# Antiepileptic Drugs

By

Y. Chandravadana,
Associate professor,
Krishna Teja Pharmacy college, Tirupati .

# Treatment

- Try to find a cause. (e.g. fever, head trauma, drug abuse)
  - Recurrent seizures that cannot be attributed to any cause are seen in patients with epilepsy.
- Therapy is aimed at control
  - *drugs do not cure.*
- *The type of seizure determines the choice of drug!*
- More than 80% of patients with epilepsy can have their seizures controlled with medications.

# Treatment

- Monotherapy with anticonvulsant
  - Increase dose gradually until seizures are controlled or adverse effects become unacceptable.
  - Multiple-drug therapy may be required.
- Achieve steady-state kinetics
- Monitor plasma drug levels
- Avoid sudden withdrawal

# Pharmacokinetics

- Most classical antiepileptic drugs exhibit similar pharmacokinetic properties.
- Good absorption.
- Low plasma protein binding (except for phenytoin, BDZs, valproate, and tiagabine).
- Conversion to active metabolites (carbamazepine, primidone, fosphenytoin).
- Cleared by the liver but with low extraction ratios.
- Distributed in total body water.
- Plasma clearance is slow.
- At high concentrations phenytoin exhibits zero order kinetics.

# Therapeutic Range

| Drug | Effective Level (μg/mL) | High Effective Level[2] (μg/mL) | Toxic Level (μg/mL) |
|---|---|---|---|
| Carbamazepine | 4–12 | 7 | > 8 |
| Primidone | 5–15 | 10 | < 12 |
| Phenytoin | 10–20 | 18 | > 20 |
| Phenobarbital | 10–40 | 35 | > 40 |
| Ethosuximide | 50–100 | 80 | > 100 |
| Valproate | 50–100 | 80 | > 100 |

Nausea and vomiting

Drowsiness-sedation

Ataxia

Rash

Hyponatremia


Weight gain
or
Weight loss

Teratogenicity

Osteoporosis

Notable adverse effects of antiseizure medications.

# Treatment of Seizures

**Strategies:**

- Modification of ion conductances.
- Increase inhibitory (GABAergic) transmission.
- Decrease excitatory (glutamatergic) activity.

# Drug treatment of seizures

- Life-long treatment may be necessary.
- It may take weeks to establish adequate drug plasma levels and to determine the adequacy of therapeutic improvement.
- **Lack of compliance** is responsible for many treatment failures.

# Classification of epilepsies and drug selection.

1. **Partial seizures**
    1. **Carbamazepine, phenytoin**
    2. Valproic acid, lamotrigine, gabapentin, benzodiazepines, barbiturates
    3. Adjunct: Tiagabine, topiramate, levetiracetam, zonisamide

## 2. Generalized seizures:

### A. Tonic-clonic (grand mal):

1. **Carbamazepine, phenytoin**
2. Valproic acid, lamotrigine, gabapentin, benzodiazepines, barbiturates
3. Adjunct: Topiramate, zonisamide

## B. Absence (petit mal):

1. **Ethosuximide**
2. Valproic acid (when absence seizures coexist with tonic-clonic seizures)
3. Clonazepam
4. Adjunct: Lamotrigine, benzodiazepines

## C. Myoclonic syndromes:

1. **Valproic acid**
2. Clonazepam and other benzodiazepines
3. Adjunct: levetiracetam

