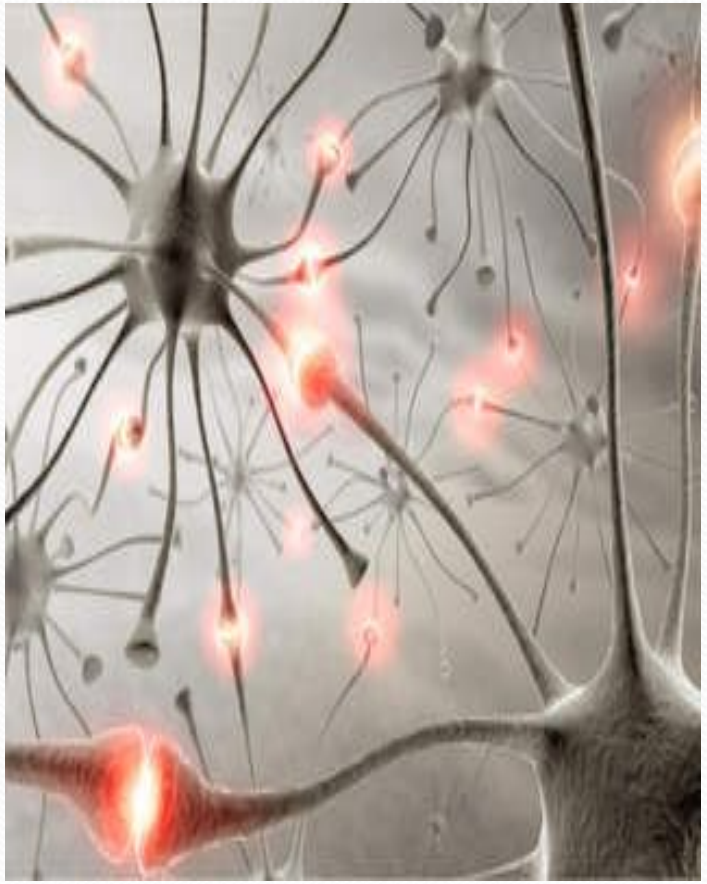
Anti epileptic drugs(AED) L1



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:This lecture consists of 2 parts

1st part is a key points about the disease (for your information)

2nd part is the objectives (about drug informations)

:Objectives

know types of antiepileptic drugs .1

Know MOA, kinetics, pharmacological action, .2 clinical indication, interaction and adverse effects .of drugs

1st part

Seizure: is a transient alteration in brain function (motor, consciousness, sensation, vision….) due to a **disordered** .rhythmic **depolarization** of a population of brain neurons

Epilepsy: a disorder of brain function that is characterized by **periodic** and **unpredictable** occurrence of seizure, the most common **4th** neurologic disorder after migraine, stroke and .Alzheimer's disease

Convulsion: is an involuntary, violent and spasmodic .contraction of skeletal muscles

Normally when we move any muscle of our body there are **signals arising from the brain resulting from firing ,(depolarization) of certain** neurons

while in epilepsy there is **uncontrollable spontaneous firing** .of some neurons in the brain

Neuron Physiology

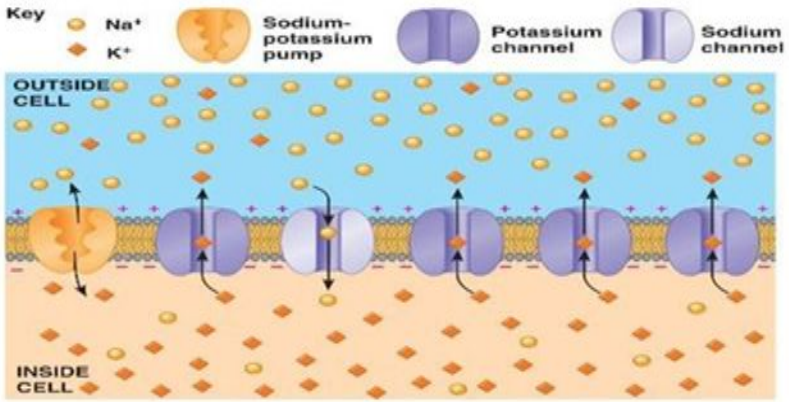
Action Potentials- nerve impulses which are sent by a change in electrical charge in the cell membrane.
Depends on ions:

- Sodium (Na+) highly concentrated outside of cells
- Potassium (K+) highly concentrated inside cells

