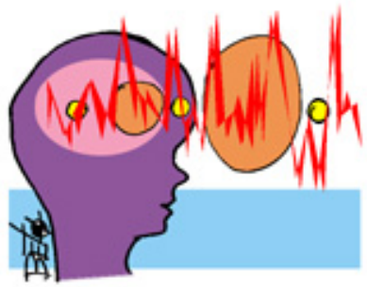
Epilepsy



Epilepsy is a disorder of neuronal excitability and comprehends any neurologic disorder that is characterized by recurrent, spontaneous seizures

Seizures is a sudden, stereotype episode with a change in motor activity, sensation, behavior or consciousness that is due to an abnormal electrical discharge in the brain

A seizure is the symptomatic event and epilepsy is the disorder

Neurobiology of Seizures

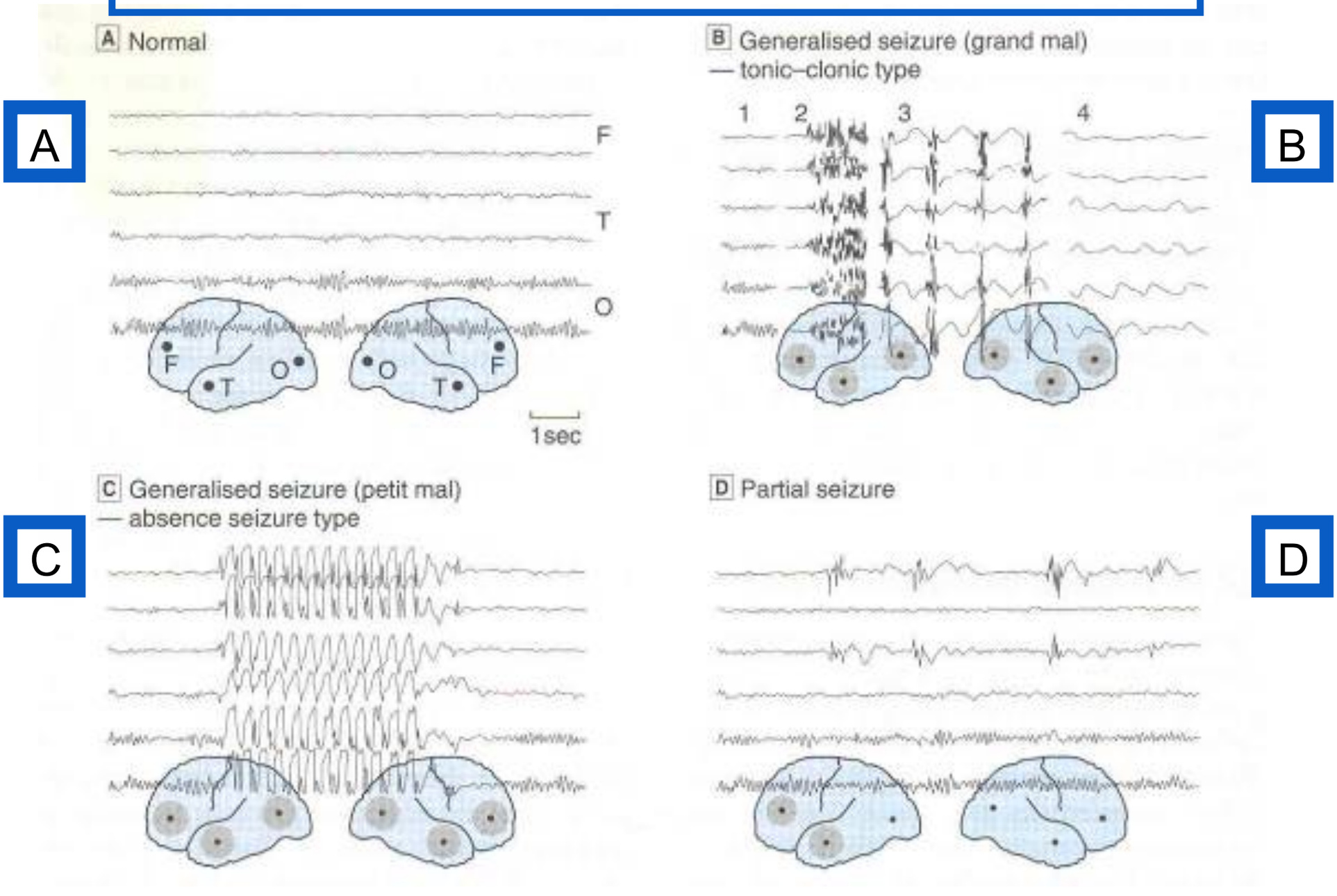
- Seizures are thought to arise from the disruption of the balance between inhibitory and excitatory synaptic transmission

- This impairment causes an synchronous, abnormal neuronal discharges within an area of the brain, the seizure focus. Once initiated, the abnormal discharges may (or may not) spread from one region of the brain to another

- The behavioral manifestations of an epileptic attac are determined by the functions normally served by the cortical site at which the seizure arises

- Seizures are accompanied by characteristic changes in the electroencephalogram (EEG)

EEG records in epilepsy



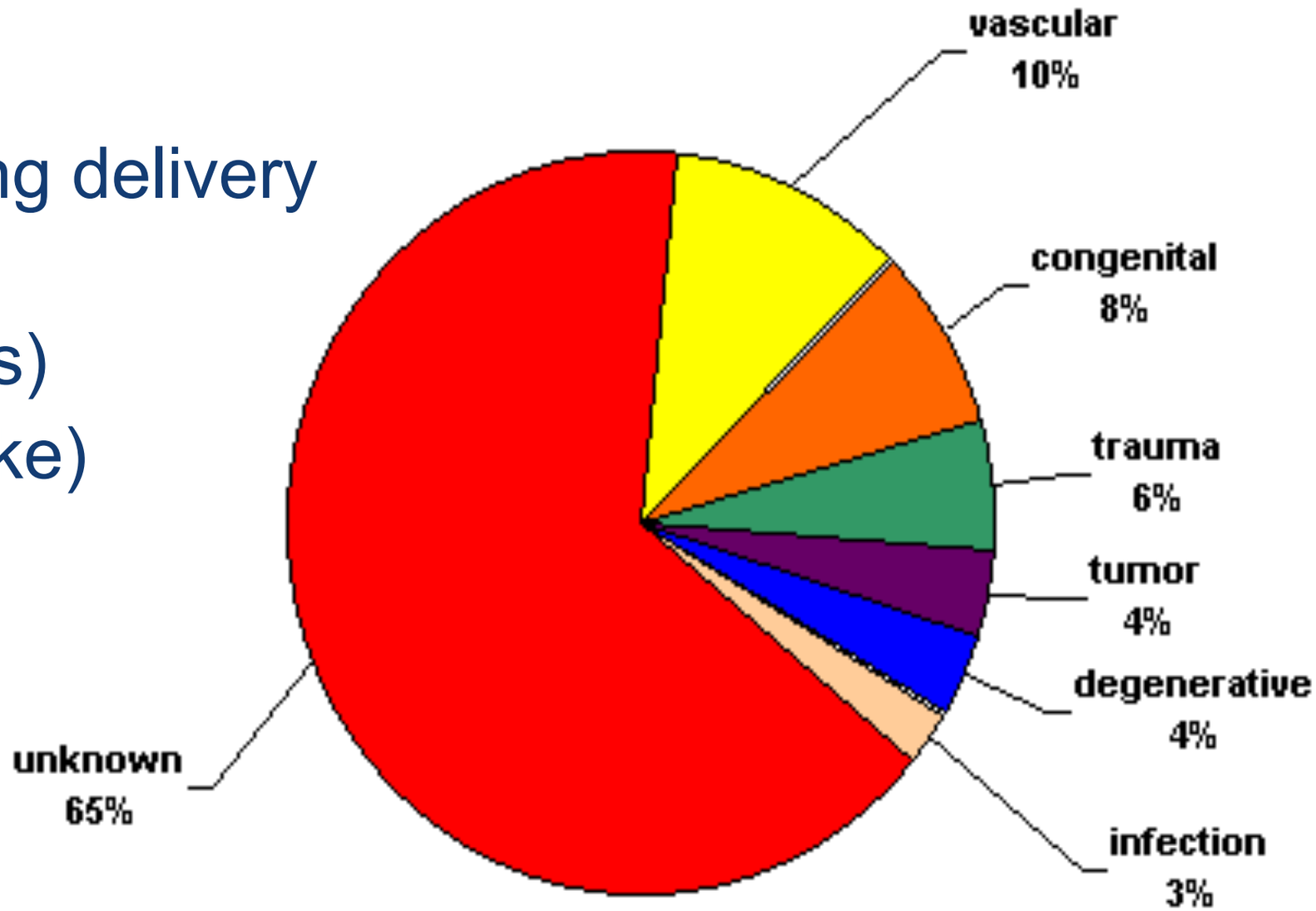
A Normal EEG recorded from frontal (F), temporal (T) and occipital (O) sites on both sides, as shown in the inset diagram. **B** Sections on EEG recorded during a generalized tonic-clonic (grand mal) seizure. 1. Normal record. 2. Onset of tonic phase. 3. Clonic phase. 4. Post-convulsive coma. **C** Generalized absence seizure (petit mal) showing sudden brief episode of 3/s 'spike and wave' discharge. **D** Partial seizure with synchronous abnormal discharges in left frontal and temporal regions.