## 3. Status epilepticus:

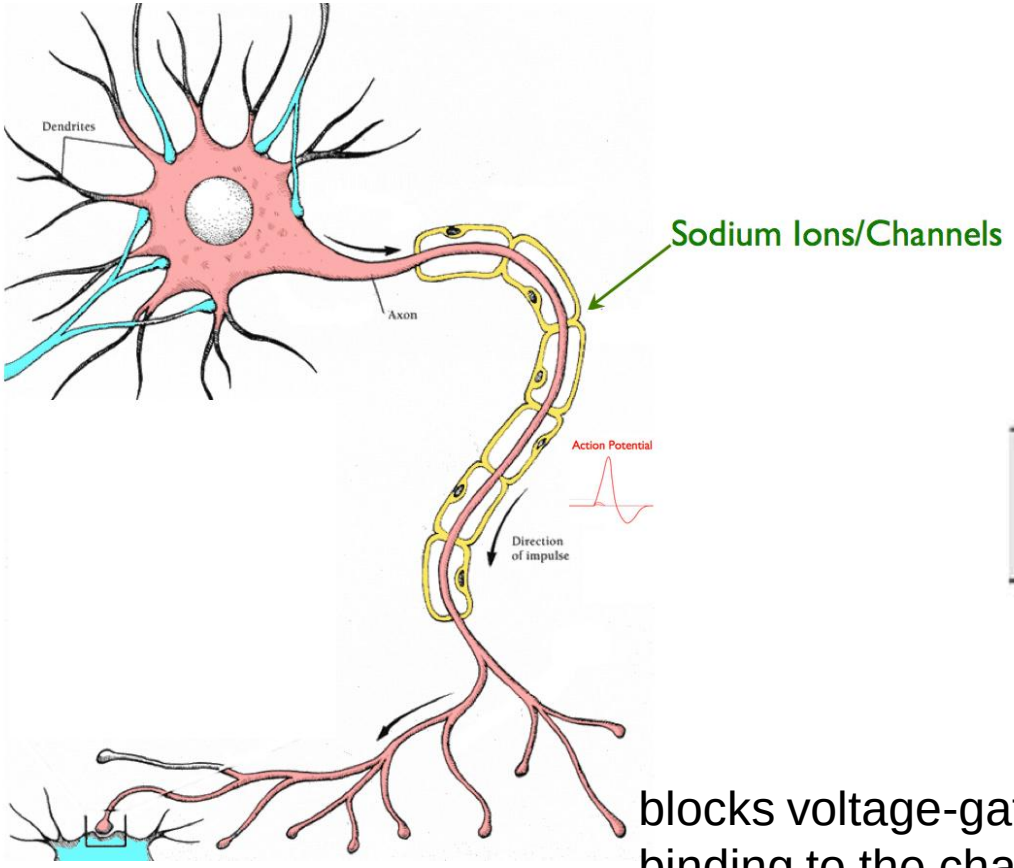
- Treatment is **intravenous diazepam** or **lorazepam** followed by **intravenous fosphenytoin** (or phenytoin) or **phenobarbital.**

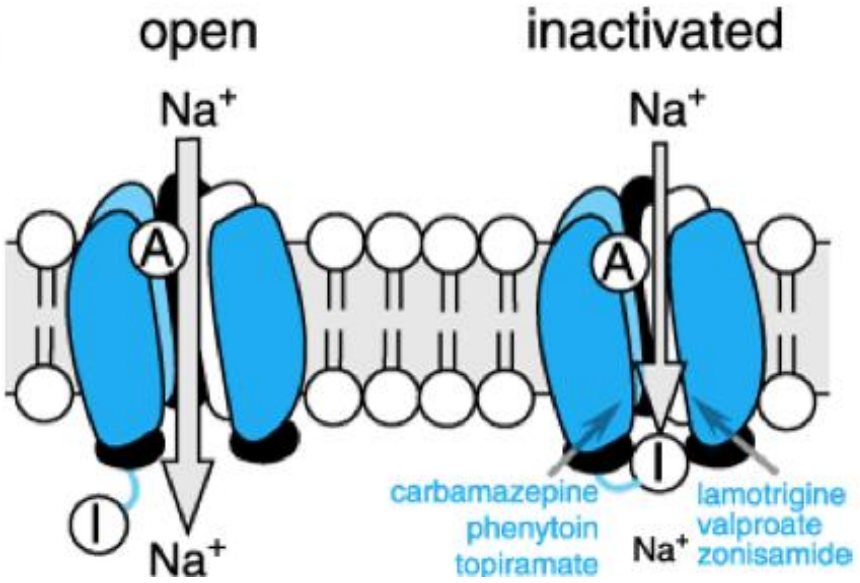
# Mechanisms of Action

- 3 main categories of therapeutics:

1. Inhibition of voltage-gated Na+ channels to slow neuron firing.
2. Enhancement of the inhibitory effects of the neurotransmitter GABA.
3. Inhibition of calcium channels.

