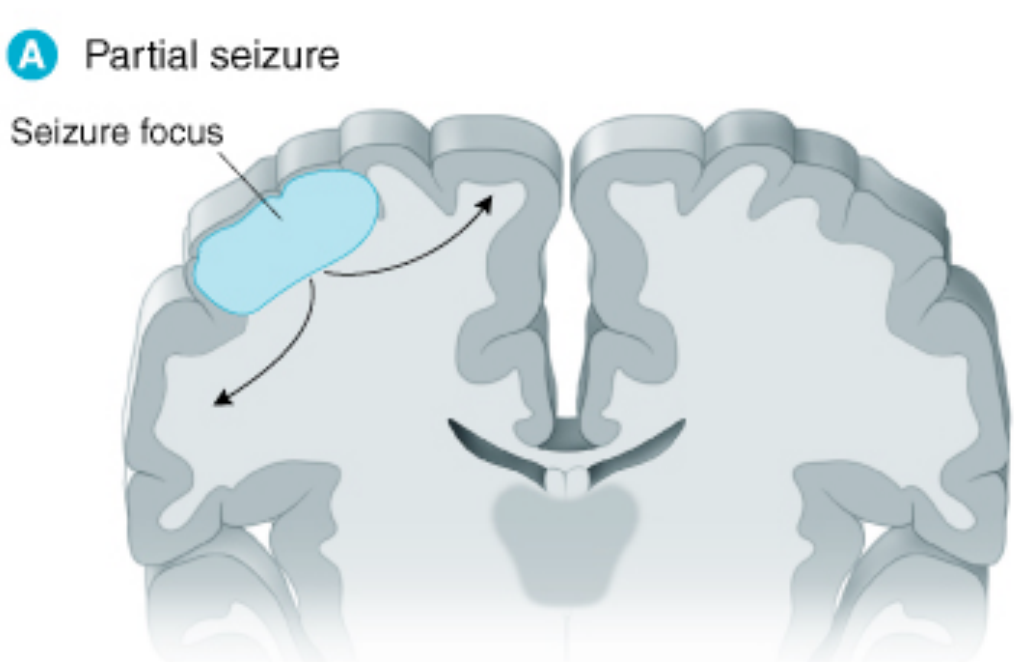


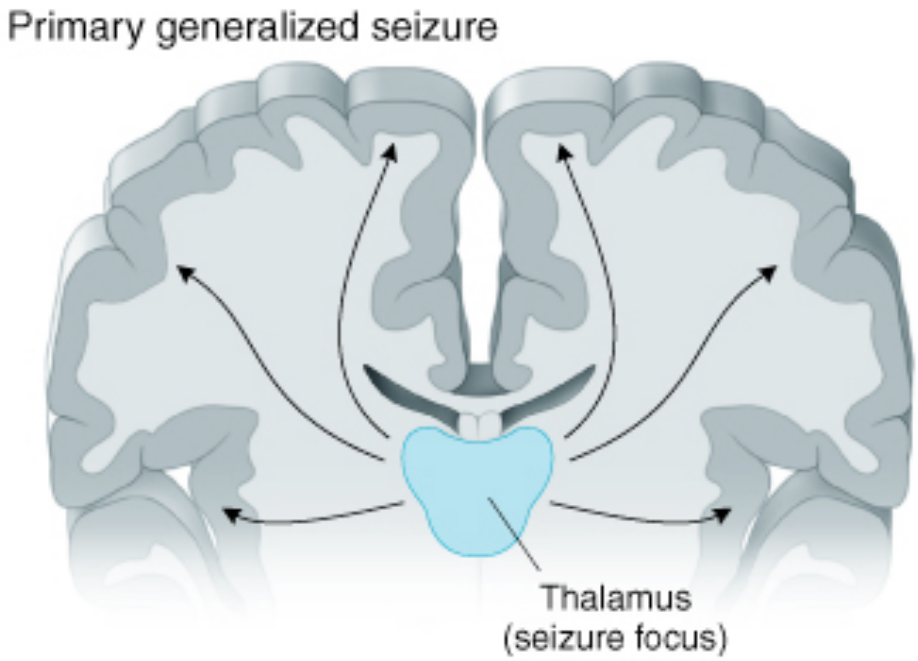
Generation of seizures

- 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

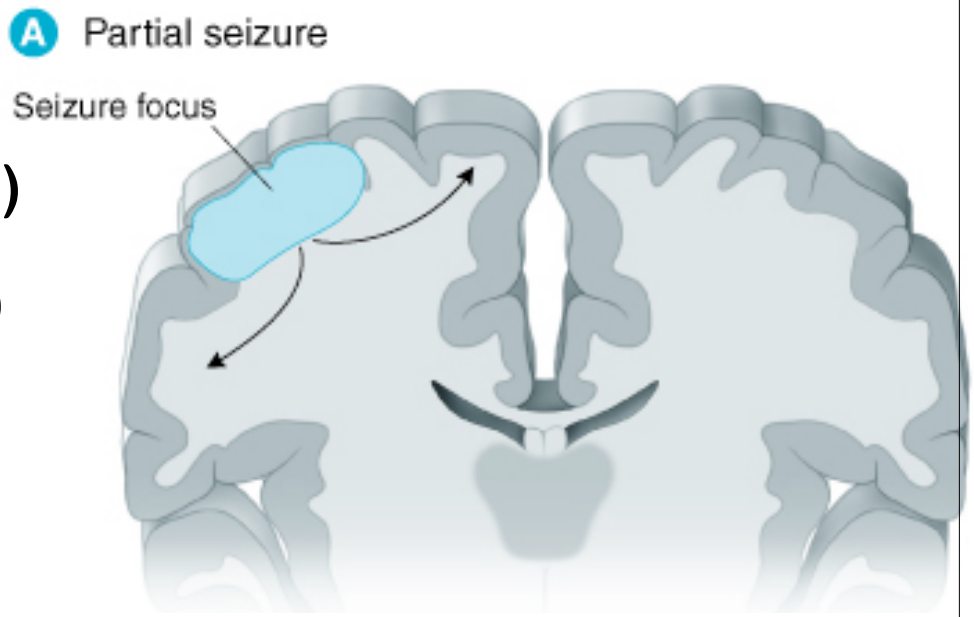
- Partial or local seizures - starting at a focus, with limited spread, e.g., in a single limb
- Generalized seizures - widespread seizure activity involving both hemispheres





