Antiepileptics

Samar Hunaiti

Definitions

- A seizure is a transient alteration of behavior due to the disordered, synchronous, and rhythmic firing of populations of brain neurons.

- Epilepsy refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures (recurrent seizures)

- Convulsion – Involuntary spasmodic contractions of skeletal muscles

Epilepsy is a chronic disorder characterized by recurrent seizures

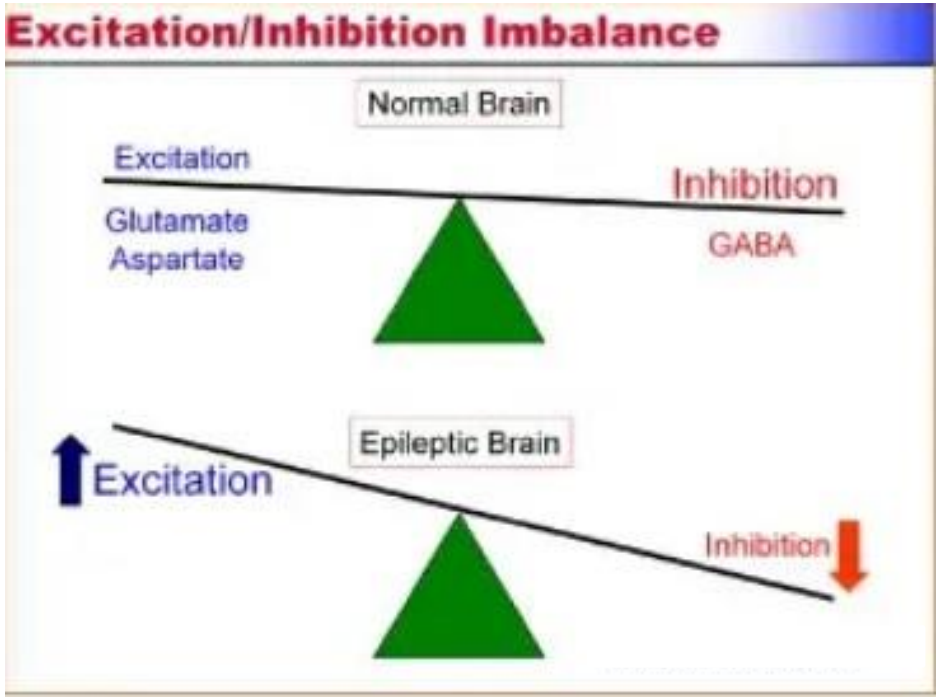
Causes of epilepsy

- Genetic or heredity
- Brain lesions- Birth trauma
- Infections- Meningitis, brain abscess
- Metabolic disorders- Hyperpyrexia, Hypoglycaemia, Hypocalcaemia
- Sudden drug withdrawal- alcohol,barbiturates

Mechanisms of Seizure Generation

- Too much excitation
  - ❖ Neurotransmitter—glutamate, aspartate ↑
  - ❖ Ionic—inward Na^+, Ca^{++} currents

- Too little inhibition
  - ❖ Neurotransmitter—GABA ↓
  - ❖ Ionic—inward Cl^-, outward K^+ currents


Excitation/Inhibition Imbalance
Normal Brain
Excitation
Glutamate
Aspartate
Inhibition
GABA
Epileptic Brain
Excitation
Inhibition

Classification of Epilepsy

Two major categories, namely partial and generalized seizures there is some overlap and many varieties of each.

• Partial seizures (focal)

The seizure activity is restricted to a discreet area in one cerebral hemisphere

- Simple partial seizure
- Complex partial seizure(psychomotor seizures)
- Partial evolving to secondary generalized seizures

• Generalised seizures

Arise from both cerebral hemispheres and diencephalon simultaneously involving the entire body.

- Grand mal (Tonic Clonic):
- Absence (Petit mal)
- Myoclonic
- Atonic(Akinetic)
- Tonic
- Clonic
- Status epilepticus