Etiology of Seizures

Genetic (autosomal dominant genes)
Congenital defects

Acquired:
Brain damages during delivery
Severe head trauma
Infections (Meningitis)
Ischemic injury (stroke)
Tumors
Drug abuse
Drug withdrawal
Fever in children

Unknown



Genetic (or idiopathic) Epilepsies: central role of ion channels

Mutations in genes that encode subunits of voltage-gated and ligand-gated ion channels that cause increased excitability or brain abnormality

Voltage-gated ion channels: mutations of Na+, K+ and Cl- channels (associated with forms of generalized epilepsy and infantile seizure syndromes)

Ligand-gated ion channels: mutation of nicotinic acetylcholine receptors and GABA receptor subunits (associated with frontal and generalized epilepsies, respectively)

Epilepsy genes and their associated epilepsy syndromes

Gene	Syndrome[a]
Voltage-gated ion channels	
Na^+ channels:	
SCN1A	$GEFS^+$ and SMEI
SCN2A[b]	BFNIS and $GEFS^+$
SCN1B	$GEFS^+$
K^+ channels:	
KCNA1[b]	Partial seizures
KCNQ2	BFNS and myokymia
KCNQ3	BFNS
Cl^- channels:	
CLCN2[b]	IGE
Ligand-gated ion channels	
GABA receptors:	
GABRA1[b]	ADJME
GABRG2	CAE, FS and $GEFS^+$
Neuronal nicotinic acetylcholine receptors:	
CHRNA4	ADNFLE
CHRNB2	ADNFLE
Non-ion-channel genes	
LGI1	ADPEAF
MASS1[b]	Possible $GEFS^+$

ADJME: autosomal dominant juvenile myoclonic epilepsy;
ADNFLE:autosomal dominant nocturnal frontal lobe epilepsy;
ADPEAF: autosomal dominant partial epilepsy with auditory features
BFNIS: benign familial neonatal infantile seizures
BFNS: benign familial neonatal seizures
CAE: childhood absence epilepsy
FS: febrile seizures
GEFS: generalized epilepsy with febrile seizures
IGE: idiopathic generalized epilepsy
SMEI: severe myoclonic epilepsy of infancy.

Pathophysiology of Seizures

Multifactorial: Determining factor is the result of interaction between genetically determined seizure threshold, underlying pathological and metabolic conditions, and acute precipitating factors

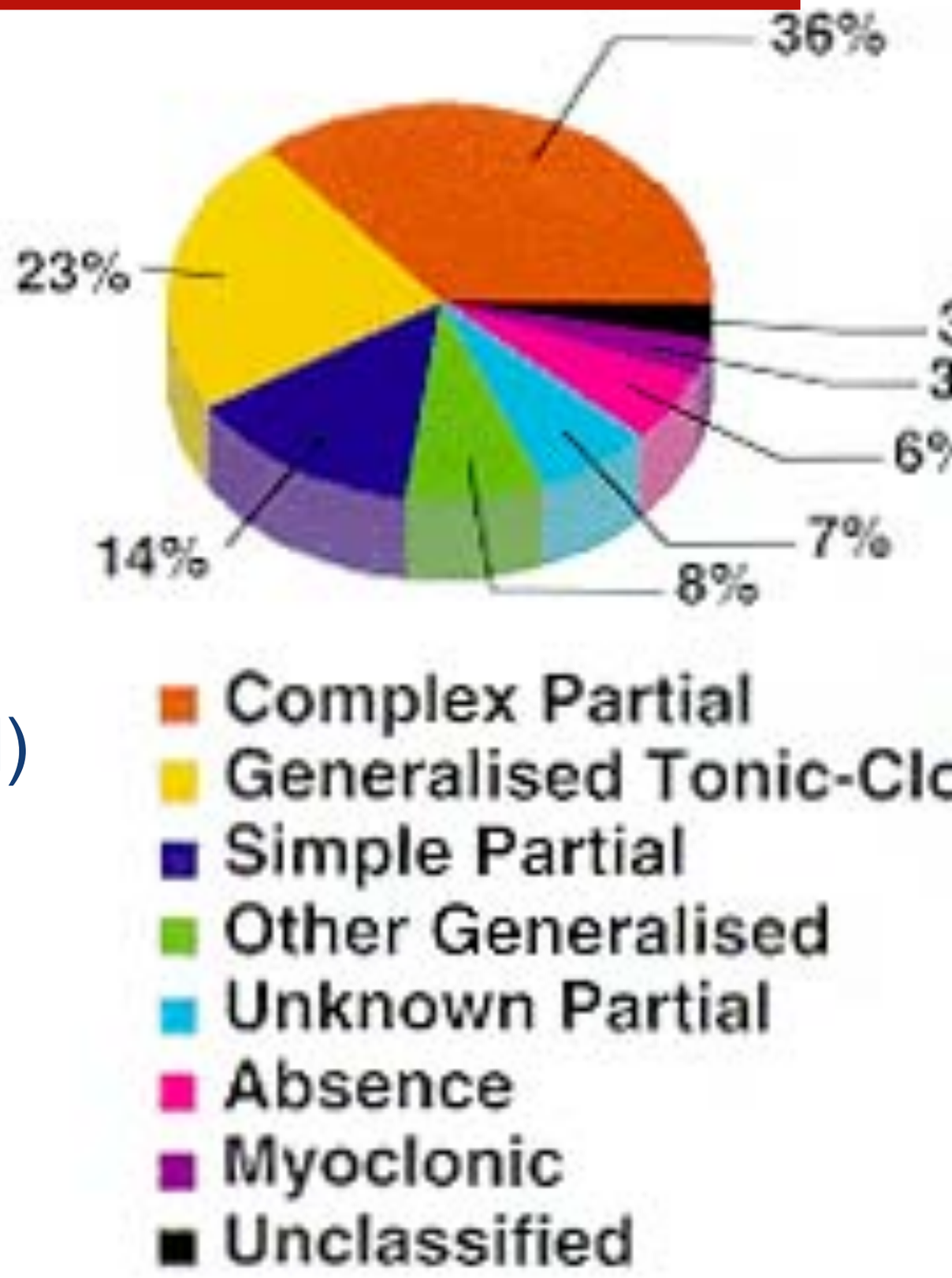
Triggers: fatigue, stress, poor nutrition, alcohol and sleep deprivation

In predisposed persons, certain stimuli (Visual stimuli- flickering light, Thinking, Music - certain frequencies, Reading) can precipitate *reflex seizures*

Classification of Seizures types

Two categories

1. Partial (focal) seizures
   - simple
   - complex
2. Generalized seizures
   - tonic-clonic (grand mal)
   - myoclonic
   - atonic
   - absence (petit mal)



Special epileptic syndromes

Status epilepticus

Medical emergency in which seizures are repeated continuously

Hypoxia, hypoglycemia, acidosis, hypothermia, brain damage, death

Febrile seizures

Tonic-clonic motor activity X 1-2 min

During illness

Children 3 mos- 5 yrs

Prevention!