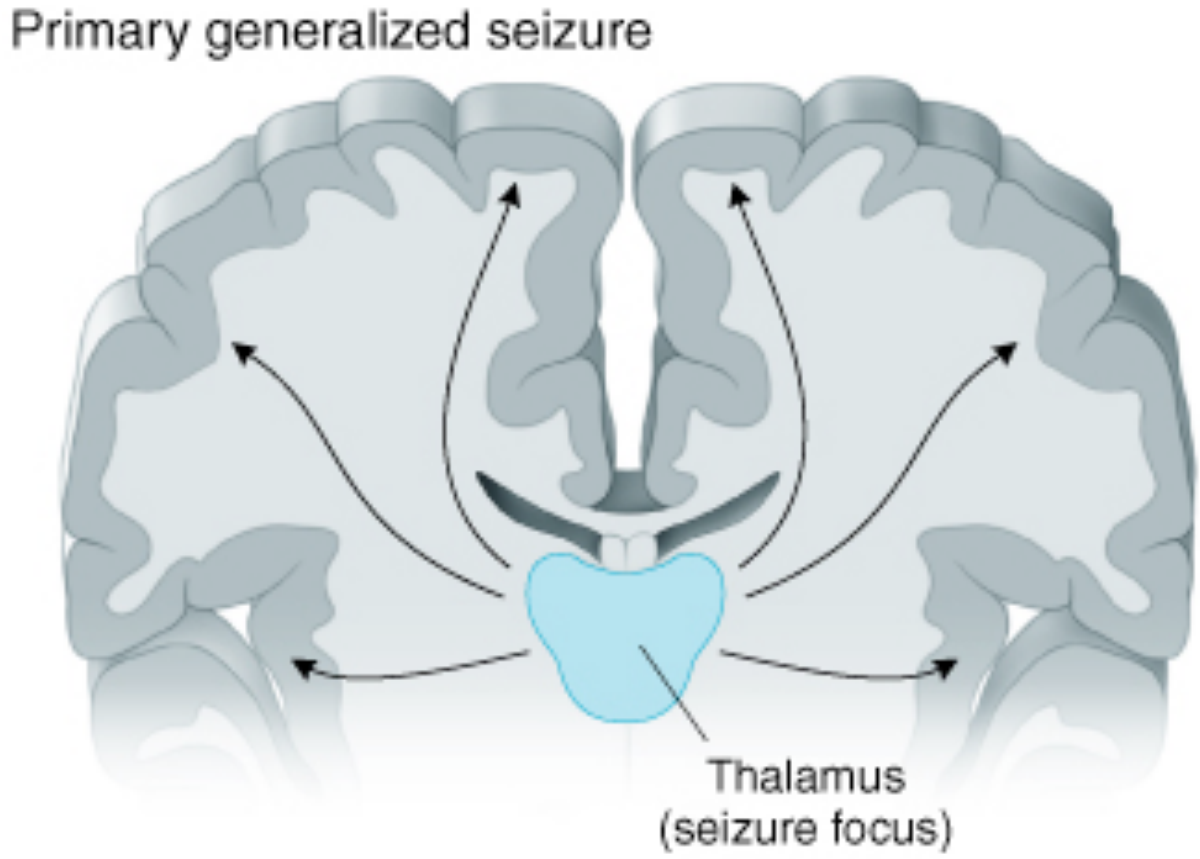
Partial seizures

- 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

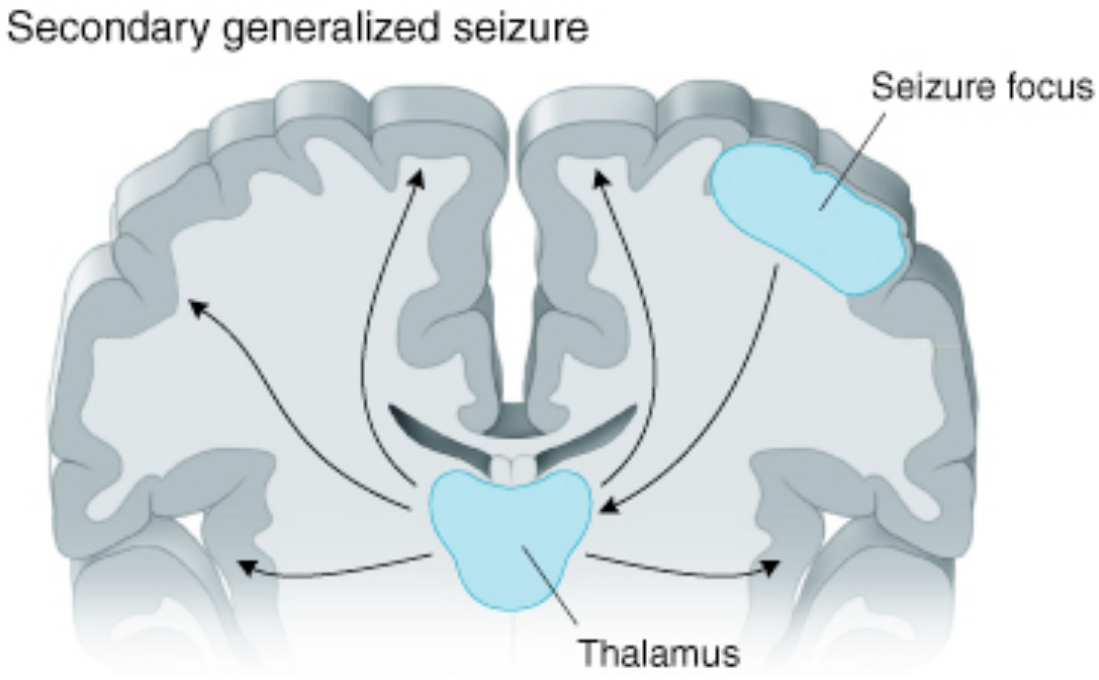


Generalized seizures

