EPILEPSY & ANTI-EPILEPTIC DRUGS

R. MAITI, SENIOR LECTURER IN PHARMACY

EPILEPSY

Convulsion:

- Sudden attack of involuntary muscular contractions and relaxations.

Seizure:

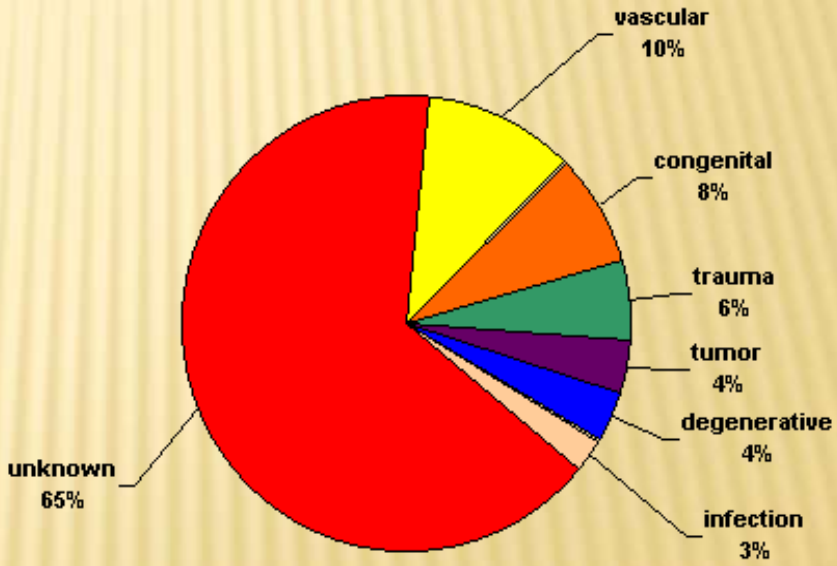
- The clinical manifestation of an abnormal hyper-synchronized impulse discharge in a population of cortical excitatory neurons

Epilepsy:

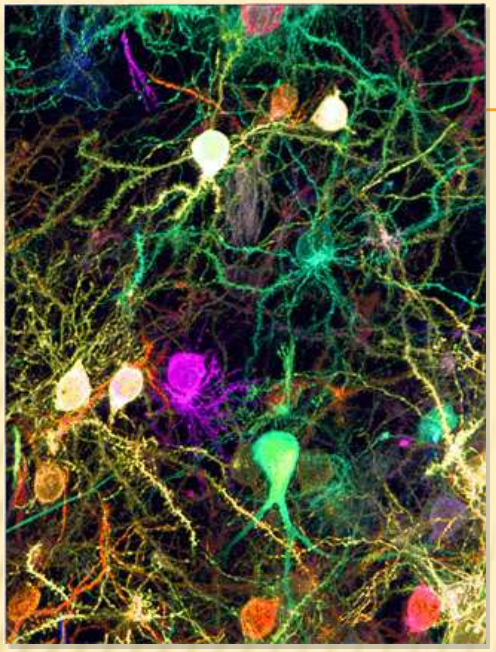
- A tendency toward recurrent seizures unprovoked by acute systemic or neurologic insults

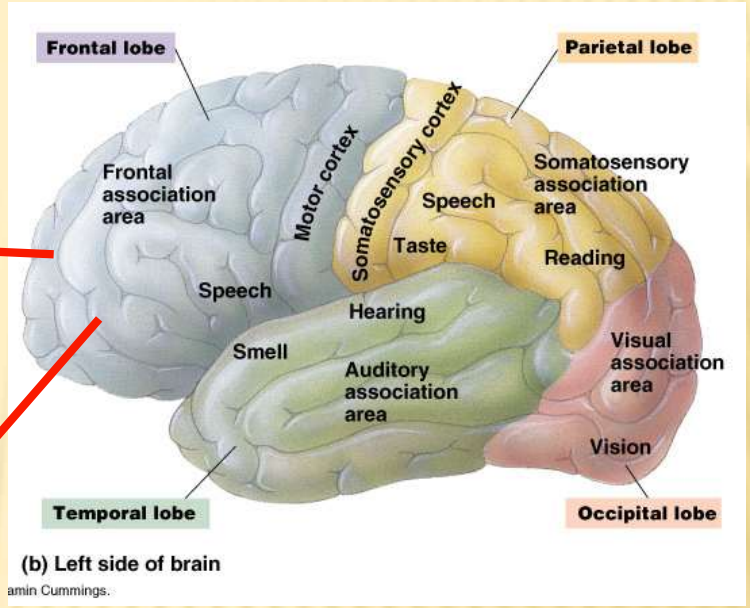
EPILEPSY

- Causes:
  - Genetic (autosomal dominant genes)
  - Congenital defects
  - Severe head trauma
  - Ischemic injury, tumor
  - Drug abuse
  - *Unknown*



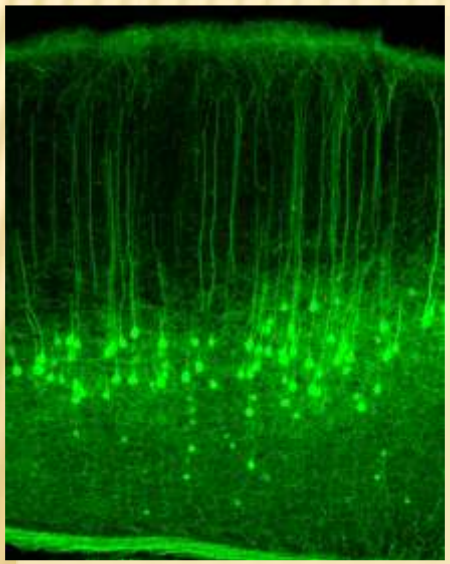
The Brain





(b) Left side of brain

amin Cummings.



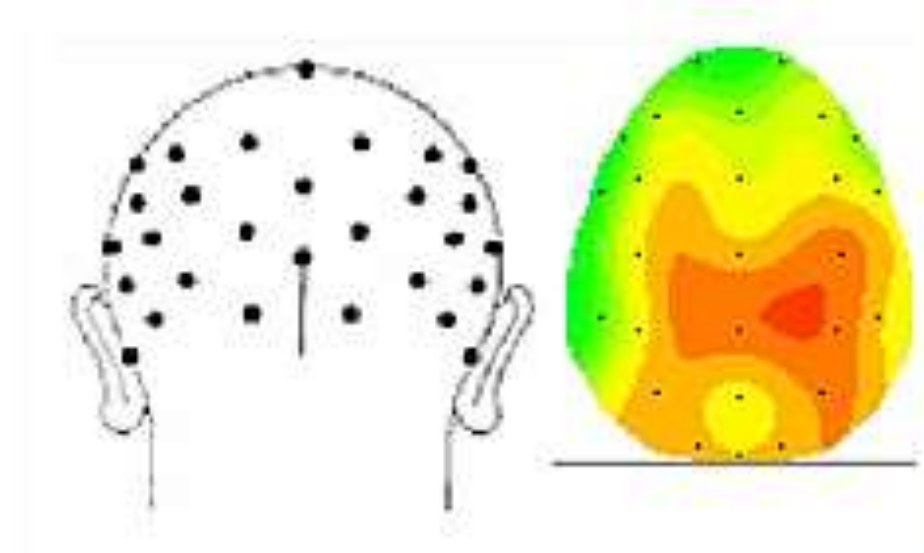
An extremely complex organ made up of billions of connections between neurons.