Ion movement

- Ions move from high concentration to a low concentration passively

Na+/K+ pumps move ions actively using ATP



Pathophysiology

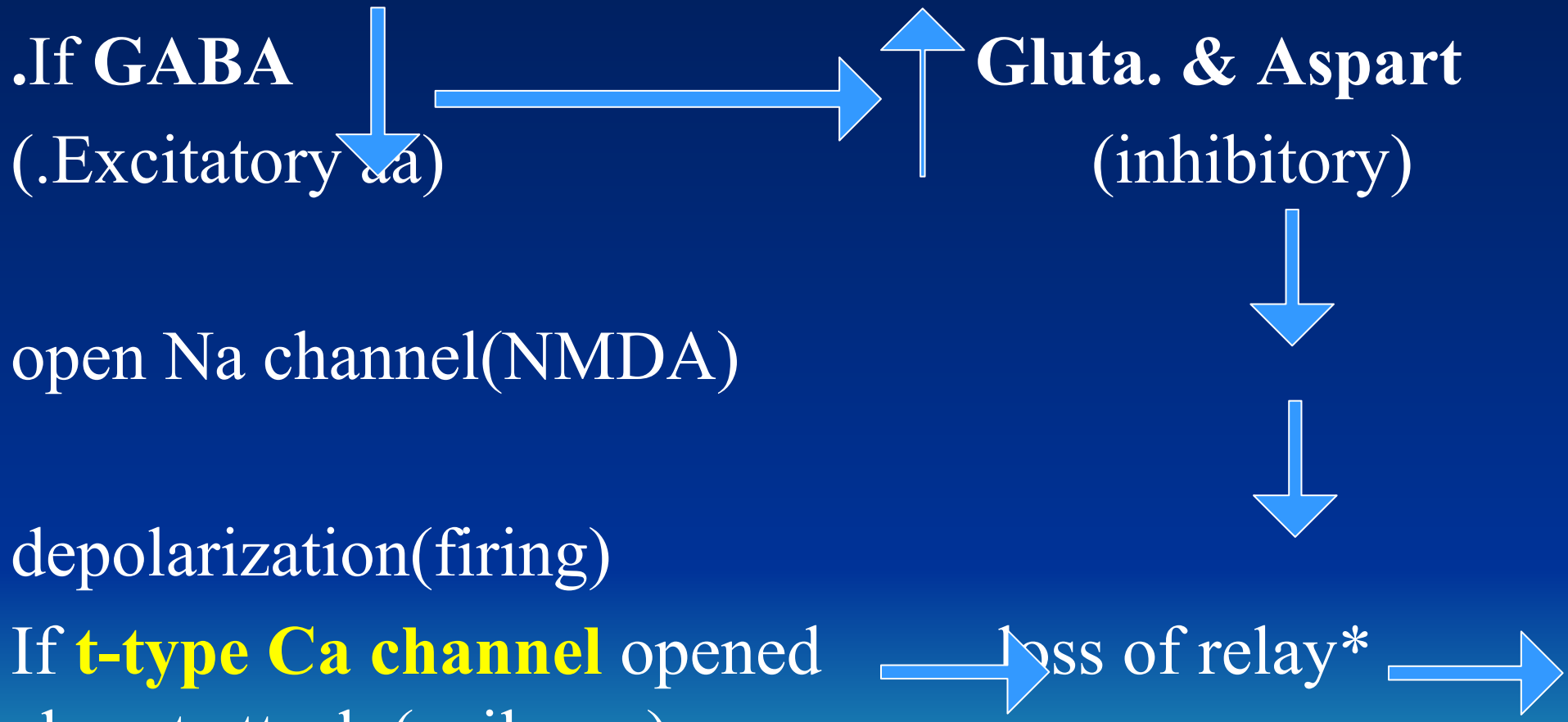
Normally **GABA** (an **inhibitory** neurotransmitter) are likely-presented in **balance** with **glutamate** & **aspartate(excitatory** .neurotransmitters)

if GABA is decreased or **excitatory** neurotransmitters increased , this lead to disturbance of balance ⟶ more .**dominant** action of **excitatory** neuro

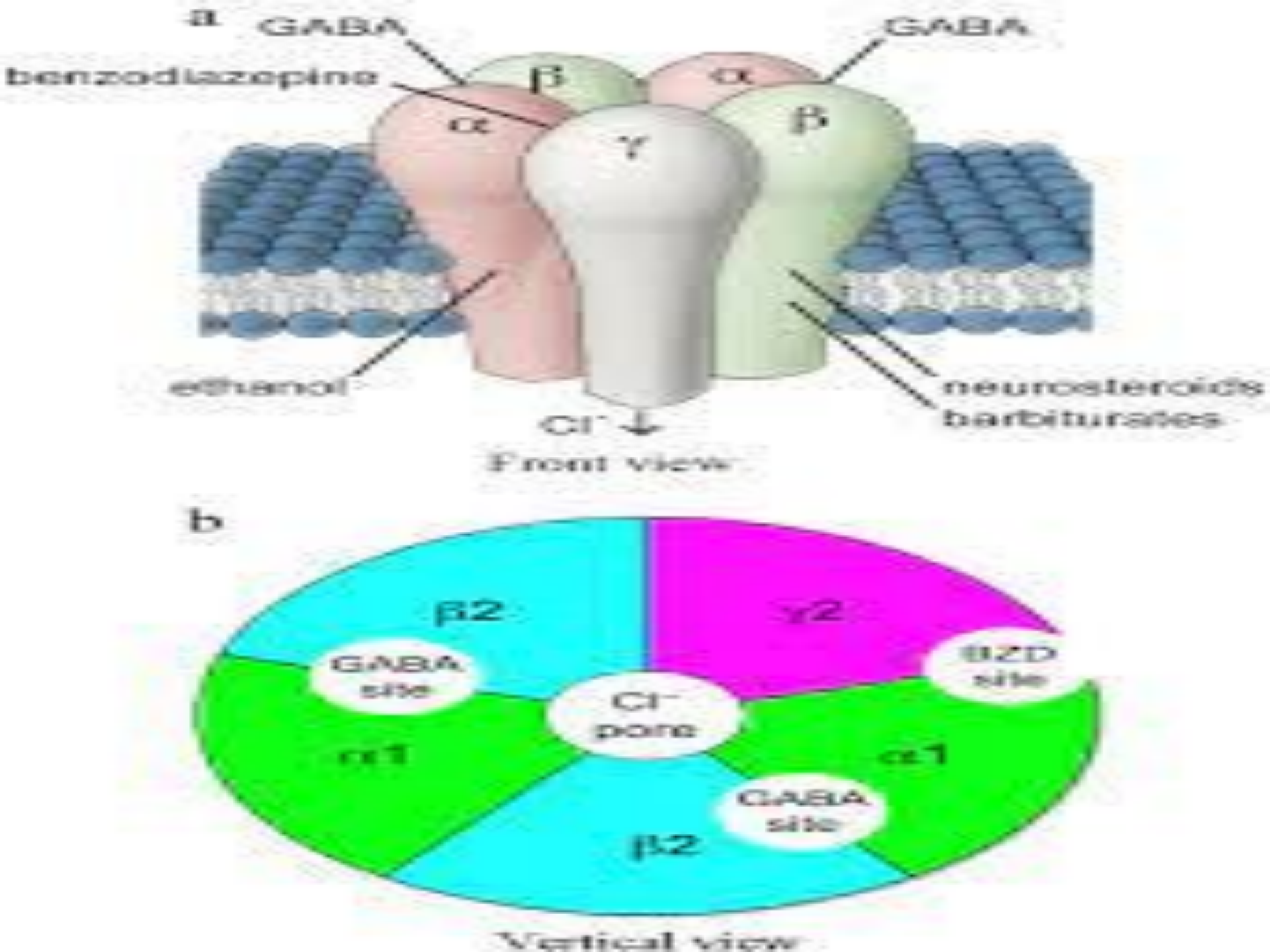
when this **disturbance** in balance occur , glutamate and aspartate neuro. Will activate **Na channel** ⟶ Na channel will open ⟶ **depolarization** (firing) occurs and . epilepsy will developed