- 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

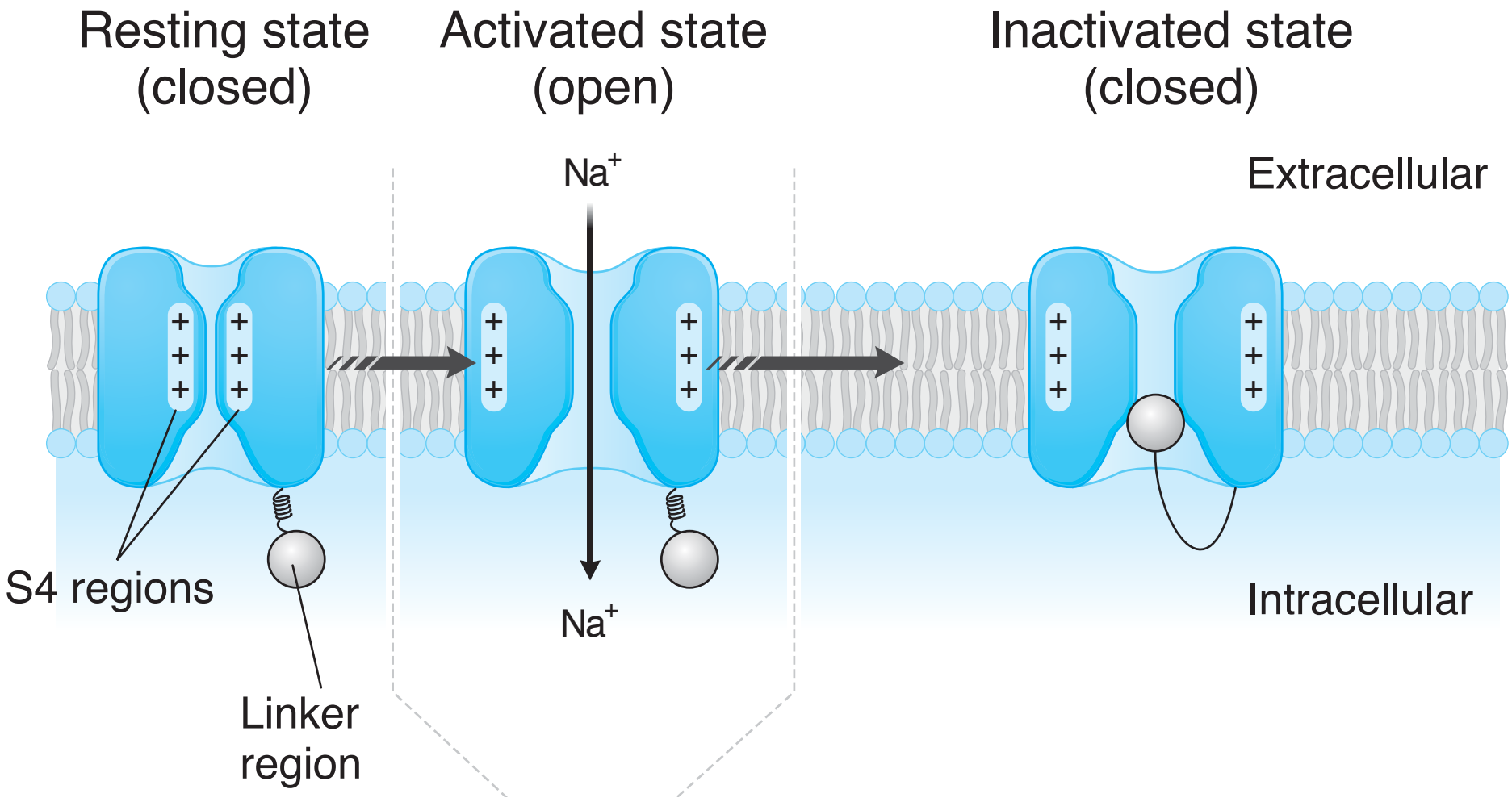


Action of antiepileptic drugs

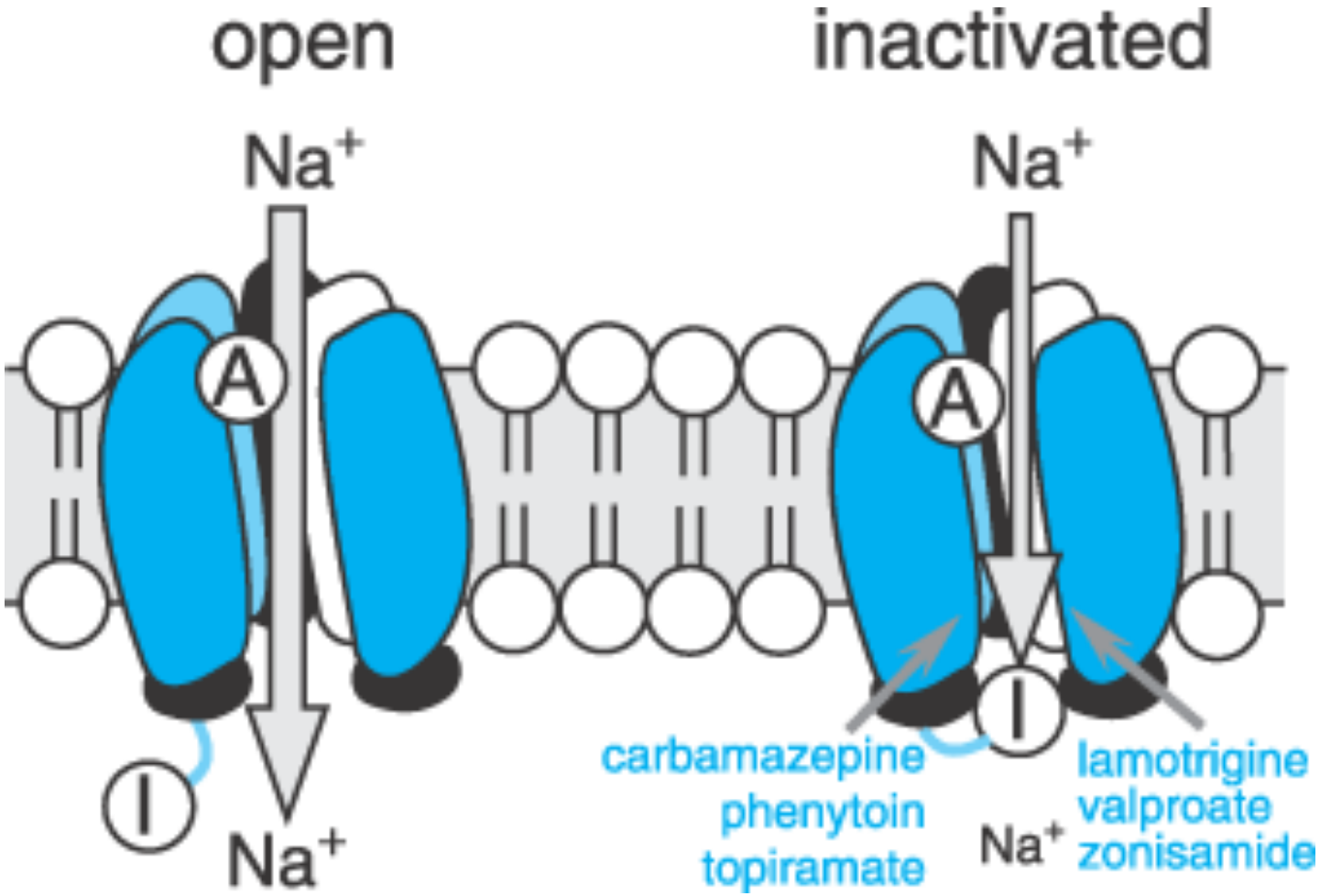
- Suppression of neuronal discharge within the focus
- Suppression of propagation of seizure activity

Suppression of sodium influx

- These drugs suppress sodium influx through voltage-gated Na+ channels, reducing excitability
- Closed, open and inactivated states