Partial Seizure

Short alteration in consciousness, repetitive unusual movements (chewing or swallowing movements), psychologic changes and confusion

Simple Partial Seizures

- Arise in one cerebral hemisphere (focal) with minimal spread of abnormal discharge
- Normal consciousness and awareness are maintained
- Motor symptoms (most commonly legs, arms, face)
- Hallucinations of sight, hearing or taste, along with somatosensory changes (tingling)
- Autonomic nervous system responses

Complex Partial Seizures

- Local onset, then spreads
- Impaired consciousness
- Clinical manifestations vary with site of origin and degree of spread
- - presence and nature of aura
- - automatisms
- - other motor activity
- Temporal lobe epilepsy most common

Generalized Seizures

Both cerebral hemisphere are involved with a temporary lapses in consciousness lasting a few seconds

Tonic-clonic seizures (grand mal)

Tonic Seizures: sudden stiffening of the body, arms, or legs

Clonic Seizures: rhythmic jerking movements of the arms and legs without a tonic component

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

Generalized seizures

Absence seizures (Petit mal)

- consciousness is altered
- attack may be associated with mild clonic jerking of the eyelids or extremities, postural tone changes, autonomic phenomena and automatisms
- sudden onset and abrupt cessation: duration less than 10 sec and rarely more than 45 sec
- in a pediatric population, absence seizures occupy a greater proportion

Antiepileptic Drugs (AEDs)

- **A drug which decreases the frequency and/or severity of seizures in people with epilepsy**

- **Treats the symptom of seizures, not the underlying epileptic condition**

- **Goal of the therapy: improve quality of life by minimizing seizures and adverse drug effects**

- **Currently no “anti-epileptogenic” drugs are available**

Classification of Antiepileptic Drugs (AEDs)

Classical	Newer
Phenytoin	**Lamotrigine**
Carbamazepine	**Felbamate**
Valproate (valproic acid)	**Topiramate**
Phenobarbital	**Gabapentin**
Primidone	**Tiagabine**
Ethosuximide	**Vigabatrin**
	Oxycarbazepine
	Levetiracetam

In *general*, the newer AEDs have less adverse effects (e.g. CNS sedation) than the classical AEDs

Cellular Mechanisms of Seizure Generation

Too much excitation

Ionic: inward Na^+, Ca^{++} currents

Neurotransmitter: glutamate, aspartate

Too little inhibition

Ionic: inward Cl^-, outward K^+ currents

Neurotransmitter: GABA

Strategy of the AEDs Therapy

1. **Decrease excitatory neurotransmitter system: glutamate**
2. **Increase inhibitory neurotransmitter system: GABA**
3. **Block voltage-gated inward positive currents: Na^+ or Ca^{++}**
4. **Increase outward positive current: K^+**

Many AEDs are pleiotropic, i.e. act via multiple mechanisms

1. Decrease excitatory neurotransmitter system: glutamate

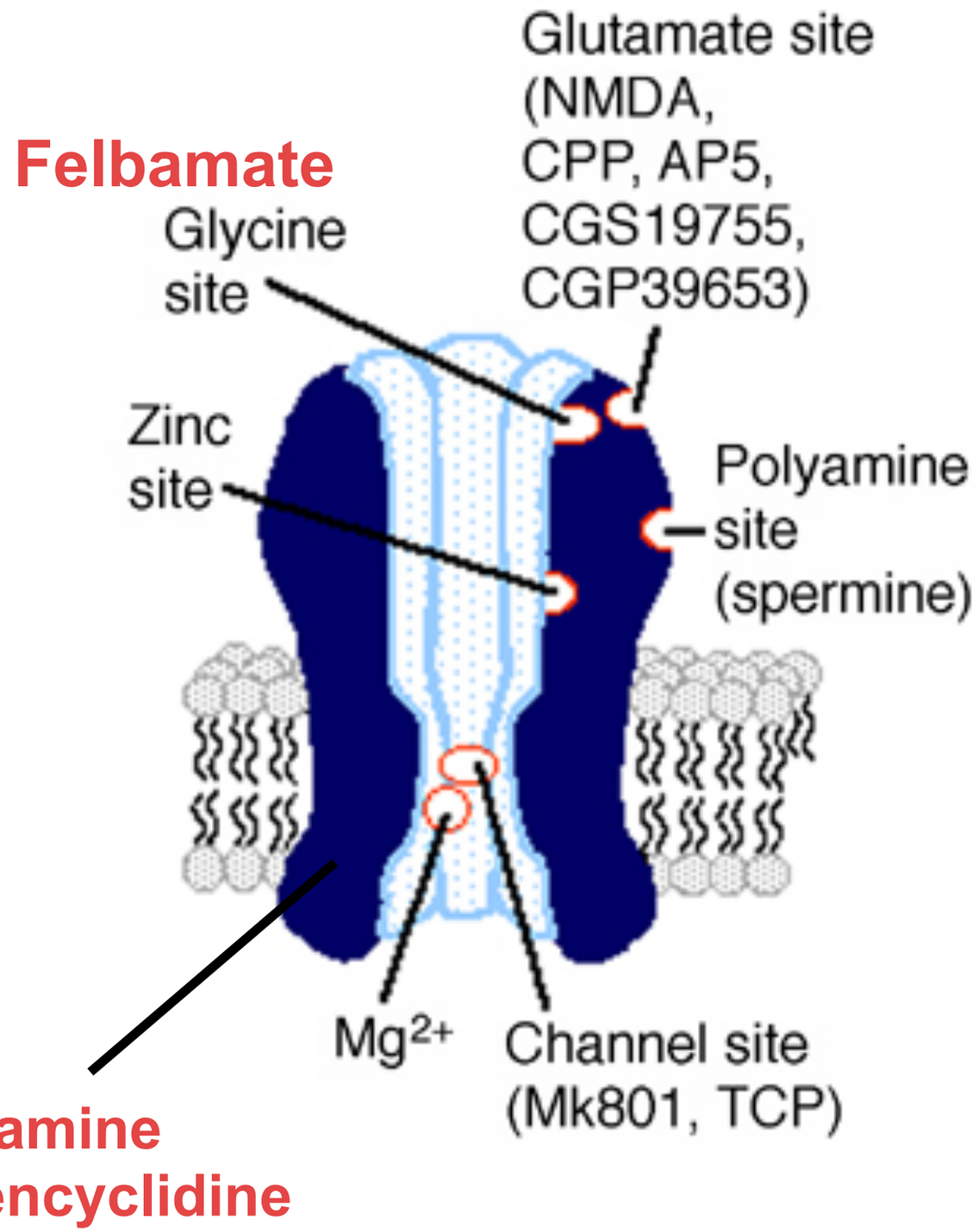
Modulation of glutamate ionotropic receptors