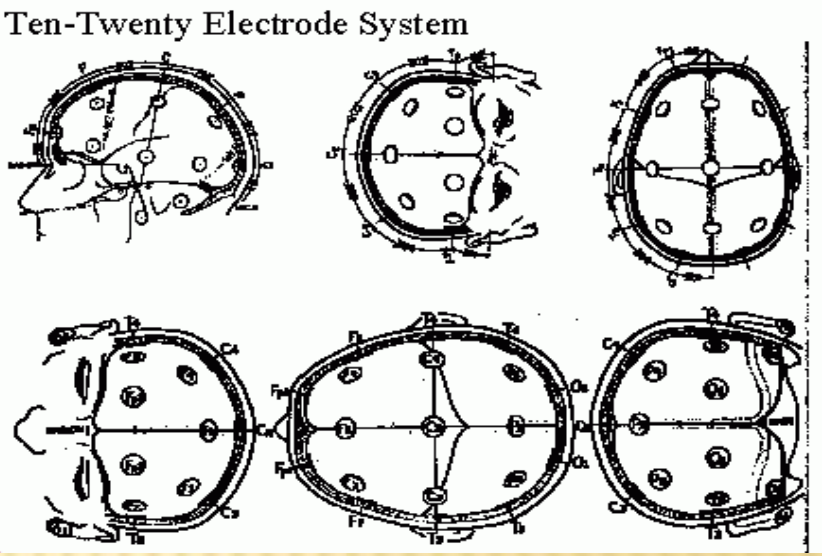
These connections are each highly controlled and regulated.

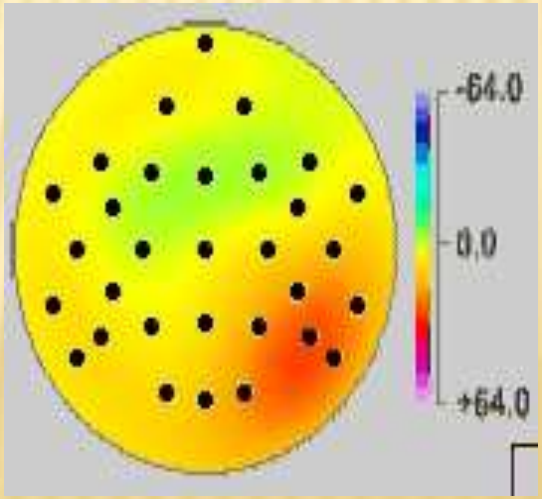
EPILEPSY

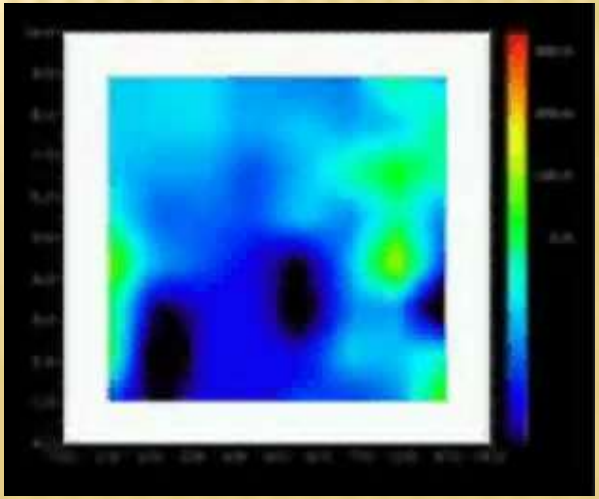
- Neurons communicate between themselves using small molecules called neurotransmitters.
- These neurotransmitters modulate and regulate the electrical activity of a given neuron, and tell it when to fire an action potential or when not to.
  - Glutamate = excitatory (tells the neuron to fire)
  - GABA = inhibitory (dampens the neuron firing rate)
- The action potential is an electrical signal that travels down the axon, and is created using sodium ions (Na+), and inhibited by potassium ions (K+).
- Usually these processes work synergistically to produce normal behavior and activity.
- When dysfunctional, abnormal electrical activity occurs and can produce seizures.