# I. Na+ Channel Inhibitors




blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery

# Na+ Channel Inhibitors

- Phenytoin (Dilantin, Phenytek)
- Fosphenytoin (Cerebyx)
- Carbamzepine (Tegretol, Carbatrol)
- Oxcarbazepine (Trileptal)
- Valproic Acid (Valproate; Depakene, Depakote)
- Lamotrigine (Lamictal)
- Topiramate (Topamax)
- Zonisamide (Zonegran)

# Na+ Channel Inhibitors

1. Phenytoin (Dilantin, Phenytek):

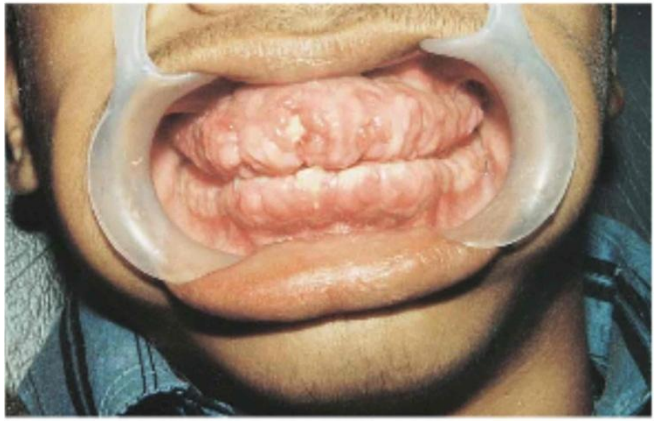
- Oldest nonsedative antiepileptic drug.
  - Indications:
    - First choice for partial and generalized tonic-clonic seizures
    - Some efficacy in clonic, myoclonic, atonic,
    - No effect on infantile spasms or absence seizures
  - Drug Interactions:
    - Decreases blood levels of many medications
    - Increases blood levels of phenobarbital & warfarin

# Na+ Channel Inhibitors

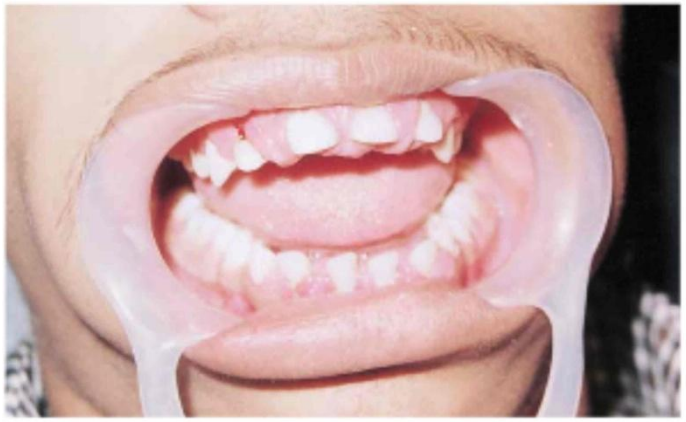
Phenytoin (Dilantin, Phenytek):

- Adverse Effects:
  - Hirsutism & coarsening of facial features
  - Acne
  - Gingival hyperplasia (20-40%)
  - Decreased serum concentrations of folic acid, thyroxine, and vitamin K with long-term use.
- "Fetal hydantoin syndrome":
- includes growth retardation, microencephaly, and craniofacial abnormalities (e.g., cleft palate) and is possibly due to an epoxide metabolite of phenytoin.