NMDA receptor

- Ketamine, phencyclidine: open channel blockers
- Felbamate: antagonism at the strychnine-insensitive glycine site

AMPA receptor

- Topiramate: antagonism at AMPA site
- Perampanel: non-competitive antagonist

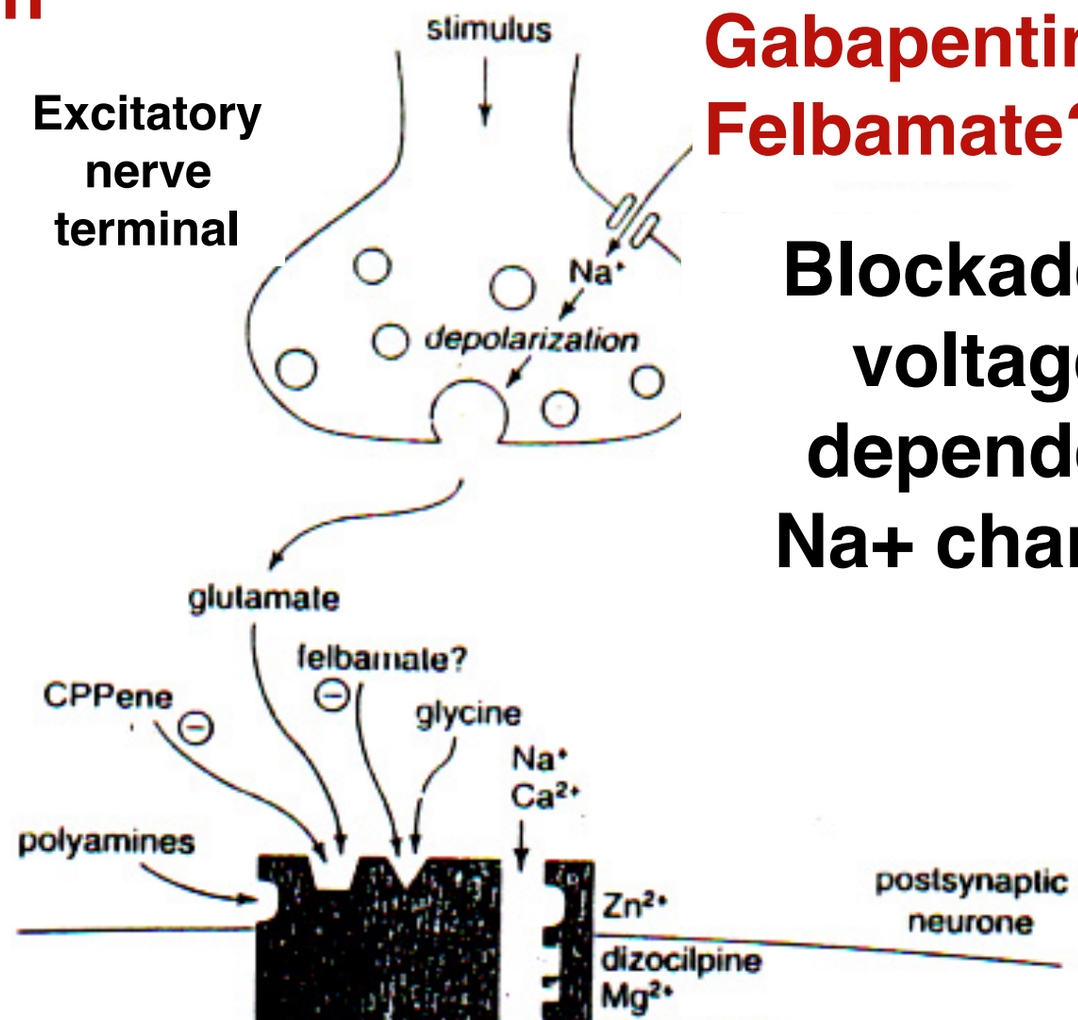


1. Decrease excitatory neurotransmitter system: glutamate

Modulation of glutamate-mediated transmission

Gabapentin

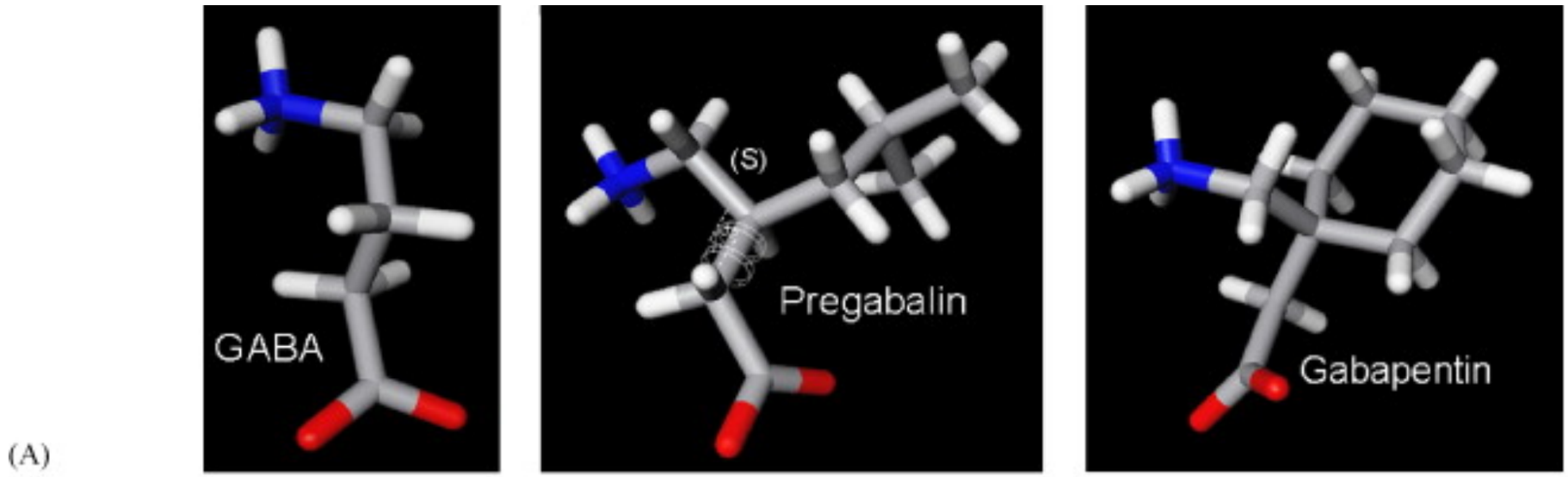
Blockade of voltage-dependent Ca2+ channel



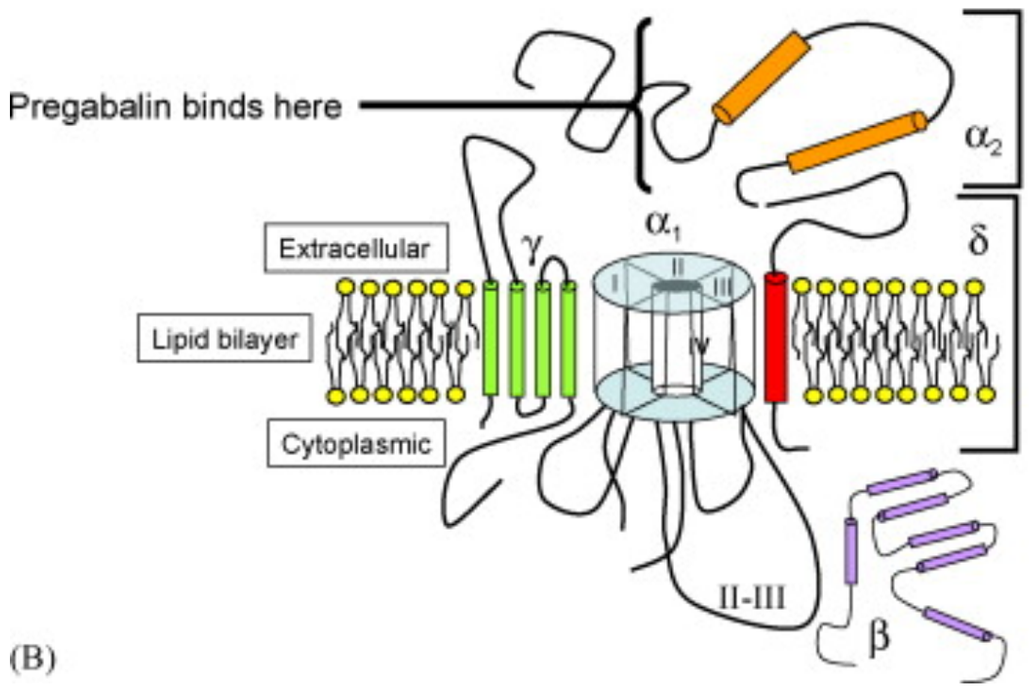
Carbamazepine
Phenytoin
Valproic acid
Lamotrigine
Gabapentin?
Felbamate?