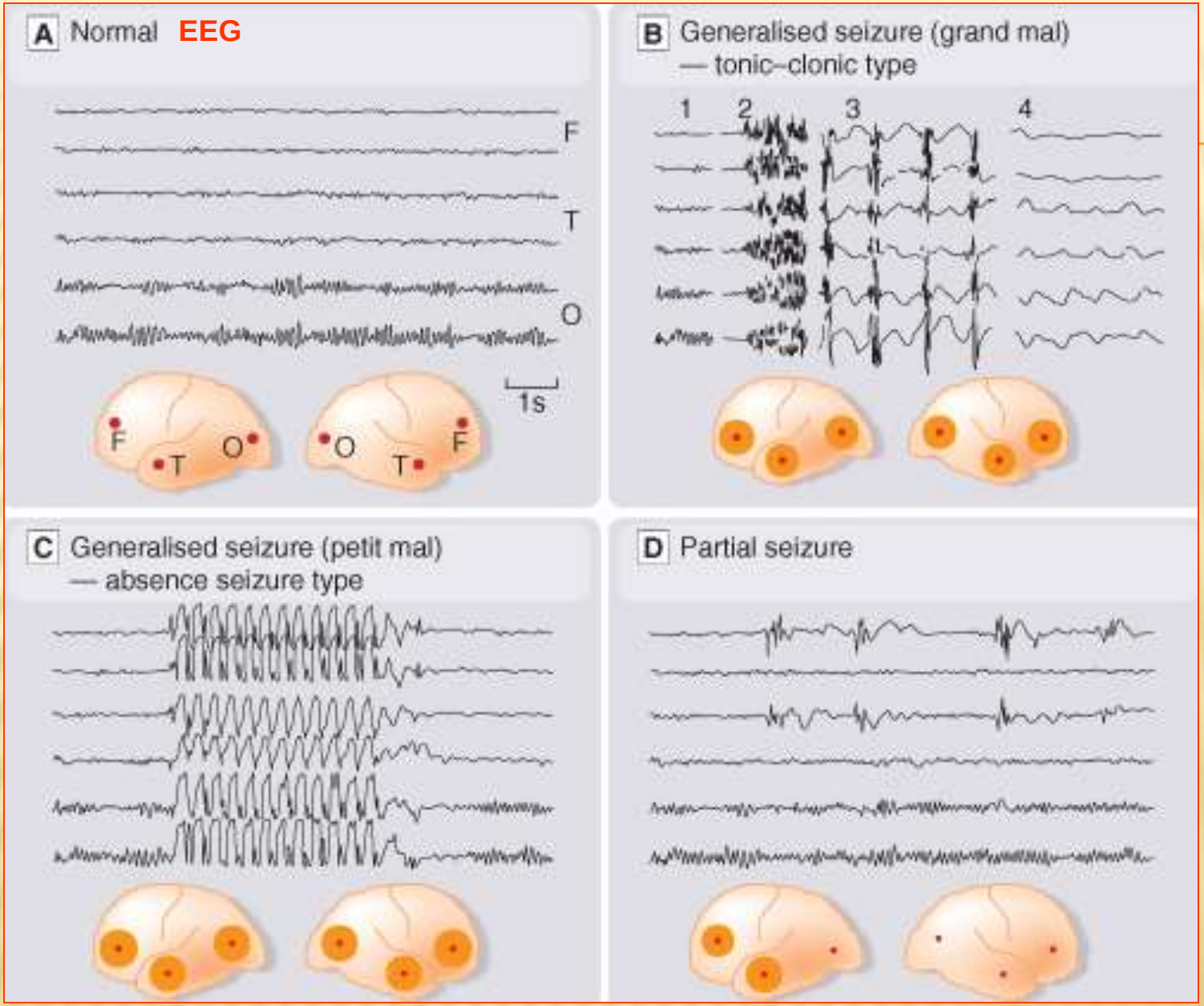
SCALP EEG DATA ACQUISITION











Cortex:

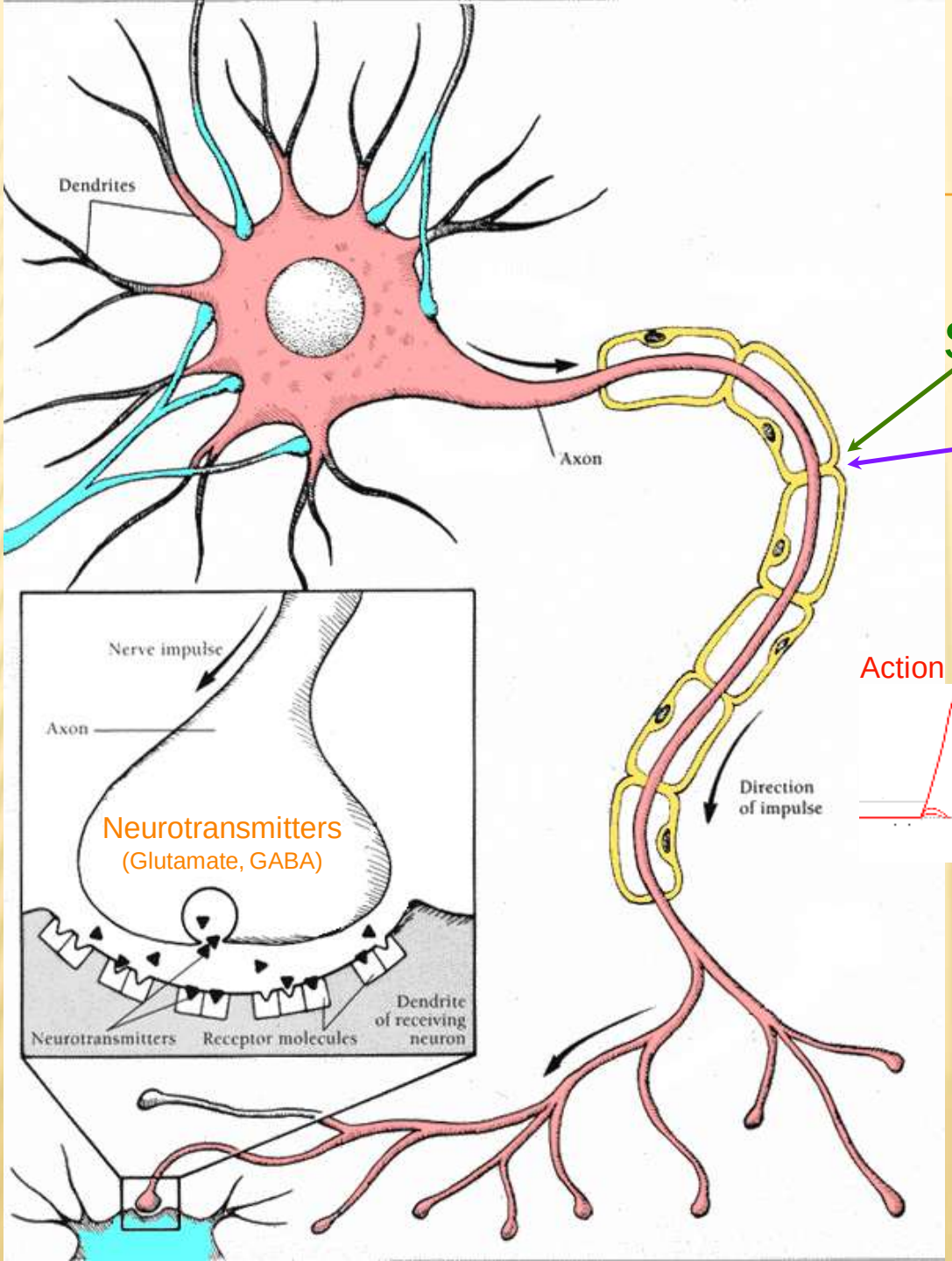
F – frontal

O – occipital

T – temporal

Rang et al. Pharmacology – 5th Ed. (2003)