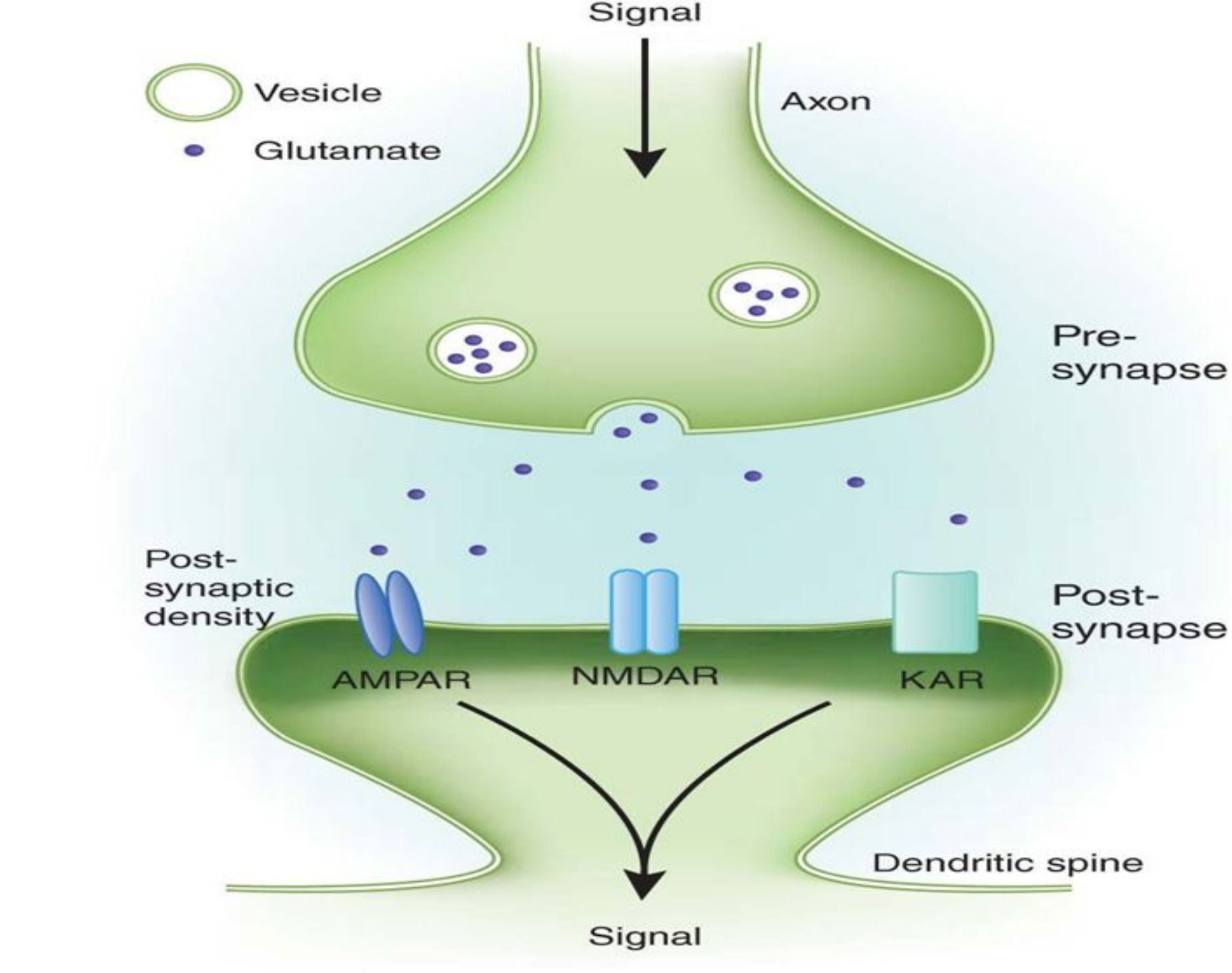
Opening of **t-type calcium channel suddenly, Ca channel** - relay between center and cortex of brain its opening leads to disturb connection (open connection) and epilepsy occur (**absent** seizure)

GABA in balance action with **glutamate * and aspartate**



note: N-methyl-D-aspartate (NMDA) receptors, a family of ionotropic* glutamate receptors, play an important role in learning and memory (ion


a
GABA
GABA
benzodiazepine
β
α
α
γ
β
ethanol
neurosteroids
barbiturates
Cl⁻
Front view
b
β2
γ2
GABA site
BZD site
Cl⁻ pore
α1
α1
GABA site
β2
Vertical view


Signal
Vesicle
Glutamate
Axon
Pre-
synapse
Post-
synaptic
density
AMPAR
NMDAR
KAR
Post-
synapse
Dendritic spine
Signal

Symptoms: depend on **site** and **size** of seizure occurrence

Site

if the affected area:

- Temporal lobe
  auditory hallucination
- Occipital lobe
  visual abn.
  generalization
- Motor cortex
  convulsion or jerky
  movement

size

-Focal

neralize

ocal with

ary

Classification of epileptic seizures:

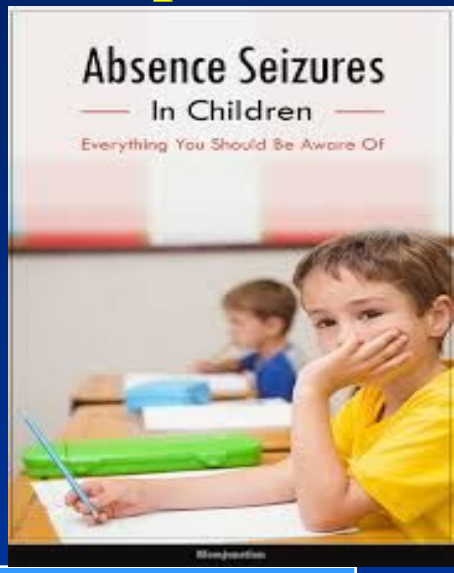
1-**Generalized seizures**: It begins over the entire surface of brain (both hemisphere) there is **loss of consciousness** from the beginning