# Phenytoin Induced Gingival Hyperplasia



17 year old boy treated with 300mg/day phenytoin for 2 years (unsupervised)



Partial recovery at 3 months after discontinuation

- *Fosphenytoin* is a prodrug
- rapidly converted to *phenytoin* in the blood, providing high levels of *phenytoin* within minutes.
- *Fosphenytoin* may also be administered intramuscularly (IM).
- *Phenytoin sodium* should never be given IM because it can cause tissue damage and necrosis.
- Fosphenytoin is the drug of choice and standard of care for IV and IM administration.
- Due to sound-alike and look-alike names, there is a risk for medication error to occur.
  - The trade name of *fosphenytoin* is Cerebyx®
  - Celebrex®, the cyclooxygenase-2 inhibitor
  - Celexa®, the antidepressant.

# Na+ Channel Inhibitors

2. Carbamzepine (Tegretol, Carbatrol):

- Tricyclic, antidepressant (bipolar)
  - Indications:
    - First choice for complex partial and generalized tonic-clonic seizures.
  - Contraindications:
    - May exacerbate absence or myoclonic seizures.
    - Blood disorders
    - Liver disorders

# Na+ Channel Inhibitors

## Carbamazepine (Tegretol, Carbatrol):

- Drug Interactions:
  - CBZ metabolism is affected by many drugs, and CBZ affects the metabolism of many drugs.
- Determination of plasma levels and clearance may be necessary for optimum therapy.

- **Adverse Effects:**
  - **Common:** Diplopia and ataxia (most common), gastrointestinal disturbances; sedation at high doses
  - **Occasional:** Retention of water and hyponatremia; rash, agitation in children
  - **Rare:** Idiosyncratic blood dyscrasias and severe rashes

3. Oxcarbazepine (Trileptal):
   - FDA approved in 2000 for partial seizures
     - Complex partial seizures
     - Primary & secondarily generalized tonic-clonic seizures
   - Is a prodrug whose actions are similar to those of carbamazepine; it has a short half-life of 1—2 hour.
   - Its activity is due to a 10-hydroxy metabolite with a half-life of 10 hours.
   - Fewer adverse effects than CBZ, phenytoin

# Na+ Channel Inhibitors

4. Valproic Acid (Valproate; Depakene, Depakote):
   - Other Mechanisms of Action:
     1) Some inhibition of T-type Ca2+ channels.
     2) Increases GABA production and decreases GABA metabolism. (Inhibition of GABA transaminase )
   - Indications:
     - Simple or complex partial, & primary generalized tonic-clonic
     - Also used for absence, myoclonic, and atonic seizures.
     - Highly effective for photosensitive epilepsy and juvenile myoclonic epilepsy.
   - Contraindications:
     - Liver disease

# Na+ Channel Inhibitors

4. Valproic Acid (Valproate; Depakene, Depakote):

   – Drug Interactions:

     • Affects metabolism of many drugs through liver enzyme inhibition

# Na+ Channel Inhibitors

4. Valproic Acid (Valproate; Depakene, Depakote):

– Adverse Effects:

- Weight gain (30-50%)
- Dose-related tremor
- Transient hair loss
- Polycystic ovary syndrome and menstrual disturbances
- Bone loss
- Ankle swelling

# Na+ Channel Inhibitors

5. Lamotrigine (Lamictal):
   - Other Mechanism of Action:
     - May inhibit synaptic release of glutamate.
   - Indications:
     - Adjunct therapy (ages 2 & up):
       - Simple & complex partial seizures
       - Generalized seizures of Lennox-Gastaut Syndrome
     - Monotherapy (adults):
       - Simple & complex partial seizures
   - Contraindications:
     - May make myoclonic seizures worse.

# Lennox-Gastaut syndrome

- is the most distressing of childhood epilepsies.
- The children suffer frequent fits of many different types, and experience gradual mental deterioration.
- Infantile spasms often evolve into Lennox-Gastaut syndrome, and the age of onset is from 1 to 8 years, peaking at 3 to 5 years.