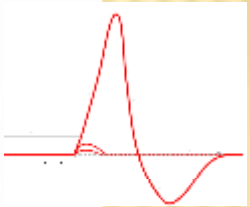
Classification of seizures



Sodium Ions/Channels

Potassium Ions/Channels

Action Potential

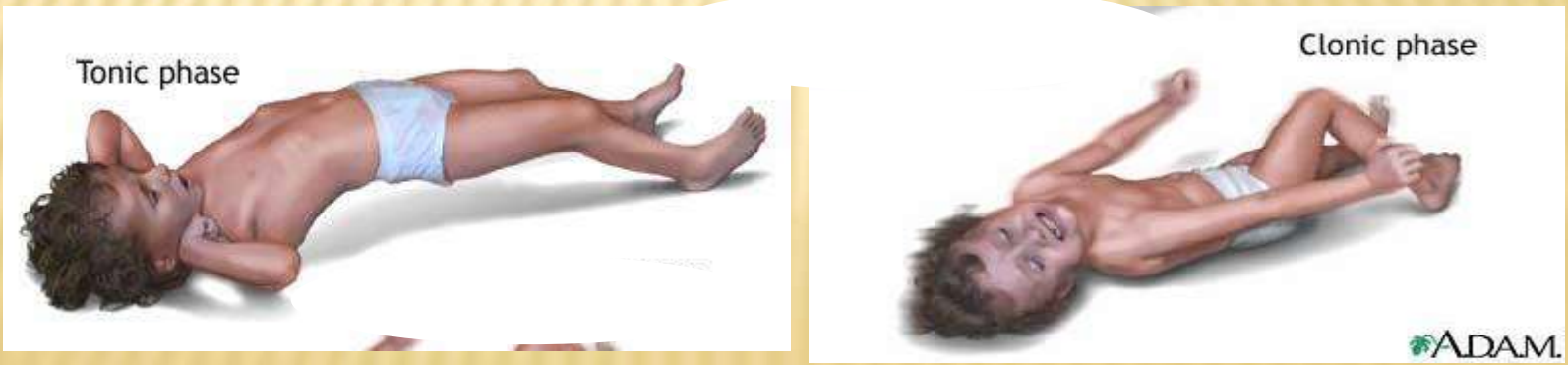


EPILEPSY- TYPES OF SEIZURES

- **Generalized Seizures** - Excessive electrical activity in both cerebral hemispheres.
- Usually originates in the thalamus or brainstem.
- Affects the whole body.
- Loss of consciousness is common.

GENERALIZED SEIZURES

- **Myoclonic**: Brief shock-like muscle jerks generalized or restricted to part of one extremity.
- **Atonic**: Sudden loss of muscle tone.
- **Tonic Seizures:** sudden stiffening of the body, arms, or legs
- **Clonic Seizures:** rhythmic jerking movements of the arms and legs without a tonic component
- **Tonic-clonic (grand mal):**
  - Tonic phase followed by clonic phase



http://www.nlm.nih.gov/medlineplus/ency/images/ency/fullsize/19076.jpg

GENERALIZED SEIZURES

- Absence (petit mal): Person appears to "blank out" - "Daydreaming"
  - Simple Absence (primarily effects consciousness only)
  - Complex Absence
  - Atypical Absence (Includes physical symptoms like eye blinking or lip movements)

- Lenox-Glastaut Syndrome.
  - Atypical absence, atonic and myclonic

- Status Epilepticus: A seizure lasting longer than 30 min, or 3 seizures without a normal period in between
  - May be fatal
  - Emergency intervention required

PARTIAL (FOCAL) SEIZURES

- Excessive electrical activity in one cerebral hemisphere. -Affects only part of the body.
- Simple Partial: Person may experience a range of strange or unusual sensations.
  - Motor
  - Sensory
  - Autonomic
  - **Key feature**: preservation of consciousness.
- Complex Partial:
  - Loss of awareness at seizure onset. Person seems dazed or confused and exhibits meaningless behaviors.
  - Typically originate in frontal or temporal lobes (e.g. Temporal lobe epilepsy)

SEIZURE FACTS

- Seizures are not usually life threatening.
- The brain almost always stops the seizure on its own.
- Breathing may cease for a few seconds, and the patient may turn blue.
- People don't feel pain during a seizure; muscles may be sore afterward.
- Person may be "different" for a while after the seizure.

TREATMENT ASPECT

- 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 ASPECT

- 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

ANTISEIZURE DRUGS

1. **Carboxamides** (*enzyme inductors* – CYP450)**:** Carbamazepine (+ neuropathic pain – n. trigeminus, postherpetic pain, etc.), Oxcarbazepine
2. **Hydantoins:** Phenytoin (*enzyme inductor)*, used in digitalis intoxication too
3. **Barbiturates** (Phenobarbital – *enzyme inductors*) and their analogues (Primidone – prodrug)
4. **Succinimides:** Ethosuximide (casp. 250 mg – petit mal)
5. **Valproates** (*enzyme inhibitors*)**:** Sodium valproate (Depakin®)
6. **Benzodiazepines:** Clonazepam, Clorazepate, Diazepam $t_{1/2}$ 43 h, amp. 10 mg/2 ml i.m./i.v., Lorazepam, Nitrazepam
7. **GABA analogues:** Gabapentin, Tiagabine
8. **Hetereogenic anticonvulsants:** Lamotrigine, Levetiracetam, Pregabalin (partial seizures, peripheral neuropathic pain), Topiramate, Vigabatrin

MOA OF ANTIEPILEPTIC DRUGS

Antiepileptics inhibit the neuronal discharge or its spread in one or more of the following ways:

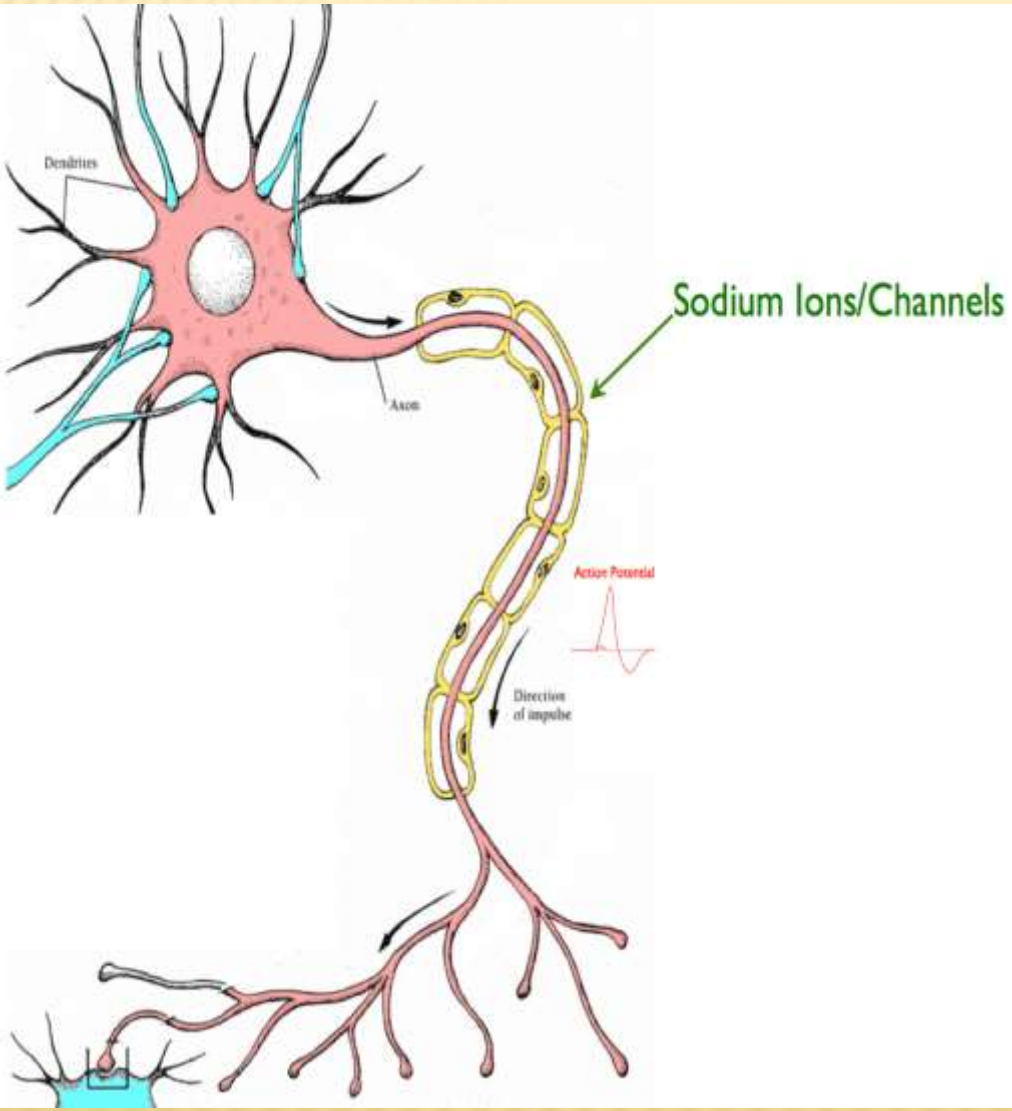
(1) Enhancing GABA synaptic transmission: barbiturates, benzodiazepines, gabapentin, levetiracetam, tiagabine, vigabatrin, topiramate, valproate; the result is increased permeability to chloride ion, which reduces neuronal excitability. Valproate and topiramate block GABA transaminase and tiagabine blocks reuptake of GABA.