Focal (in past named as Partial) :involve **only a portion -2** .of the brain, typically **part of one lobe** of one hemisphere

Focal secondarily generalization: it starts as focal then**-3** **.**spread to both hemisphere and becomes tonic-clonic

:Generalized seizure .1

a- Absence seizure("petit mal") : occurs in young children characterized by **brief loss of consciousness(4 –20 seconds**, usually **<10** seconds). By other words (**abrupt onset** of impaired consciousness associated with starring and cessation of ongoing activity), with **no warning** and wih **immediate** resumption of .consciousness **(no postictal abnormality)**



Pre-ictal (pre attack= aura)	ictal (= during attack)	Postictal(= after attack)

b. Myoclonic seizure: brief **shock-like** involuntary, .single or multiple contraction of muscle(<100 milliseconds)

C. Tonic clonic seizures("grand mal"): characterized by tonic followed by clonic contraction . The person loses consciousness, apnea, falls, stiffness,…… (**tonic phase**), and jerks (**clonic phase**). usually last for **less than 3 minutes** but are followed by **confusion** and **tiredness** of .variable duration (**postictal period**)

d- **Febrile seizure**: attack associated with **fever** in children .(occurs from 6 month -5 years). It is **not epilepsy**

.e- **Atonic type**: there is **sudden loss** of muscle **tone**

.f- Tonic type: increase body tone

Status epilepticus: a prolong seizure for >20 min. : a** process in which the seizures tend to occur one after the ** .other **without** preservation of conscious in between


Tonic phase
A
Clonic phase
B
Postictal phase
C

:**Focal onset seizure (**previously = **partial)** .2

A. Focal aware onset (previously **Simple partial)**: it .is associated with **preservation** of consciousness

Note : The electrical discharge does **not spread**, and the patient does not lose consciousness

B. Focal impaired onset (Complex partial): it is associated with impaired consciousness, associated .with movement

others infantile spasms (West's syndrome), Lennox-Gastaut syndrome, juvenile**

*……myoclonic epilepsy

2nd part

:Drugs

: The antiepileptic drugs can act by

Block Na or t- type Ca++ **channels**.1

Increase the activity of **inhibitory** neurotransmitter.2 .(**GABA**)

Decrease the activity of **excitatory** neurotransmitter.3 .like glutamate and aspartate

.

Classification of AEDs

Classical = 1st generation(including benzodiazepine)

Newer = 2nd generation (↓ excitatory neuro.)

1st differ from 2nd by Older, no action on excitatory n., more side effects

1st generation antiepileptic

Phenytoin : (diphenyl hydantoin) -1

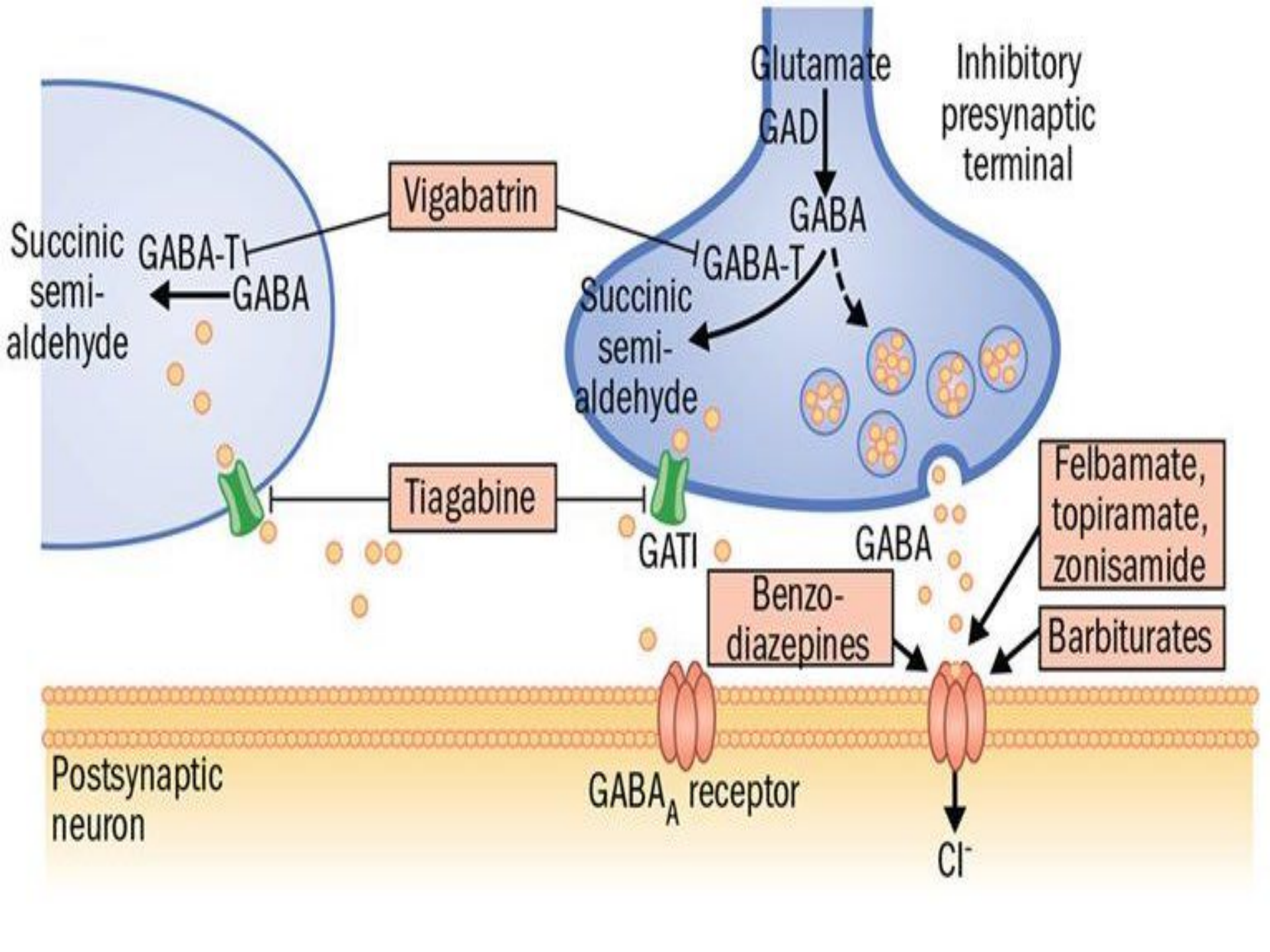
- **Phenytoin (1st generation)**
- **Fosphenytoin(2nd generation) after enter the body Converted to phenytoin.**