Blockade of voltage-dependent Na+ channel

Pregabalin and Gabapentin:
a serendipitous example of drug discovery



(A)



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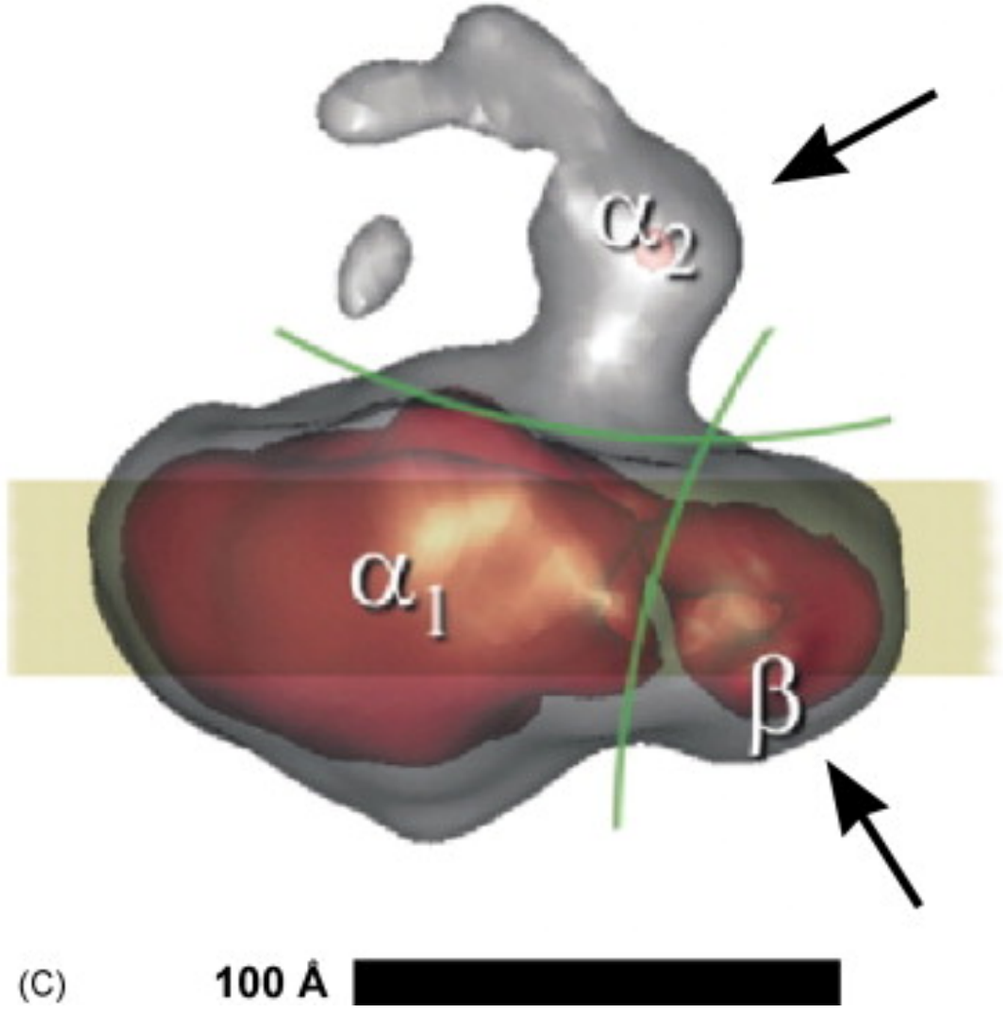


(C)

2. Increase inhibitory neurotransmitter system: GABA

Modulation of GABA ionotropic receptors

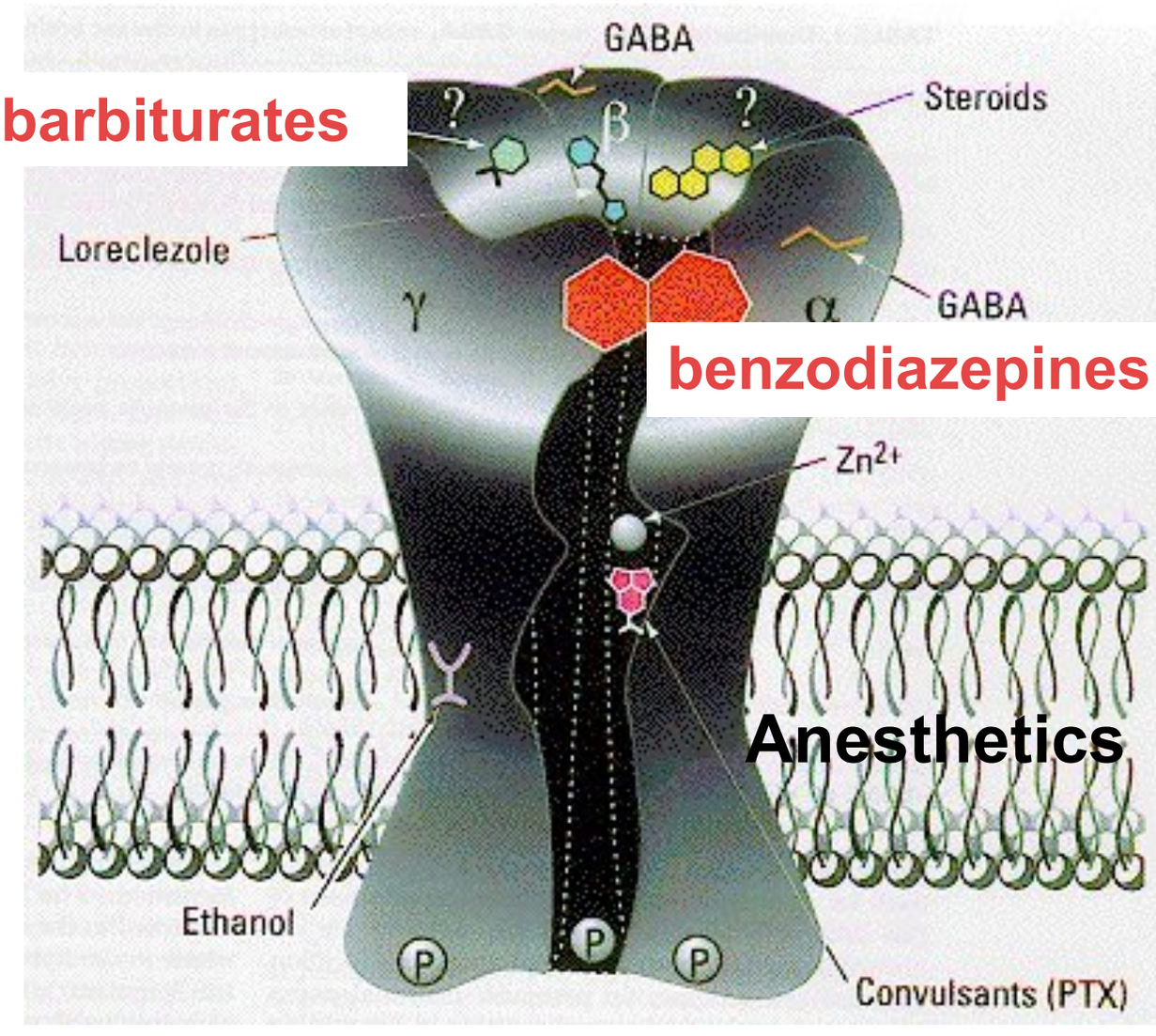
Benzodiazepines (diazapam, clonazepam)