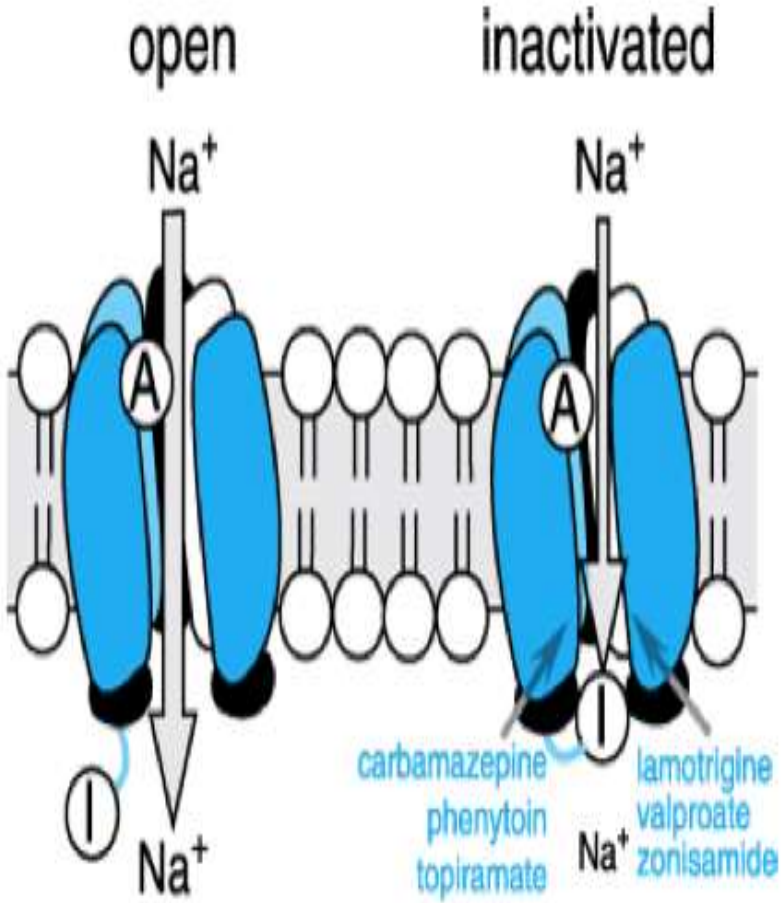
(2) Reducing cell membrane permeability to voltage-dependent sodium channels: carbamazepine, lamotrigine, oxcarbazepine, phenytoin, topiramate, valproate.

(3) Reducing cell membrane permeability to calcium T-channels: valproate, ethosuximide; the result is diminishing of the generation of action potential.

(4) Inhibiting excitory neurotransmitter glutamate: lamotrigine.

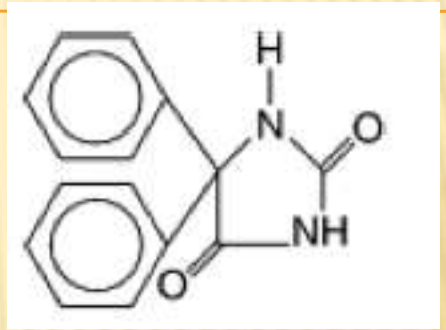
NA+ CHANNEL INHIBITORS





NA+ CHANNEL INHIBITORS

- Phenytoin :



  - 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 :
  - Adverse Effects:
    - Hirsutism & coarsening of facial features
    - Acne
    - Gingival hyperplasia (20-40%)
      - Brush teeth >8 times per day
        - A primary reason not to prescribe for children
    - Decreased serum concentrations of folic acid, thyroxine, and vitamin K with long-term use.

PHENYTOIN INDUCED GINGIVAL HYPERPLASIA

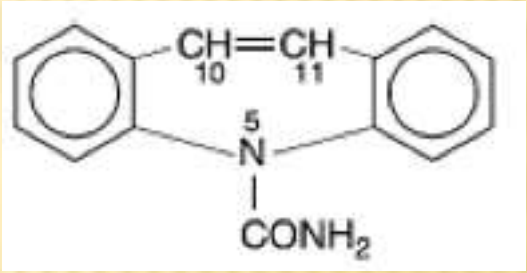
17 year old boy treated with 300mg/day phenytoin for 2 years (unsupervised)

Partial recovery at 3 months after discontinuation

Images in Clinical Medicine (Feb 2000) 342:325

NA+ CHANNEL INHIBITORS

- Carbamazepine :



  - 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

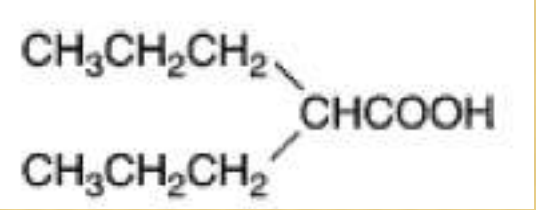
- Carbamazepine :
  - Drug Interactions:
    - CBZ metabolism is affected by many drugs, and CBZ affects the metabolism of many drugs.
  - Adverse Effects:
    - Mild leukopenia or hyponatremia
    - Circulating concentrations of thyroid hormones may be depressed; TSH remains normal.