:Phenytoin Mechanism of action

block Na + channel in brain and heart(Decreasing -1 movement of Na and K in neurons) leading to .decrease firing

At **high conc**. It **enhances** the activity of **GABA** -2

But it produces some **drowsiness** and **lethargy** **without progression to .hypnosis (bs** phenytoin is not generalized CNS depressant)


Glutamate
GAD
Inhibitory presynaptic terminal
GABA
Vigabatrin
GABA-T
Succinic semi-aldehyde
GABA-T
GABA
Succinic semi-aldehyde
Tiagabine
GATI
GABA
Felbamate, topiramate, zonisamide
Benzo-diazepines
Barbiturates
Postsynaptic neuron
GABA$_A$ receptor
Cl$^-$

:Pharmacokinetics

Pharmaceutical form : greatly affects the **bioavailability** **-1**
.of phenytoin

.It has a **plasma protein binding** activity.2

Phenytoin is subjected to **zero order kinetics** and at.3
therapeutic level it transfers to **1st order kinetics**(dose
.dependent)

It is hepatic enzyme **inducer**. it induces **insignificantly** its.4
own metabolism but the metabolism of **other** drugs
significantly induced including other antiepileptic drugs
so

phynetoin **accelerates metabolism** of many drugs like **vitamin D**, **folate** leading to **reduce their therapeutic .efficacy**

Affected by **liver enzymes inhibitors** like Sodium .5 .valproate, cimetidine, and erythromycin

Taken **orally (the best)or intravenously i.v ..** bs Phenytoin .6 is insoluble and crystallizes out in intramuscular i.m injection site, so i.m is contraindicated because of the risk .of necrosis and damage the tissue

Intravenous phenytoin is **irritant** to veins and tissues .7 .because of high pH, **thus** giving **slowly in large vein** .**Fosphynetoin** is water soluble, can be taken **i.v****

:Therapeutic uses

:A- The epileptic uses

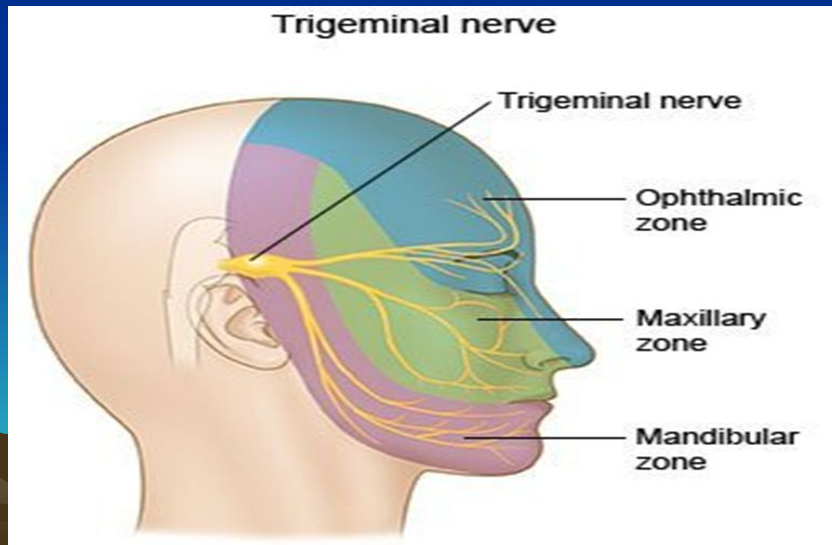
.Tonic-clonic seizures .1

Status epilepticus (by slow I.V.):**1st** we start with **rapid** acting drug .2
.like **diazepam** then with **long** acting **phenytoin**

:B- Non epileptic uses

.**Trigeminal neuralgia** (**2nd choice** drug after carbamazepine) -1

Anti-arrhythmic(class I B) in **cardiac arrhythmia**-2
.(stabilizing effect to the tissues)



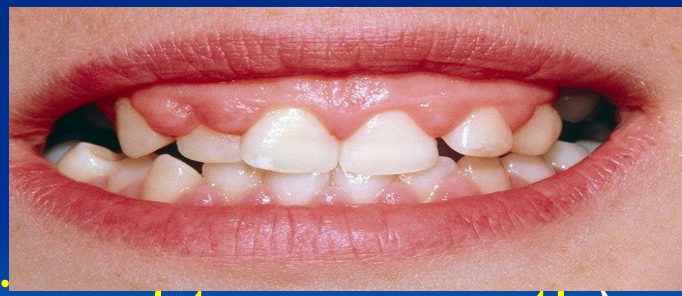
:Side effects

Decrease the ability to learn. Also impairment of cognitive function .1

CNS side effects including: **NAD** nystagmus, ataxia and diplopia, .2
. sedation up to delirium