- Increase frequency of GABA-mediated chloride channel openings

Barbiturates (phenobarbital, primidone)

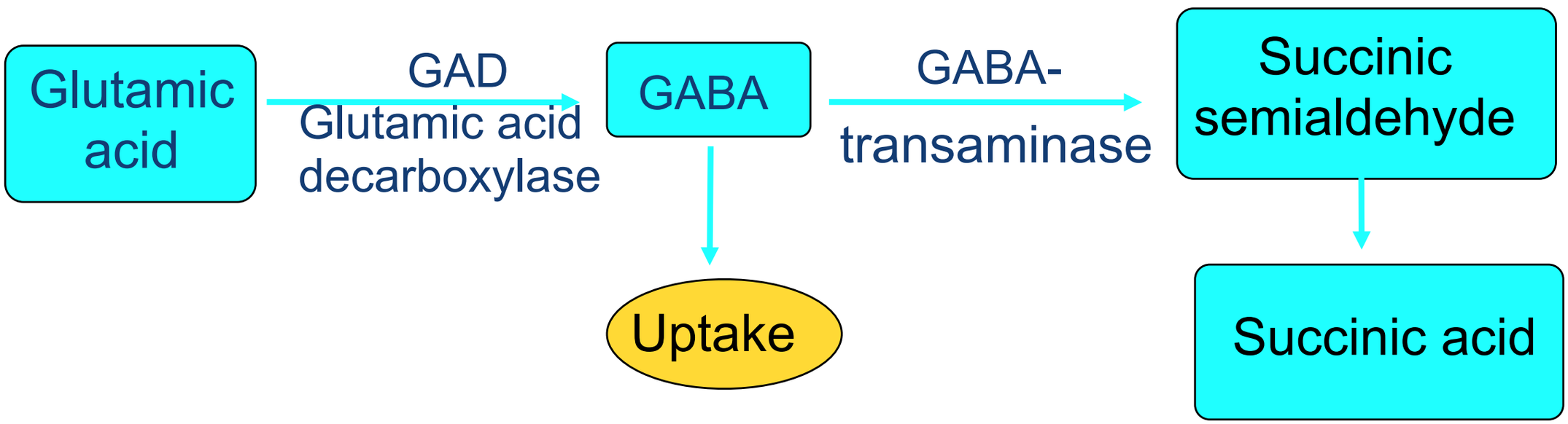
- Prolong GABA-mediated chloride channel openings
- Some blockade of voltage-dependent sodium channels

Topiramate



2. Increase inhibitory neurotransmitter system: GABA

Enhancement of GABAergic transmission



- **Inhibitors of GAD (*isoniazide*) induces convulsions**
- **Inhibitors of GABA-transaminase are potential anticonvulsants (*valproic acid, vigabatrin*)**
- **Inhibitors of GABA reuptake are potential anticonvulsants (*tiagabine, vigabatrin*)**

3. Block voltage-gated inward positive currents: Na^+

Phenytoin, Carbamazepine

Block voltage-dependent sodium channels at high firing frequencies (use dependent)

Oxcarbazepine

Blocks voltage-dependent sodium channels at high firing frequencies

Also effects K+ channels

Zonisamide

Blocks voltage-dependent sodium channels and T-type calcium channels

3. Block voltage-gated inward positive currents: Ca^{++}

- Absence seizures are caused by oscillations between thalamus and cortex that are generated in thalamus by T-type (transient) Ca^{2+} currents

- Ethosuximide is a specific blocker of T-type currents and is highly effective in treating absence seizures

4. Increase outward positive current: K^{+}

- Valproic acid

- Retiagabine

Sodium channel blockade

Carbamazepine

Eslicarbazepine acetate

Felbamate

Lacosamide

Lamotrigine

Oxcarbazepine

Phenytoin

Rufinamide

Topiramate

Zonisamide

α_2-δ modulation

Gabapentin

Pregabalin

Calcium channel blockade

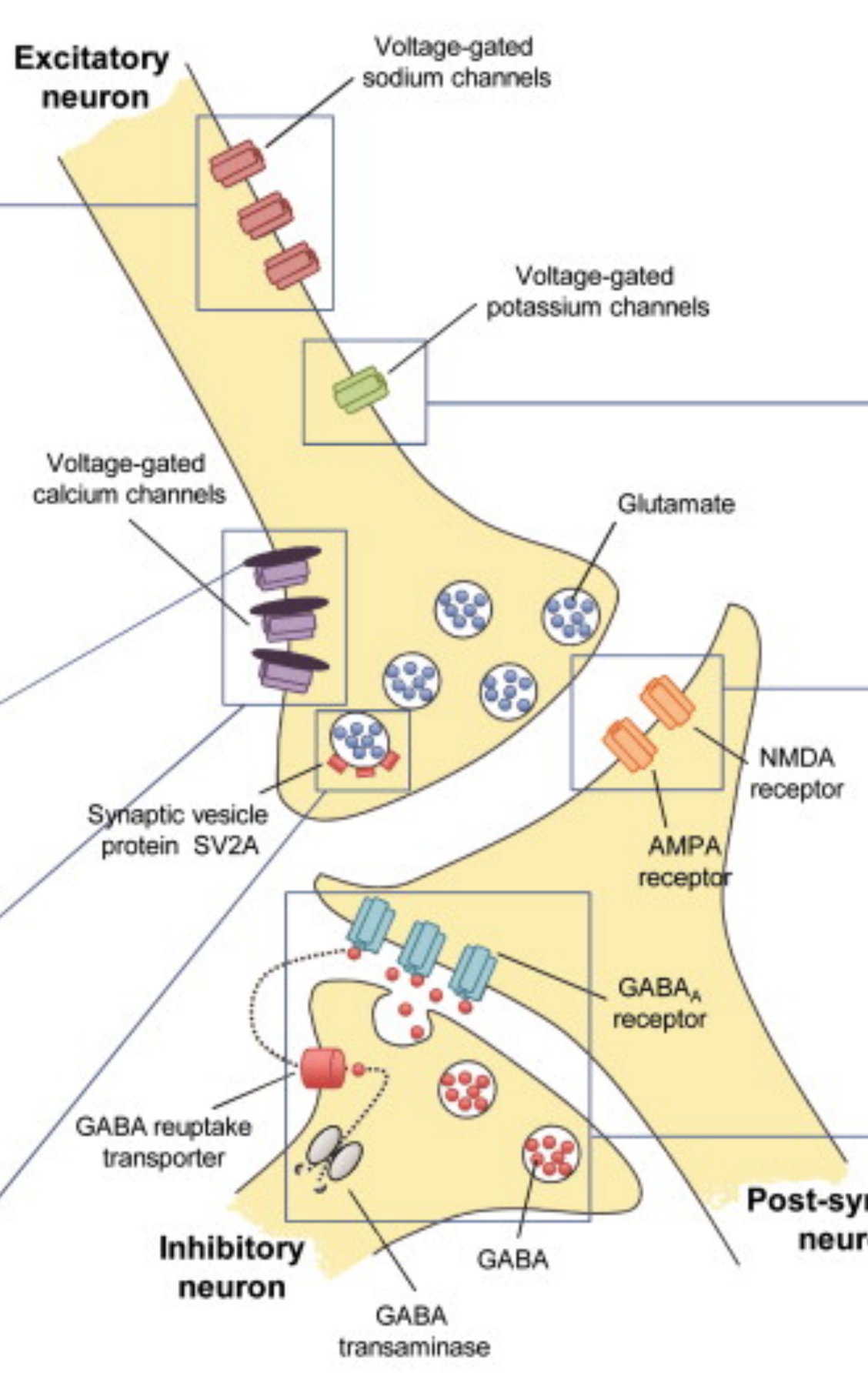
Ethosuximide

Lamotrigine

Zonisamide

Modulation of SV2A-mediated neurotransmitter release

Levetiracetam



Potassium channel activation

Retigabine (KCNQ)