# Na+ Channel Inhibitors

5. Lamotrigine (Lamictal):

   - Adverse Effects:
     - Rash (10%)
       - Rare progression to serious systemic illness
     - Increased alertness

# Na+ Channel Inhibitors

6. Topiramate (Topamax):

- Other Mechanism of Action:
  - Enhances post-synaptic GABAA receptor currents.
  - Kainate receptor antagonist (blocks a certain type of glutamate channel)

- Indications:
  - Adjunct therapy for partial and primary generalized
  - seizures in adults and children over 2.
  - Decreases tonic and atonic seizures in children with Lennox-Gastaut syndrome.
- Contraindications:
  - History of kidney stones

# Na+ Channel Inhibitors

6. Topiramate (Topamax):

– Drug Interactions:

- CBZ, phenytoin, phenobarbital, & primidone decrease blood levels

– Adverse Effects:

- Nervousness & paresthesias
- Psychomotor slowing, word-finding difficulty, impaired concentration, interference with memory
- Weight loss & anorexia
- Metabolic acidosis

# Na+ Channel Inhibitors

7. Zonisamide (Zonegran):

- is a sulfonamide derivative that has a broad spectrum of action
  - Other Mechanism of Action:
    - Inhibits T-type Ca2+ currents.
    - Binds to GABA receptors.
    - Facilitates dopaminergic and serotonergic neurotransmission.

# Na+ Channel Inhibitors

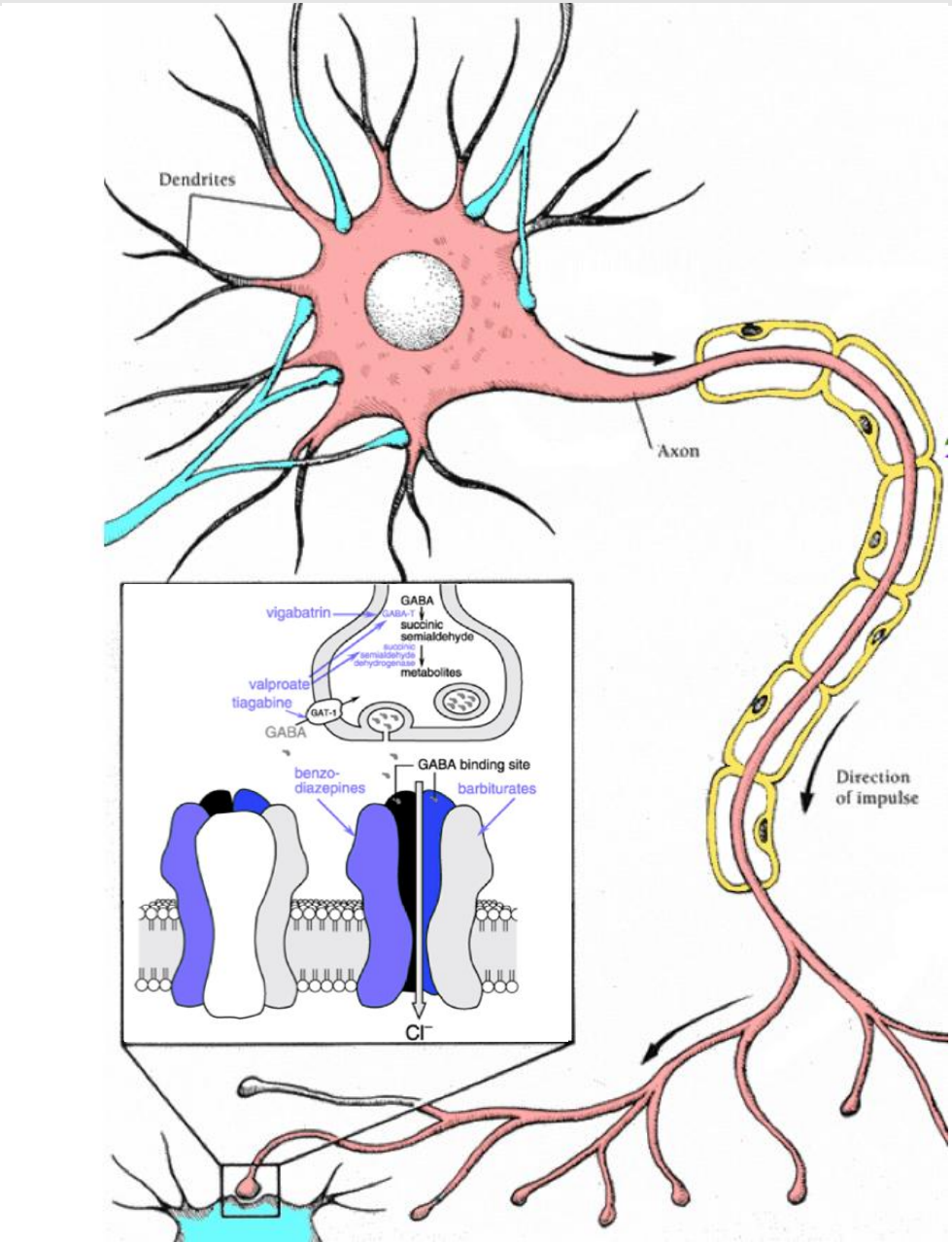
7. Zonisamide (Zonegran):
   - Indications:
     - Approved for adjunct treatment of partial seizures in adults.
     - Appears to have a broad spectrum:
       - Myoclonic seizures
       - Infantile spasms
       - Generalized & atypical absence seizures
       - Lennox-Gastaut Syndrome
   - Drug Interactions:
     - Phenytoin and carbamazepine decrease its half-life by half.