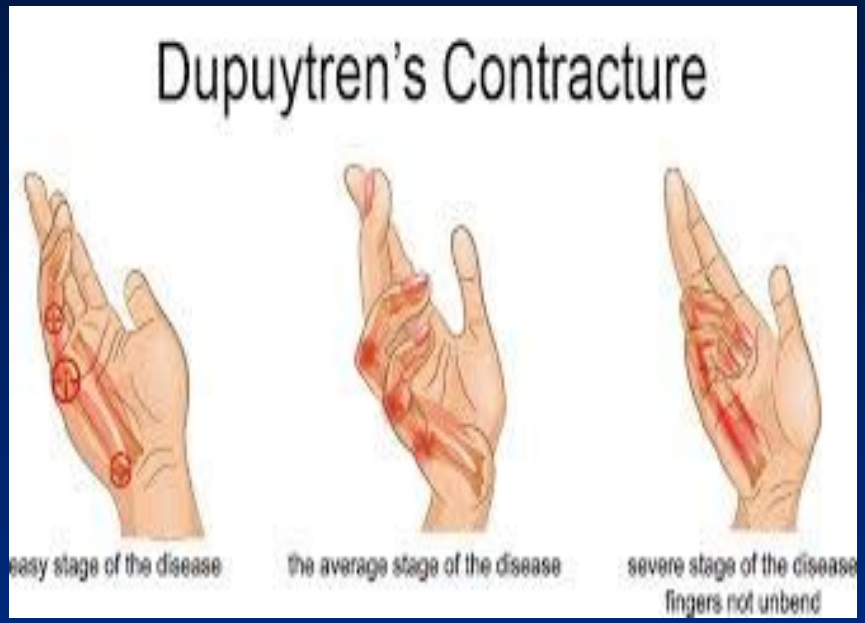
,**Allergic effects** like rashes, urticaria .3

Inhibition of collagenase enz.(after long treatment) This **leads** to .4
inhibition of collagen catabolism which causes gum hypertrophy
.(hyperplasia) and coarsening of facial features



It may cause **duputrens contracture**.5

mediated through the peripheral stimulation of tissue growth)
(.factors



Megaloblastic anemia (due to decrease folic acid level bs .6 .phenytoin accelerates metabolism of folate)

.**Osteomalacia** (bs it accelerates metabolism of Vit. D) .7

Hirsutism (Increase in fibroblast growth factor but mostly .8 .it is androgen dependent.)

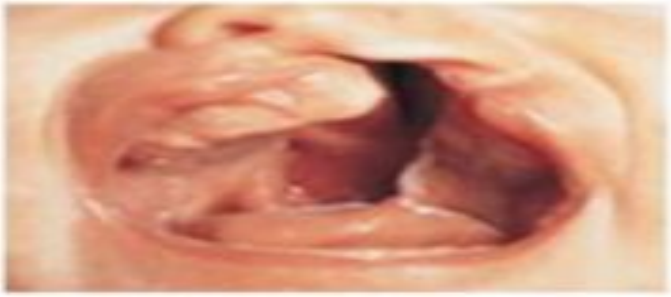
Hyperglycemia or glucosuria (bs of **decrease insulin** -9 . **release**)

Lymphadenopathy(charecteristic feature of phenytoin) -10

in pregnancy:

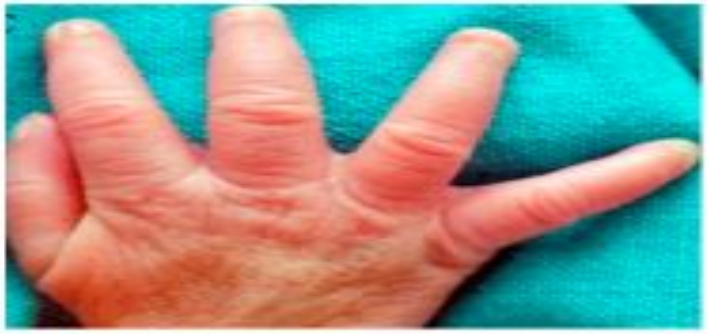
Teratogenic, in **first trimester** of pregnancy, can cause **fetal hydantoin syndrome** (Children may develop wide mouth (craniofacial defect =**cleft lip and palate**), **short nose**, mild **webbing of the neck**, **hypoplastic** nails, **microcephaly**, congenital **heart defects** and **mental** subnormality). Neural tube defect(spina bifida)

Fetal hydantoin syndrome is rare disorder caused by exposure of fetus to teratogenic effect of phenytoin- an anti-convulsant drug. Some symptoms are:



a) Cleft lip and palate

b) Short nose



c) Distal phalanges and hypoplastic nails

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HOW TO REMEMBER *SIDE EFFECTS OF PHENYTOIN*

IN 2 MINS

H	HIRSUTISM
O	OSTEOMALACIA
T	TERATOGENICITY
M	MEGALOBLASTIC ANEMIA
A	ARRHYTHMIA (at toxic doses)
I	INHIBITS INSULIN RELEASE
L	LYMPHADENOPATHY
G	GUM HYPERTROPHY
A	ATAXIA (at toxic doses)
N	NYSTAGMUS (at toxic doses)
D	DIPLOPIA (at toxic doses)
K	VITAMIN K DEFICIENCY

FETAL HYDANTOIN SYNDROME

- Cleft Lip
- Cleft Palate
- Microcephaly
- Hypoplastic phalanges

Carbamazepine (tegretol), Oxcarbazepine (2nd generatio).2

Carbamazepine is structurally related to **anti-depressants** (TRICYCLIC GROUP), **Eslicarbazepine** .(Imipramine)

:Mechanism of action

Blocking Na channels so it stabilize membrane to **-1** .depolarization

.Modulation of calcium channels by **Oxcarbazepine -2**

Carbemazepine May aggravate absence and myoclonic attack**

:Kinetics

Carbamazepine -1

It is **absorbed** completely **slowly** •

It **cross BBB** rapidly (high **lipid** solubility) •

It acts as enzymes **inducer** (induce folate metabolism leads to • megaloplastic anemia)+ auto induction (increase its on .metabolism=important characteristic)

Its **metabolism** in liver is **inhibited** by cimetidine & valproate •

- **75-85 % bioavailability, t1/2= 10-20 hr , in multiple dosing**

2- Oxcarbazepine: less potent than carbamazepine, **100% bioavailibility,** is effective for **partial** seizures, with **t1/2 of 1-2 hr** and **fewer interactions.**

3- Eslicarbazepine acetate: Similar to oxcarbazepine but it is given **once daily** and **rapidly converted** to the **active metabolite.**