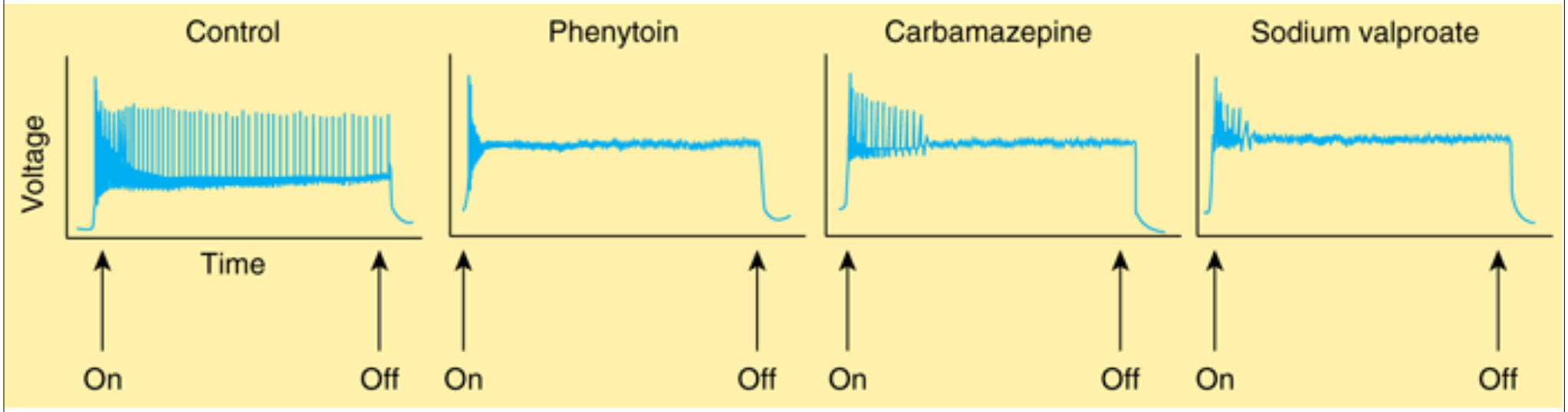
Enhanced Na+ channel inactivation



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

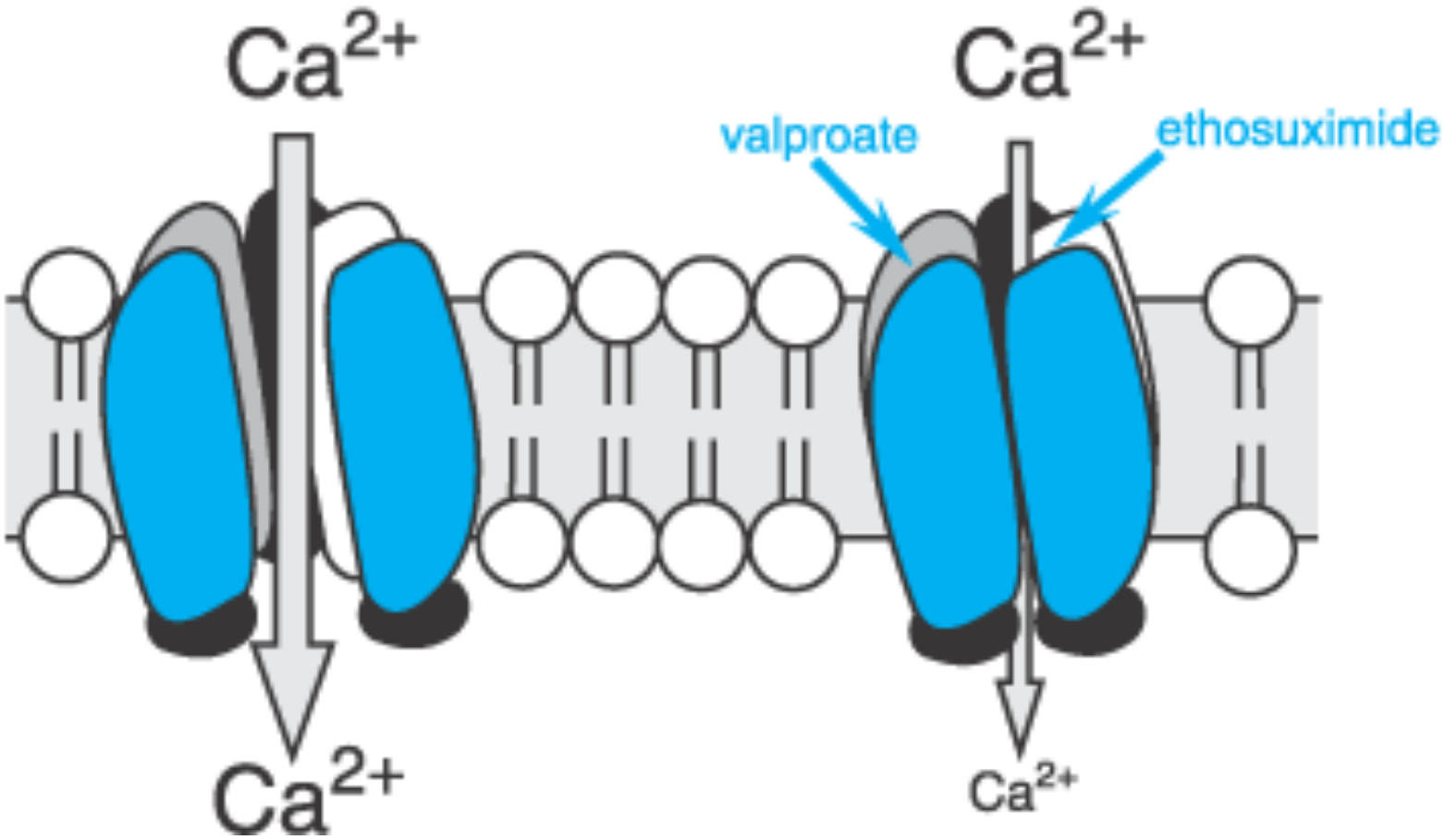


Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Suppression of Ca2+ influx