NA+ CHANNEL INHIBITORS

- Oxcarbazepine :
  - FDA approved in 2000 for partial seizures
    - Complex partial seizures
    - Primary & secondarily generalized tonic-clonic seizures
    - No effect on absence or myoclonic seizures
  - Fewer adverse effects than CBZ, phenytoin

NA+ CHANNEL INHIBITORS

- Valproic Acid :
  - Mechanisms of Action:
    - 1) Some inhibition of T-type Ca2+ channels.
    - 2) Increases GABA production and decreases GABA metabolism.
  - 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

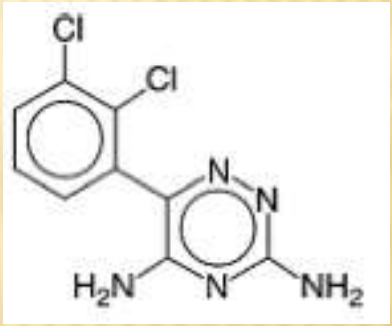
- Valproic Acid :
  - Drug Interactions:
    - Affects metabolism of many drugs through liver enzyme inhibition
      - Phenobarbital
        - “Drunkenness”
      - Clorazepam
        - Prolonged absence seizures

NA+ CHANNEL INHIBITORS

- Valproic Acid :
  - 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

- Lamotrigine :



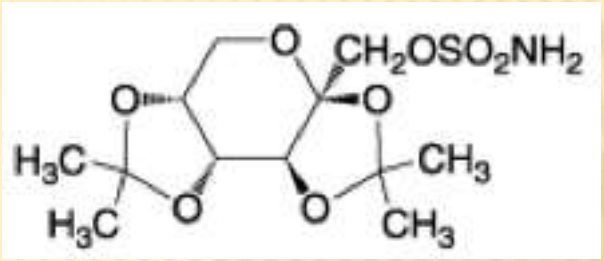
  - Mechanism of Action:
    - May inhibit synaptic release of glutamate.
  - Indications:
    - Adjunct therapy (ages 2 & up):
      - Simple & complex partial seizures
      - Generalized seizures of Lennox-Gastaut Syndrome
    - Monotherapy (adults):
      - Simple & complex partial seizures
  - Contraindications: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

NA+ CHANNEL INHIBITORS

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

NA+ CHANNEL INHIBITORS

- Topiramate :



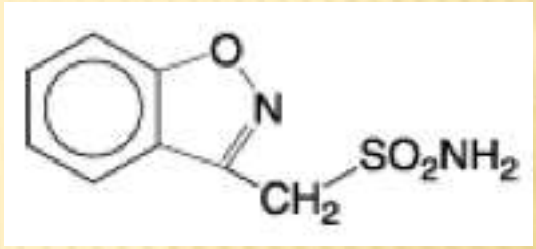
  - Mechanism of Action:
    - Enhances post-synaptic $GABA_A$ receptor currents.
    - Kainate receptor antagonist (blocks a certain type of glutamate channel)
  - Indications:
    - Adjunct therapy for partial and primary generalized tonic-clonic seizures in adults and children over 2.
    - Decreases tonic and atonic seizures in children with Lennox-Gastaut syndrome.
  - Contraindications:
    - History of kidney stones

NA+ CHANNEL INHIBITORS

- Topiramate :
  - 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

- Zonisamide :



  - Mechanism of Action:
    - Inhibits T-type Ca2+ currents.
    - Binds to GABA receptors.
    - Facilitates dopaminergic and serotonergic neurotransmission.

NA+ CHANNEL INHIBITORS

- Zonisamide :
  - 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.

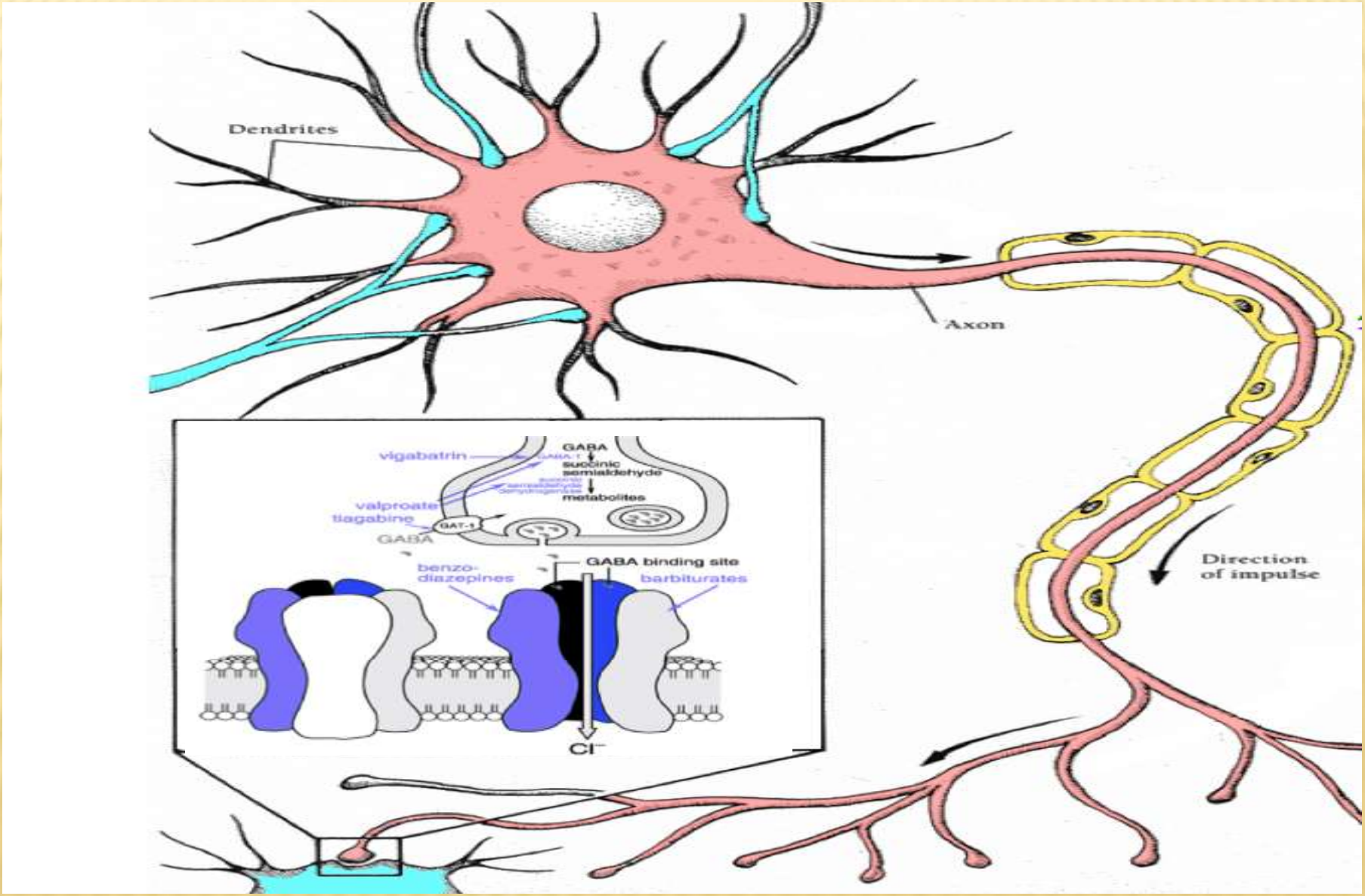
NA+ CHANNEL INHIBITORS

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

NA+ CHANNEL INHIBITORS

- Lidocaine: Only when other drugs are refractory for status epilepticus.