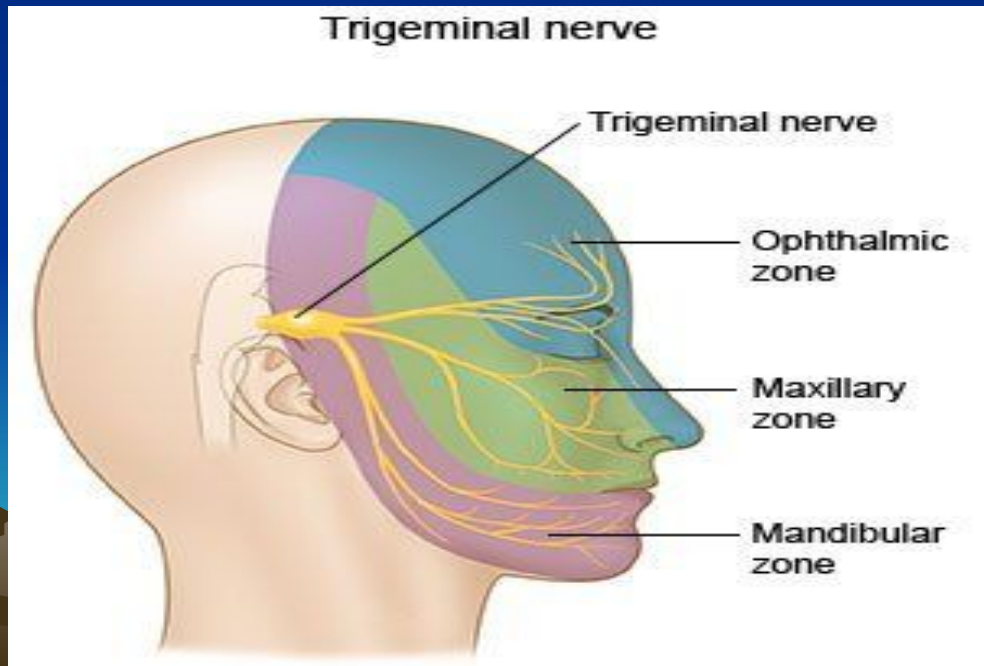
:Uses of carbamazepine

Focal seizures (**1st choice**) .1

.Tonic clonic seizure(**2nd choice**) .2

.Trigeminal neuralgia(**1st choice**) .3

Bipolar depression (in Manic depressive) patients .4



:Side effects

CNS: **NDA** (nystagmus , diplopia, ataxia). but coma and.**1** respiratory depression may occur with chronic .administration

.**GIT**: Irritation of stomach, nausea and vomiting.**2**

Blood : a- Megaloplastic anemia (bs of folate .3 .deficiency)

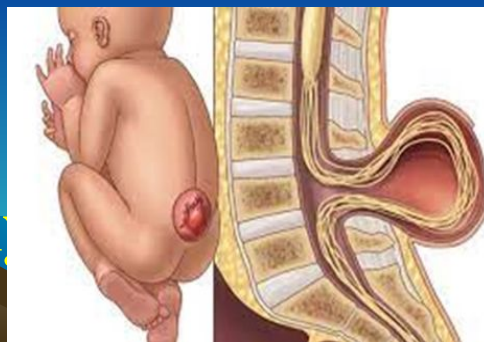
b- Agranulocytosis and thrombocytopenia(BM)

.Liver toxicity .4

Teratogenic : produce: a- craniofacial anomaly (cleft .5 palate)

b-neural tube defect (spina bifida)

Side effects profile of Eslicarbazepine are .6 serious such as **rash, psychiatric side effects, .&hyponatremia (increase ADH) occur rarel**



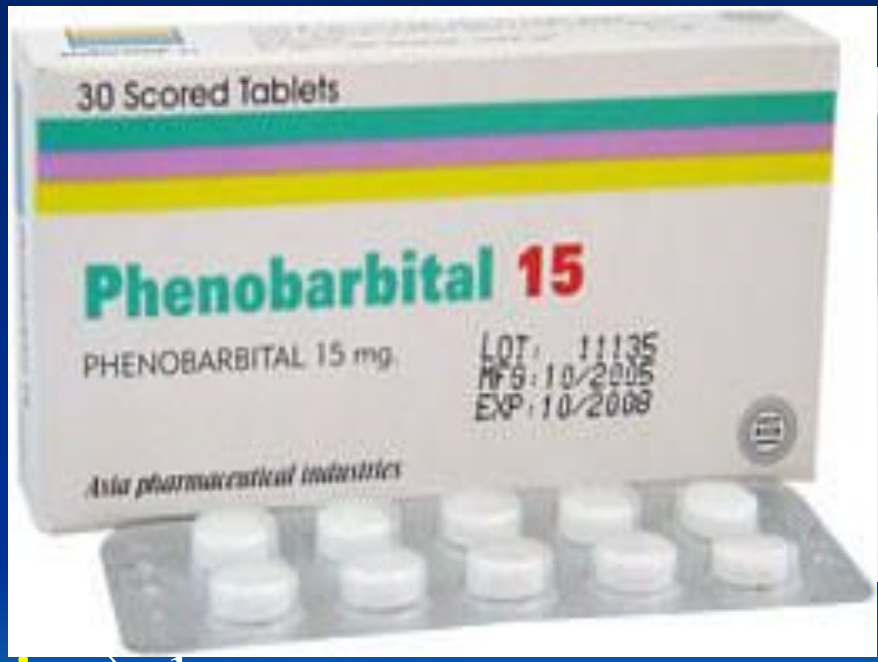
:Barbiturates .3

A. Phenobarbital: **long** acting barbiturates **act** by

Enhancing the activity of **GABA by allosteric** -1 **modulation of GABA A receptor**

Blocking of **Na channel -2**

GABA like action(GABA -3 .**(Agonist**



:Uses

.Febrile convulsions in children (**1st choice**) -1

Tonic clonic seizure **-2**

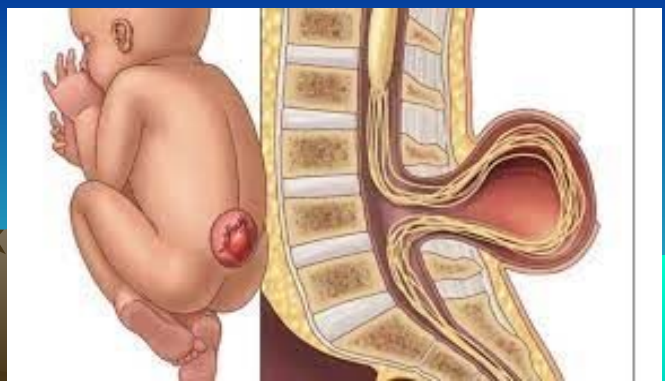
.Status epilepticus -3

Adverse effects

- **CNS**: **NDA**(nystagmus, diplopia, ataxia), dizziness, … ……. **Respiratory depression** in **toxic dose**
- **Liver**: enz. Inducer
- **Blood** :Megaloblastic anemia (due to acceleration of folate metabolism).
- **Teratogenic** : including:

  a- craniofacial anomaly (cleft palate)

  b- neural tube defect (spina bifida)
- **Tolerance and physical dependence**
- Its used **limited** bs of many **adverse**
- effects.