Antagonism of glutamate

Felbamate (NMDA)

Lamotrigine (NMDA)

Topiramate (AMPA)

Potentiation of GABA activity

Barbiturates

Felbamate

Stiripentol

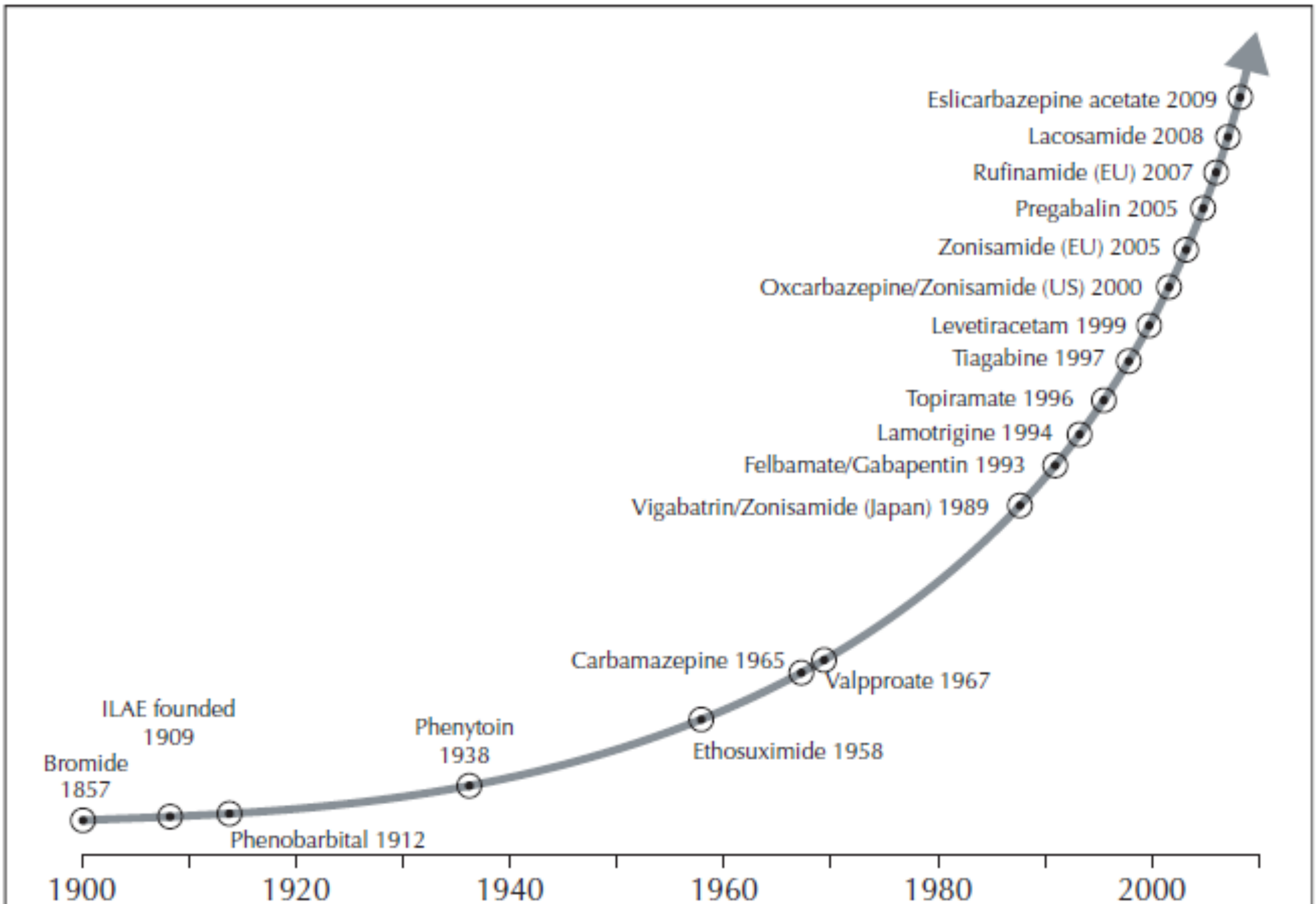
Tiagabine

Topiramate

Valproate

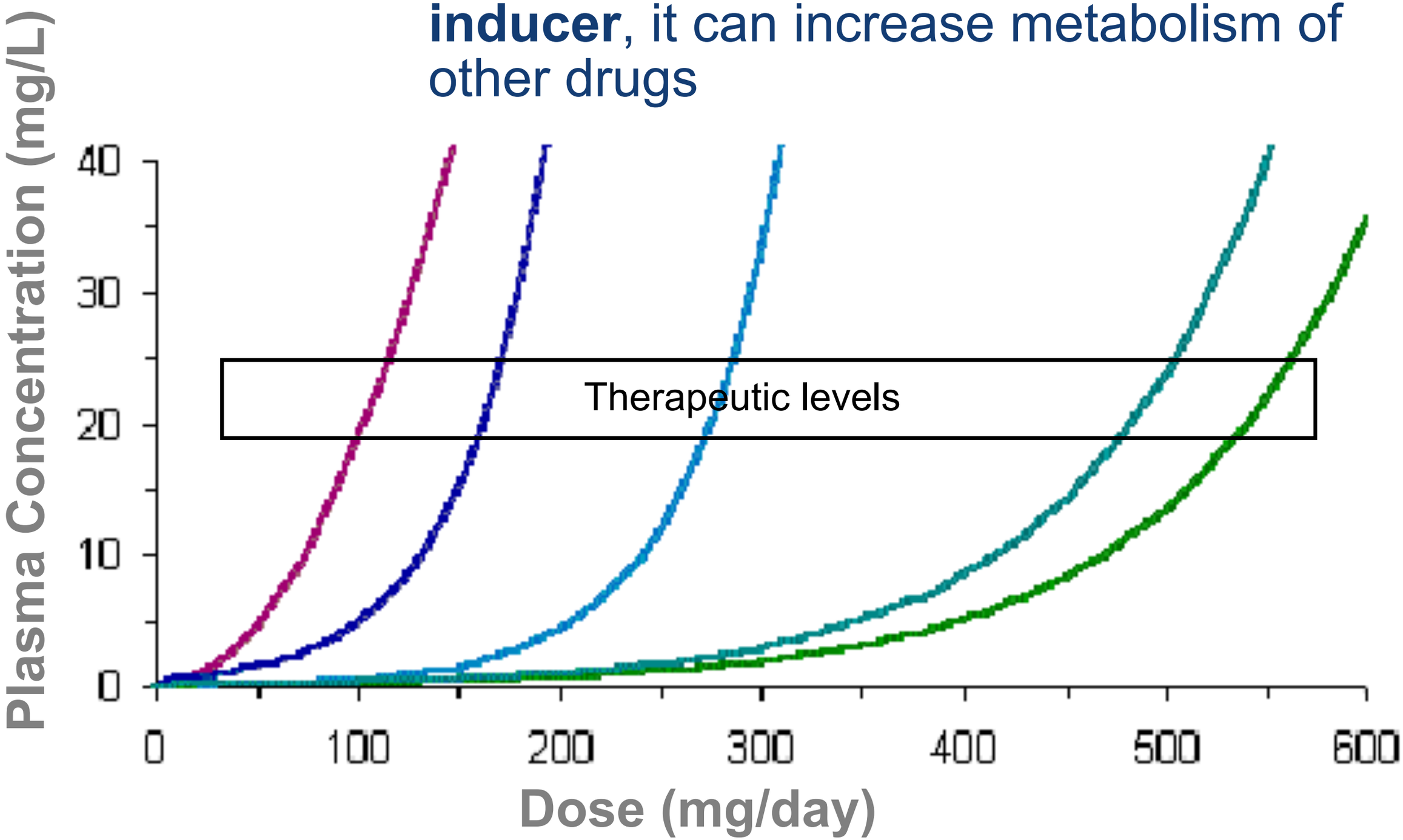
Vigabatrin

Antiepileptic drug development over the past 100 years



PHENYTOIN

- Saturable (zero order) kinetic in therapeutic dose range
- potent hepatic cytochrome P-450 enzyme **inducer**, it can increase metabolism of other drugs

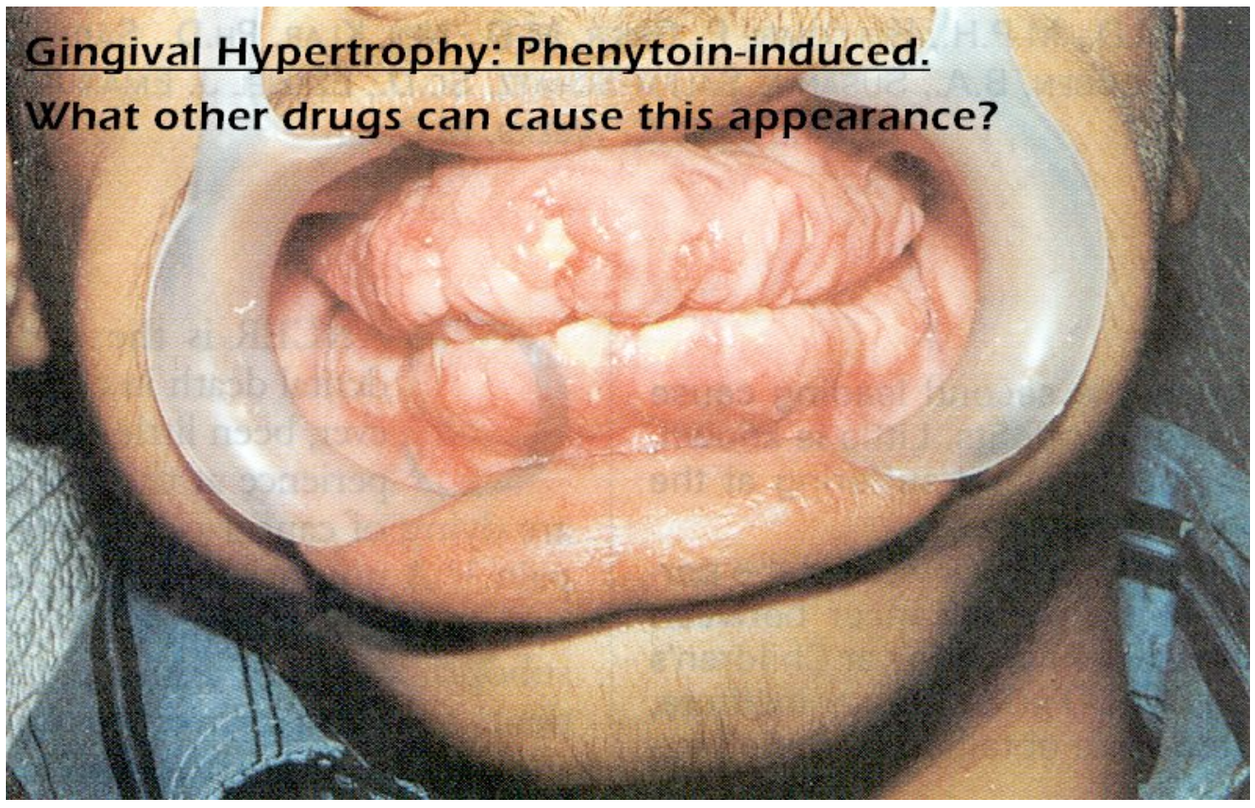


Relationship between Phenytoin Daily Dose and Plasma Concentration In 5 Patients

PHENYTOIN

Adverse effects

- CNS sedation (drowsiness, ataxia, confusion, insomnia)
- Impaired cognition
- Peripheral neuropathy
- Coarsening of facial features
- Hirsutism
- Gum hyperplasia



Newer Drugs Adverse Effects

Felbamate	• aplastic anemia and severe hepatitis
Levetiracetam	• Increased affective symptoms (anxiety, hostility, emotional lability)
Vigabatrin	• CNS sedative, ophthalmologic abnormalities (irreversible visual loss)
Topiramate	• CNS sedative (somnolence and dizziness, emotional lability, impaired concentration and psychomotor slowing, language problems)

H_3 receptors

Localised in the CNS & modulate neurotransmission

GABA-transaminase

GABA-transaminase decreases brain GABA content

$GABA_B$ receptor

Decrease neurotransmitter release by reducing Ca^{2+} entry

HCN channels

Activated cyclic necleotidegated cation (HCN) channels activating postsynaptic receptors and modulate release of the inhibitory neurotransmitter GABA through presynaptic mechanism

NMDA receptors

Associated with a conformational change in the receptor protein that opens the pore and permits cations to cross the membrane resulting in membrane depolarization and neuronal excitation