ENHANCEMENT OF GABA INHIBITION



ENHANCEMENT OF GABA INHIBITION

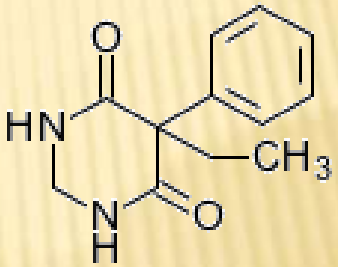
- **Barbiturate drugs:**
- Phenobarbital & Primidone:
  - Mechanism of Action:
    - Increases the duration of $GABA_A$-activated Cl^- channel opening.

ENHANCEMENT OF GABA INHIBITION

- Phenobarbital:
  - 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

ENHANCEMENT OF GABA INHIBITION

- Primidone:



D00474

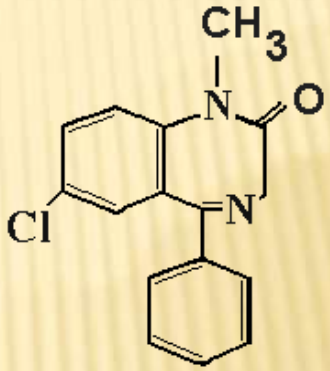
  - Indications:
    - Adjuvant or monotherapy for partial and generalized tonic-clonic seizures
    - May control refractory generalized tonic-clonic seizures
  - Contraindications:
    - History of porphyria

ENHANCEMENT OF GABA INHIBITION

- Phenobarbital & Primidone:
  - Drug Interactions:
    - Other CNS depressants
    - Increased metabolism of vitamin D and K
    - Phenytoin increases the conversion of primidone to phenobarbital.
  - Adverse Effects:
    - Agitation and confusion in the elderly.
    - Worsening of pre-existing hyperactivity and aggressiveness in children
    - Sexual side effects
    - Physical dependence

ENHANCEMENT OF GABA INHIBITION

- Benzodiazepine drugs:



  - Diazepam (Valium), lorazepam (Ativan), clonazepam (Klonopin), clorazepate (Transxene-SD)
  - Mechanism of Action:
    - Increases the frequency of $GABA_A$-activated Cl- channel opening.

ENHANCEMENT OF GABA INHIBITION

- 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

ENHANCEMENT OF GABA INHIBITION

- 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.

ENHANCEMENT OF GABA INHIBITION

- Benzodiazepine drugs:
  - Contraindications:
    - Diazepam in children under 9
    - Narrow angle glaucoma
  - Adverse Effects:
    - Hypotonia, Dysarthria
    - Muscle in-coordination (clonazepam)
    - Behavioral disturbances (especially in children)
      - Aggression, Hyperactivity, Irritability and Difficulty concentrating