B. Primidone

It metabolized in the body **slowly** to **phenobarbitone** and • **rapidly** metabolized to **PEMA** (phenyl ethyl .malonamide)

Much of its anti-convulsive activity is related to • phenobarbitone

- can be used with **carbemazepine** and **phenytoin** allowing **smaller doses** of these drugs to be used.

Side effects: similar to that of phenobarbitone. (NDA, ….)**

Case

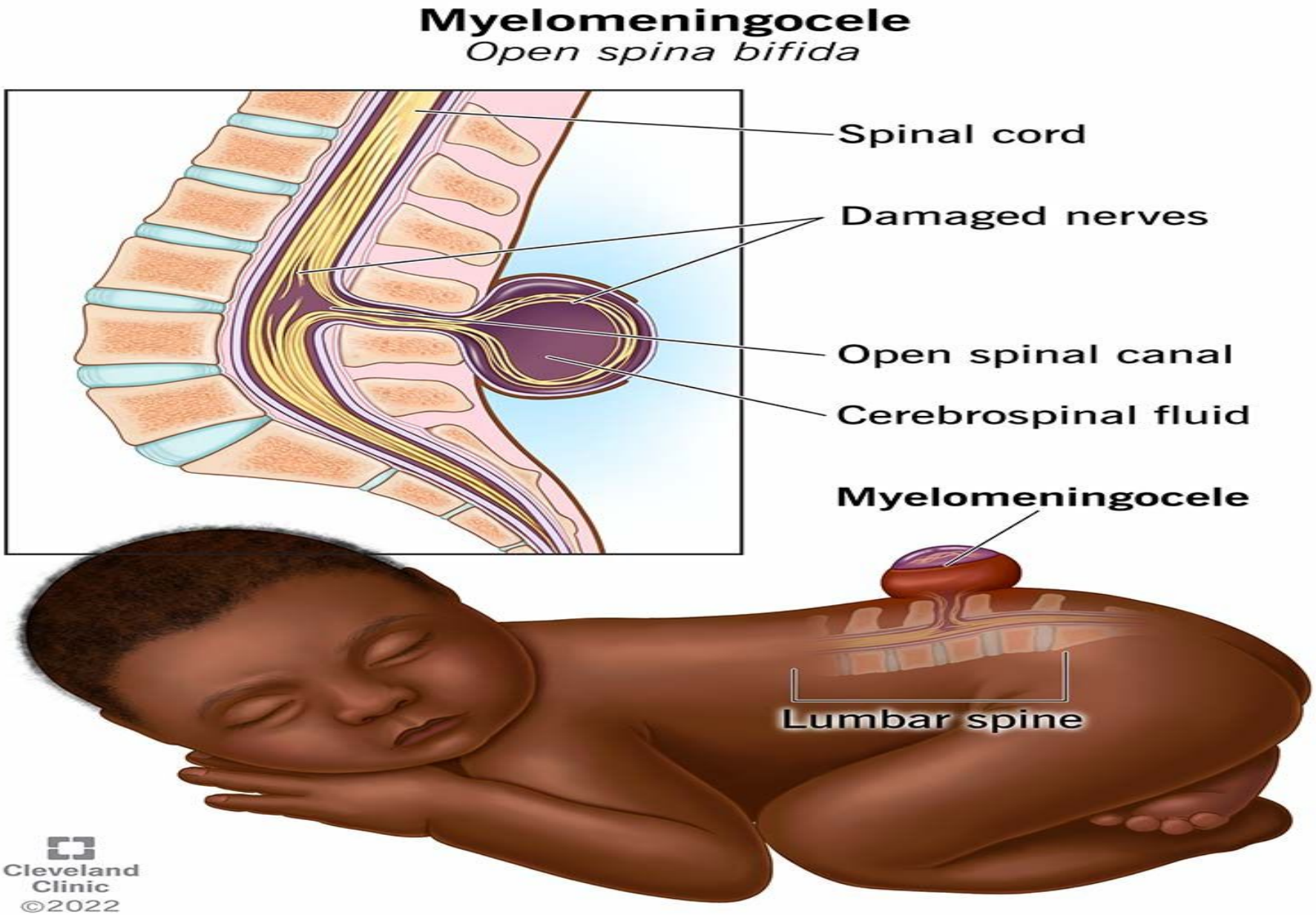
yrs old male, aknown case of epilepsy, 70 present to Medical Consultant Unit with gum hypertrophy (hyperplasia) and coarsening of facial .features

?Q1 : Which drug can cause this effects

? Q2 : Explain why this effect were happened

THANK YOU

For your informations



For your informations

Voltage sensitive calcium channels

	L-type (Long lasting current)	T-type (Transient current)	N-type (Neuronal)
1. Conductance	25 pS	8 pS	12–20 pS
2. Activation threshold	High	Low	High
3. Inactivation rate	Slow	Fast	Medium
4. Location and function	• Excitation-contraction coupling in cardiac and smooth muscle • SA, A-V node—conductivity • Endocrine cells—hormone release • Neurones—transmitter release	• SA node—pacemaker activity • 'T' current and repetitive spikes in thalamic and other neurones • Endocrine cells—hormone release • Certain arteries—constriction	• Only on neurones in CNS, sympathetic and myenteric plexuses—transmitter release
5. Blocker	Nifedipine, diltiazem, verapamil	Mibefradil, flunarizine, ethosuximide	ω-Conotoxin