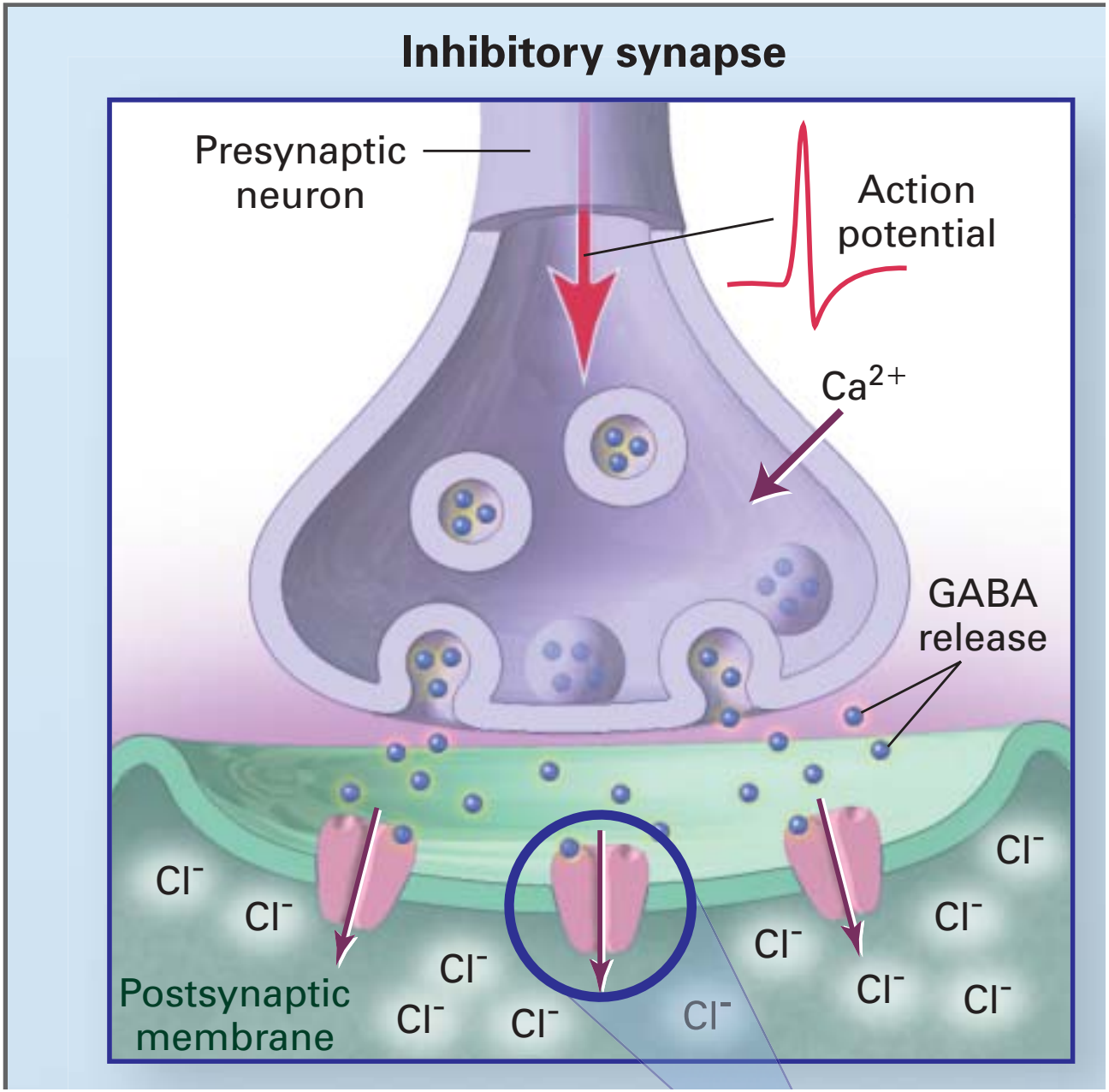
- Voltage-gated Ca2+ channels, influx, excitability
- Voltage-gated T-type Ca2+ channels in absence seizures
- Inhibition of voltage-gated T-type Ca2+ channels by drugs
- Resultant suppression of high frequency discharge
- Valproate, ethosuximide