# Na+ Channel Inhibitors

7. Zonisamide (Zonegran):

– Adverse Effects:
  - Weight loss
  - Abnormal thinking
  - Nervousness
  - Agitation/irritability
  - Usually well tolerated

# II. Enhancement of GABA Inhibition



## Enhancement of GABA Inhibition

1. **Barbiturate drugs:**

A. Phenobarbital (Luminal)
B. Primidone (Mysoline)

– Mechanism of Action:
  - Increases the duration of GABAA-activated Cl- channel opening.

## Enhancement of GABA Inhibition

### A. Phenobarbital (Luminal):

– Indications:
  - Second choice for partial and generalized tonic-clonic seizures.
  - Rapid absorption has made it a common choice for seizures in infants, but adverse cognitive effects cause it to be used less in older children and adults.
  - Status epilepticus

– Contraindications:
  - Absence Seizures

## B. Primidone (Mysoline):

- Indications:
  - Adjuvant or monotherapy for partial and generalized tonic-clonic seizures
  - May control refractory generalized tonic-clonic seizures
- Contraindications:
  - History of porphyria

## Enhancement of GABA Inhibition

- Phenobarbital (Luminal) & Primidone (Mysoline):
  - Drug Interactions:
    - Other CNS depressants
    - Increased metabolism of vitamin D and K
    - Phenytoin increases the conversion of primidone to phenobarbital.

## Enhancement of GABA Inhibition

- Phenobarbital (Luminal) & Primidone (Mysoline):

  – Adverse Effects:
    - Agitation and confusion in the elderly.
    - Worsening of pre-existing hyperactivity and aggressiveness in children
    - Sexual side effects
    - Physical dependence

## 2. Benzodiazepine drugs:

- Diazepam (Valium)
- Lorazepam (Ativan)
- Clonazepam (Klonopin)
- Clorazepate (Transxene-SD)

– Mechanism of Action:

- Increases the frequency of $GABA_A$-activated Cl- channel opening.

# 2. Benzodiazepine drugs:

- Indications:
  - Only clonazepam & clorazepate approved for long-term treatment.
  - Clorazepate
    - In combination for partial seizures
  - Clonazepam
    - Lennox-Gastaut Syndrome, myoclonic, atonic, and absence seizures
    - Tolerance develops after about 6 months

# 2. Benzodiazepine drugs:

– Indications:

- Diazepam and lorazepam are used in treatment of status epileticus.
  - Diazepam is painful to inject; lorazepam is more commonly used in acute treatment.
- Diazepam
  - Intermittent use for control of seizure clusters
  - Diazepam frequently combined with phenytoin.