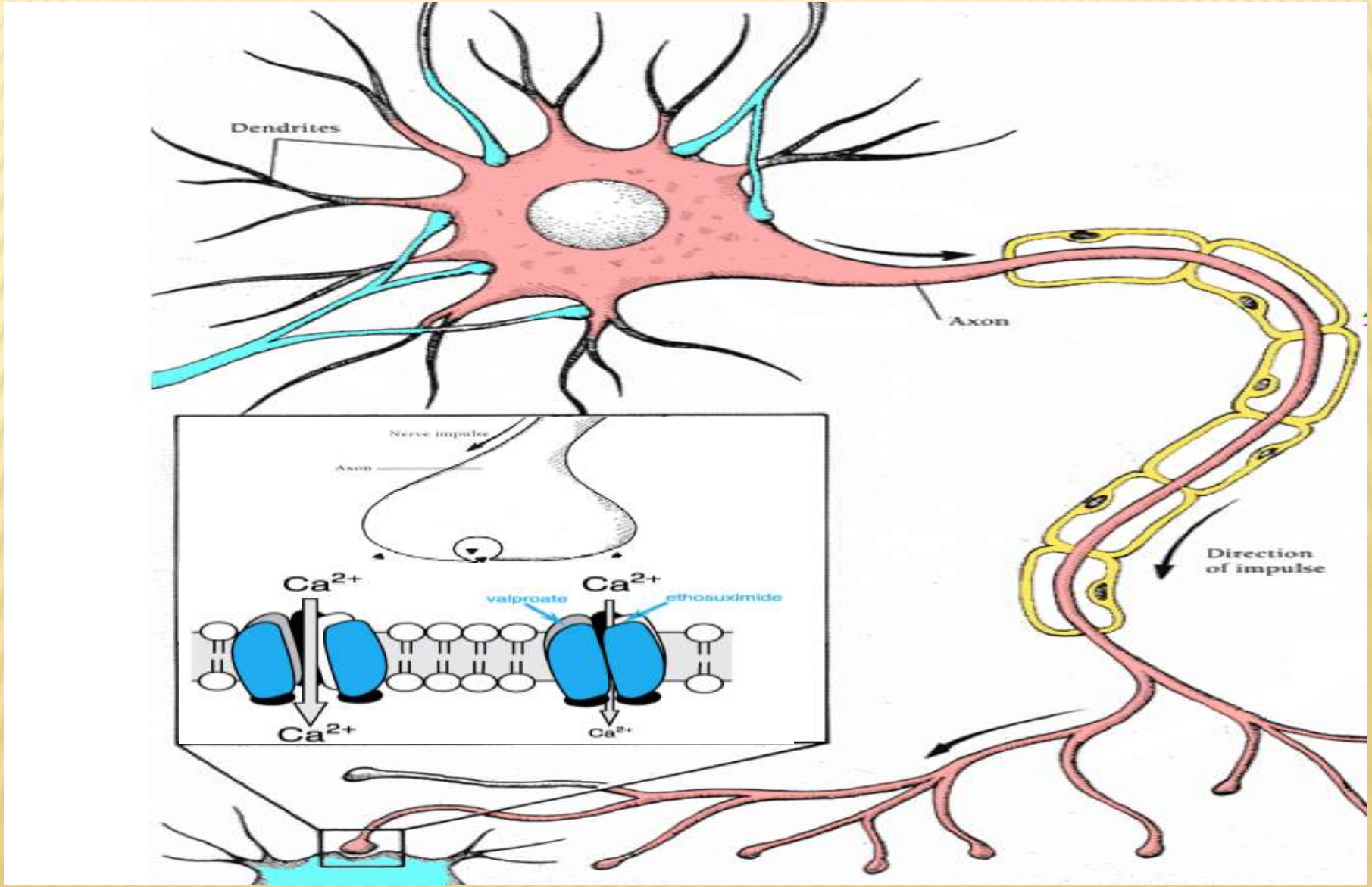
ENHANCEMENT OF GABA INHIBITION

- Tiagabine:
  - 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

ENHANCEMENT OF GABA INHIBITION

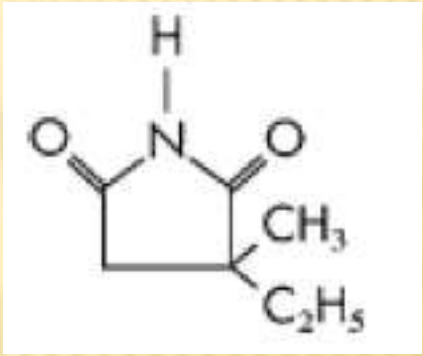
- Tiagabine:
  - Interactions:
    - Blood levels decreased by CBZ, phenytoin, phenobarbital, & primidone
  - Adverse Effects:
    - Asthenia
    - Abdominal pain

CALCIUM CHANNEL BLOCKERS



VOLTAGE-GATED Ca2+ CHANNEL T CURRENTS

- Ethosuximide:



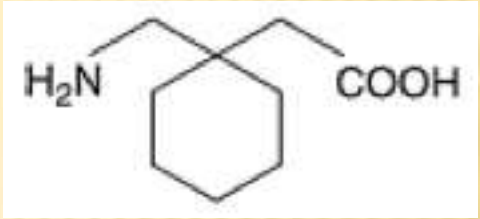
  - Mechanism of Action:
    - Reduces low threshold Ca2+currents (T currents) in the thalamic neurons.
    - Half-life is ~60 hr in adults; ~30hr in children.
  - Indications:
    - First line for absence seizures
  - Contraindications:
    - May exacerbate partial & tonic-clonic seizures

VOLTAGE-GATED Ca2+ CHANNEL T CURRENTS

- Ethosuximide:
  - Adverse Effects:
    - Psychotic behavior
    - Blood dyscrasias
    - Persistent headaches
    - Anorexia
    - Hiccups
    - Lupus-like syndromes
  - Toxicity:
    - parkinson-like symptoms
    - photophobia

BLOCKADE OF CALCIUM CHANNELS (α2–δ)

- Gabapentin:



  - 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 ($\alpha 2-\delta$)

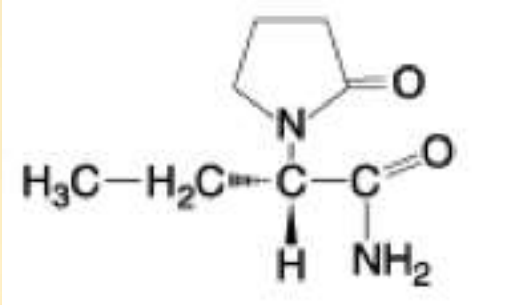
- Gabapentin (Neurontin):
  - Contraindications:
    - Can exacerbate myoclonic & absence seizures.
  - Adverse Effects:
    - Weight Gain (5%) with ankle edema
    - Irritability
    - Behavioral problems in children (6%)
    - Has been associated with movement disorders.

BLOCKADE OF CALCIUM CHANNELS ($\alpha 2-\delta$)

- Pregabalin:
  - Mechanism of Action:
    - Same as gabapentin
  - Indications:
    - Approved in 2005
    - Adjunct therapy for partial & secondarily generalized seizures
  - Contraindications:
    - No effect on absence, myoclonic, or primary generalized tonic-clonic seizures
  - Other uses:
    - Prescribed for neuropathic pain, fibromyalgia

OTHER/UNKNOWN MOA

- Levetiracetam (Keppra):



  - Mechanism of Action:
    - Not exactly known
    - Binding affinity to Synaptic Vesicle Protein 2A correlates with its anticonvulsant activity.
    - Also blocks calcium channel N-currents, increases intracellular Ca^{2+} levels, modulates GABA channel currents
  - Indications:
    - Approved in 1999 as an adjunct therapy for adults with partial seizures.
    - Some patients have success with monotherapy

OTHER/UNKNOWN MOA

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

OTHER/UNKNOWN MOA

- Magnesium chloride: Used for magnesium deficiency seizures.
- Paraldehyde: Alcohol withdrawal seizures.

SUMMARY

ANTI-EPILEPTICS

Na+ Channel Drugs

Phenytoin

Cabamazepine

Valproic Acid

Lamotrigine

Topiramate

Zonisamide

Lidocaine

GABA Drugs

Barbiturates:

Phenobarbital (Luminal)

Pimidone (Mysoline)

Benzodiazepines:

Diazepam (Valium)

Lorazepam (Ativan)

Clonazepam (Klonopin)

Clorazepate (Tranxene-SD)

- Tiagabine
- Valproic Acid
- Topiramate
- Zonisamide

Ca^{2+} Channel Drugs

Ethosuximide

Valproic Acid

Zonisamide

Gabapentin

Pregabalin

Levetiracetam

OTHER/UNKNOWN MOA

- Magnesium chloride
- Paraldehyde

PRIMARY GENERALIZED TONIC-CLONIC (GRAND MAL) SEIZURES

- **Drugs of Choice:**
  - Phenytoin
  - Carbamazepine
  - Oxcarbazepine
  - Valproate

- **Alternatives**
  - Lamotrigine
  - Topiramate
  - Zonisamide
  - Levetiracetam
  - Primidone
  - Phenobarbital
  - Diazepam

PARTIAL, INCLUDING SECONDARILY GENERALIZED SEIZURES

- **Drugs of Choice:**
  - Phenytoin
  - Carbamazepine
  - Oxcarbazepine
  - Valproate

- **Alternatives**
  - Lamotrigine
  - Topiramate
  - Zonisamide
  - Levetiracetam
  - Primidone
  - Phenobarbital
  - Gabapentin
  - Pregabalin
  - Tiagabine

ABSENCE (PETIT MAL)

- **Drugs of Choice:**
  - Ethosuximide
  - Valproate

- **Alternatives**
  - Clonazepam
  - Zonisamide

ATYPICAL ABSENCE, MYOCLONIC, ATONIC SEIZURES

- **Drug of Choice:**
  - Valproate

- **Alternatives**
  - Clonazepam
  - Topiramate
  - Zonisamide
  - Levetiracetam

THANKS TO LISTENING MINDS