Acid sensing ion channels (ASIC)

Activaion of ASICs caused postsynaptic depolarization and reduction in the Mg^{2+} block of NMDA receptors

Gap junctions (connexins)

Present between neurons, astorcytes and astrocytes-neurons. Permits release fo compounds (glutamate, ATP) from glia into extracellular fluid

GTPase enzyme

Reduce the availability of SVS for exo-endocytosis feedback loops and exhaust the available vesicle export pool

T/N type calcium channel

Modulate release fo ions, control membrane potential and inhibit neuronal excitation

Kainate receptors

Activating postsynaptic receptors and modulate release of the inhibitory neurotransmitter GABA through presynaptic mechanism

Carbonic ahnhydrase

It modulates functional consequences of GABA-A receptor through pH alterations.

Sigma receptors

Involved in modulation of neurotransmitter receptor function and neurotransmitter release

Adenosine kinase

Upregulation of the adenosine-removing enzyme adenosine kinase (ADK), resulting in focal adenosine deficency leads to seizure generation

Protein kinasses & phosphatises

Effect ionic conductance that affects second messanger systems such as cAMP & cGMP. These secondary messanger systems affect protein kinases phosphorylation which modulate the activiry of the effectors

TRPV1

Transient receptor potential vanilloid receptor 1 modulates activity-dependent synaptic efficacy, facilitates long-term potentiation of hippocampal neurons and play an important role in nerve growth factor regulated epileptogenesis

AMPA receptors

Involved in modulation of neurotransmitter release

Galanine receptors

Galanine cause neutransimitter modulations

P-glycoprotein

P-glycoprotein has been shown to reverse the drug resistant phenotype

Drug Discovery Today