Reduced Ca2+ current



Potentiation of GABA action

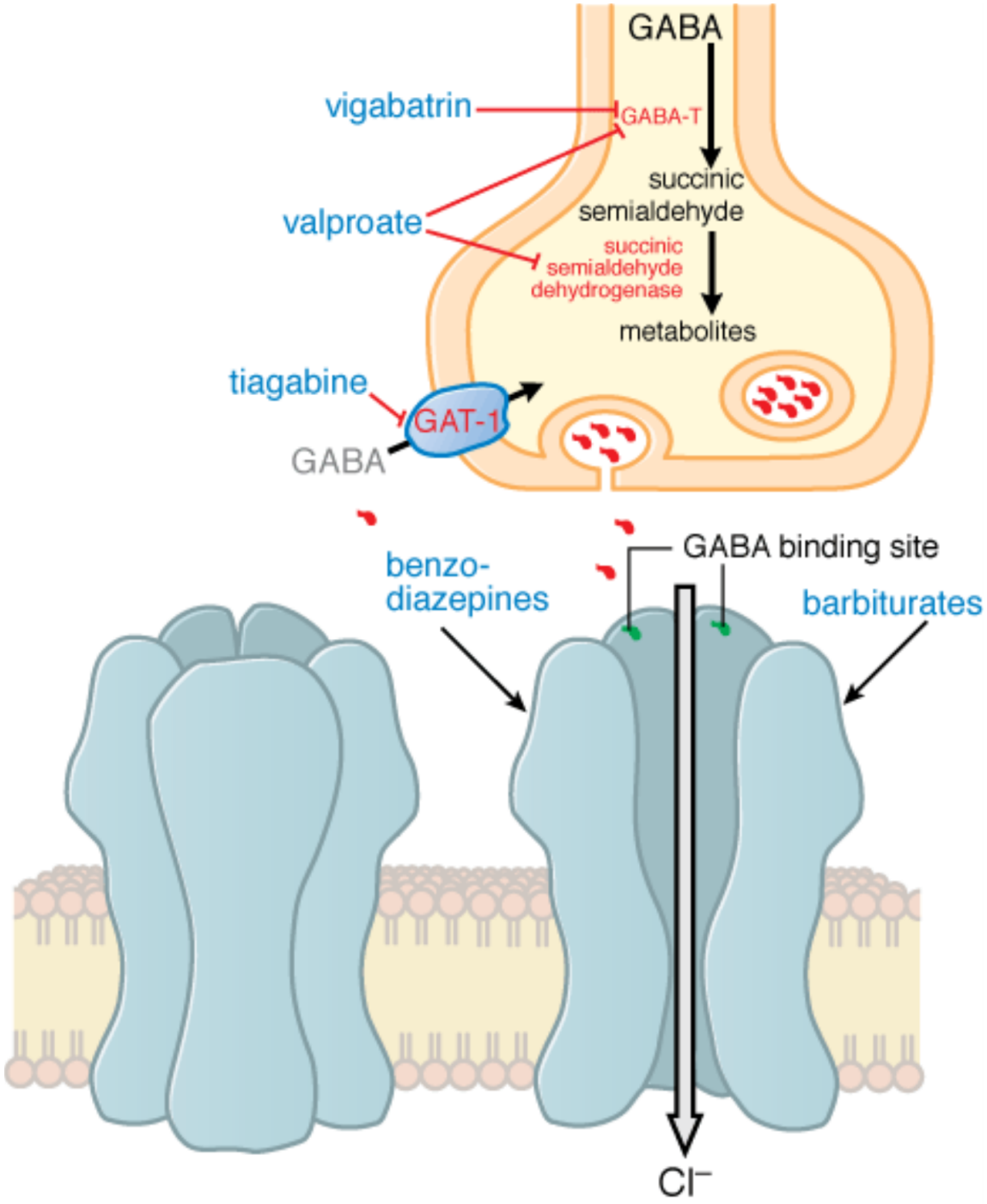
GABA as an inhibitory neurotransmitter



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