## 2. Benzodiazepine drugs:

### – Contraindications:

- Diazepam in children under 9
- Narrow angle glaucoma

### – Adverse Effects:

- Hypotonia, Dysarthria (Difficulty in articulating words, caused by impairment of the muscles used in speech)
- Muscle in-coordination (clonazepam)
- Behavioral disturbances (especially in children)
  - Aggression, Hyperactivity, Irritability and Difficulty concentrating

## 3. Tiagabine (Gabitril):

– Mechanism of Action:
  - Inhibition of GABA transporter (GAT-1) – reduces reuptake of GABA by neurons and glial cells.

– Indications:
  - Approved in 1998 as an adjunct therapy for partial seizures in patients at least 12 years old.

– Contraindications:
  - Absence seizures

## 3. Tiagabine (Gabitril):

– Interactions:

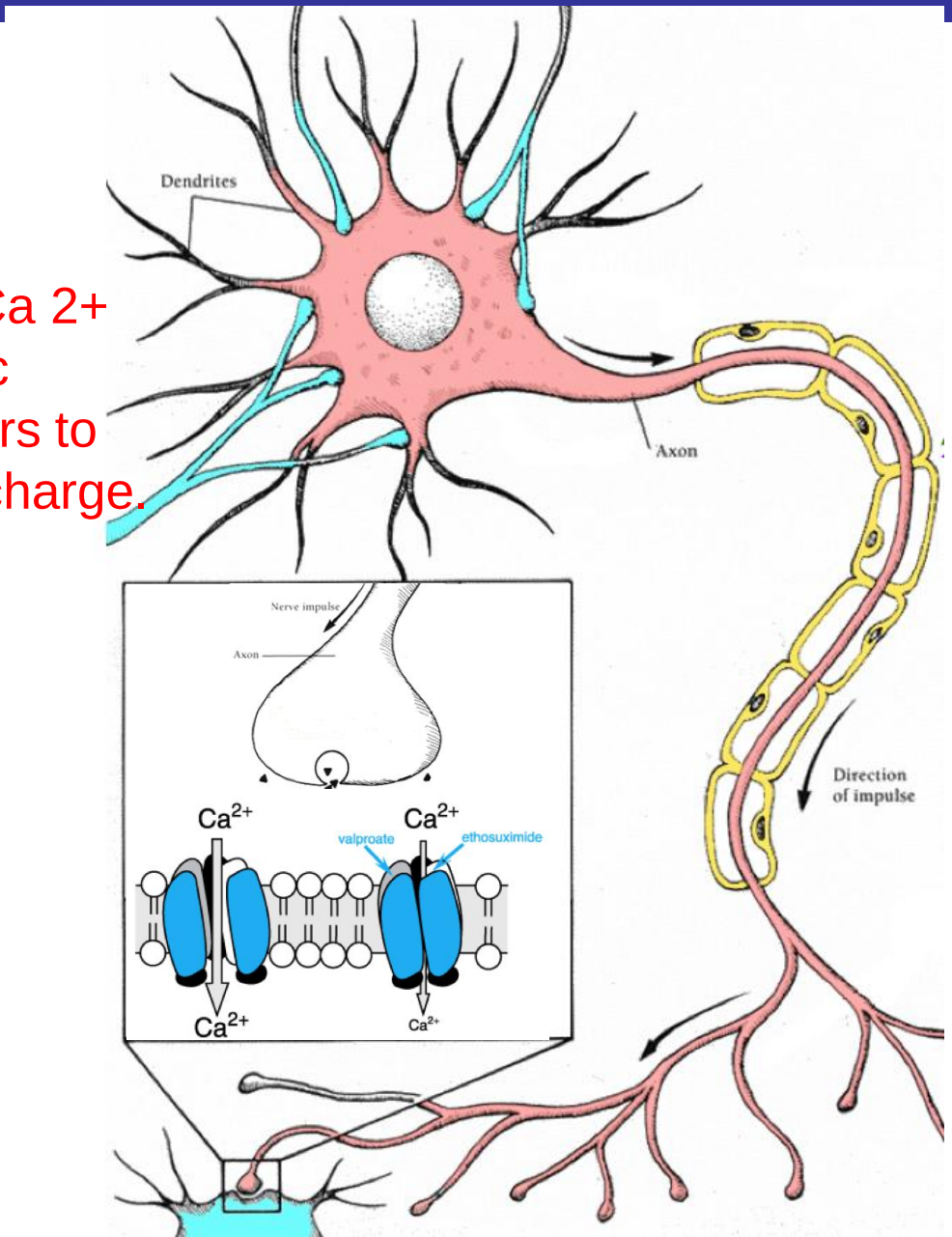
- Blood levels decreased by CBZ, phenytoin, phenobarbital, & primidone

– Adverse Effects:

- Asthenia (weakness)
- Abdominal pain

# III. Calcium Channel Blockers

inhibit low-threshold (T-type) Ca 2+ currents, especially in thalamic neurons that act as pacemakers to generate rhythmic cortical discharge.



# Voltage-Gated Ca2+ Channel T Currents

1. Ethosuximide (Zarontin):

– Mechanism of Action:
  - Reduces low -threshold Ca2+ currents (T currents) in the thalamic neurons.
  - Half-life is ~60 hr in adults; ~30hr in children.

– Indications:
  - First line for absence seizures

– Contraindications:
  - May exacerbate partial & tonic-clonic seizures

# Voltage-Gated Ca2+ Channel T Currents

1. Ethosuximide (Zarontin):

❖ Adverse Effects:

- Psychotic behavior
- Blood dyscrasias
- Persistent headaches
- Anorexia
- Hiccups
- Lupus-like syndromes

– Toxicity:

- parkinson-like symptoms
- photophobia

# Blockade of Calcium Channels ($\alpha 2\text{–}\delta$)

1. Gabapentin (Neurontin):
   - Mechanism of Action:
     - Originally designed to be a centrally acting GABA agonist.
     - Selective inhibition of v-g Ca2+ channels containing the α2δ1 subunit.
   - Indications:
     - adjunct therapy in adults and children with partial & secondarily generalized seizures.
     - Also effective as monotherapy.

# Blockade of Calcium Channels ($\alpha 2$–$\delta$)

- Gabapentin (Neurontin):
  - Contraindications:
    - Can exacerbate myoclonic & absence seizures.
  - Adverse Effects:
    - Weight Gain (5%) with ankle edema
    - Irritability
    - Behavioral problems in children (6%)
    - Has been associated with movement disorders.

## 2. Pregabalin (Lyrica):

- Mechanism of Action:
  - Same as gabapentin
- Indications:
  - Approved in 2005
  - Adjunct therapy for partial & secondarily generalized seizures
- Other uses:
  - Prescribed for neuropathic pain, fibromyalgia (A syndrome characterized by chronic pain in the muscles of soft tissues surrounding joints, fatigue, and tenderness at specific sites in the body)

# Other/Unknown MOA

- Levetiracetam (Keppra):
  - Indications:
    - Approved in 1999 as an adjunct therapy for adults with partial seizures.
    - Some patients have success with monotherapy

- Levetiracetam (Keppra):
  - Contraindications:
    - Renal dysfunction
  - Adverse Effects:
    - Asthenia
    - Infection
    - Behavioral problems in children

# Block the *N*-methyl-D-aspartate (NMDA) glutamate receptor.

- **Felbamate**

- *Felbamate* has a broad spectrum of anticonvulsant action.
- The drug has multiple proposed mechanisms including
  1) blocking voltage-dependent sodium channels
  2) competing with the glycine-coagonist binding site on the N-methyl-D-aspartate (NMDA) glutamate receptor
  3) blocking calcium channels
  4) potentiation of GABA actions.

- It is reserved for use in refractory epilepsies (particularly Lennox-Gastaut syndrome) because of the risk of aplastic anemia (about 1:4000) and hepatic failure.