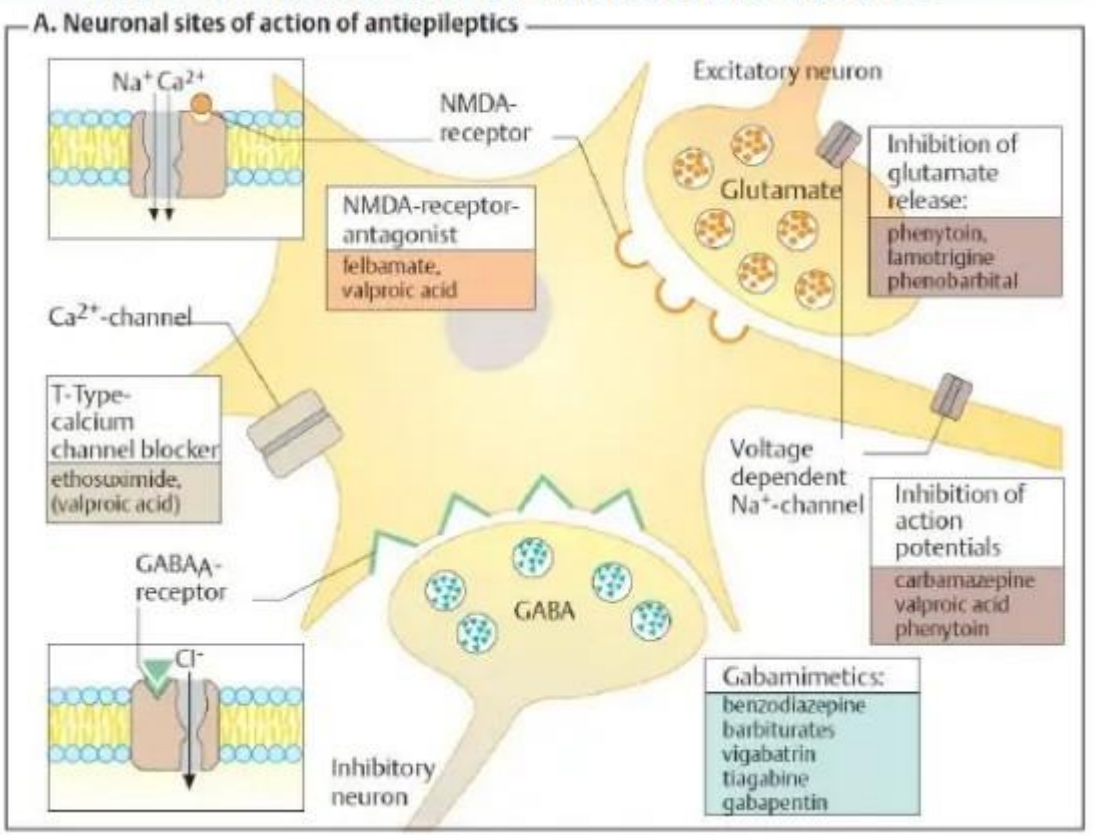
Unclassified seizure- Febrile seizures and infantile spasms

Classification of antiepileptic drugs

- Older antiepileptics: Phenytoin, Phenobarbitone, Carbamazepine, Ethosuximide, Valproic acid

- Newer antiepileptics: Gabapentin, Vigabatrin, Lamotrigine

Site of action of antiepileptics

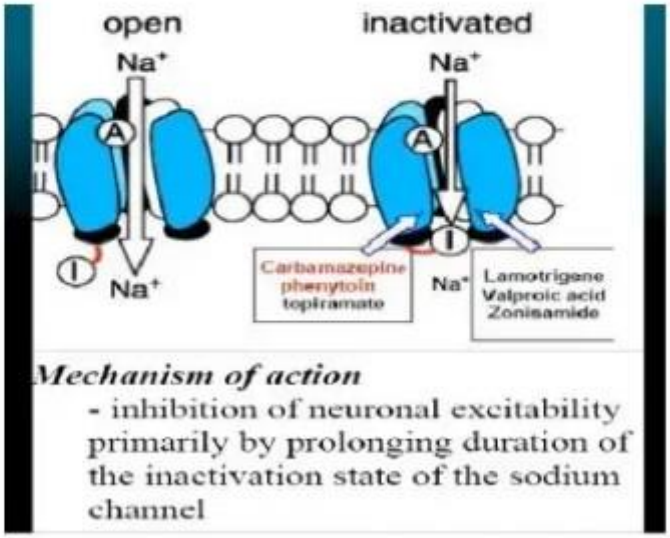


General mechanism of antiepileptic drugs

1. Inhibition of use-dependent Na+ channels:

Block voltage gated Na+ channels→ Prolong duration of inactivated state→ reduce chance of availability of activation → reduces release of glutamate

Eg: Phenytoin, carbamazepine, Valproate, Lamotrigine



2. Enhancement of GABAergic activity:

a. Activation of GABA receptors→ Opening of cl- channels (Phenobarbitone and Benzodiazepines)

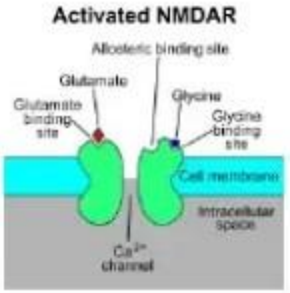
b. Inhibit GABA transaminase which metabolises GABA→ Increase neuronal concentration of GABA(vigabatrin)

c. Inhibit GABA uptake transporter → inhibit GABA uptake in the neurons→ Increase availability of GABA and inhibitory actions of GABA at the GABA- A receptors is enhanced (Tiagabine,Valproate)

d. Activation of glutamic acid decarboxylase →increase synthesis of GABA(Valproic acid)

3. Blockade of NMDA or AMPA receptors:

- Blockade of NMDA receptors- Felbamate
- Block AMPA receptors- Phenobarbital, Lomotrigine
- Inhibit glutamate synthesis- Valproate

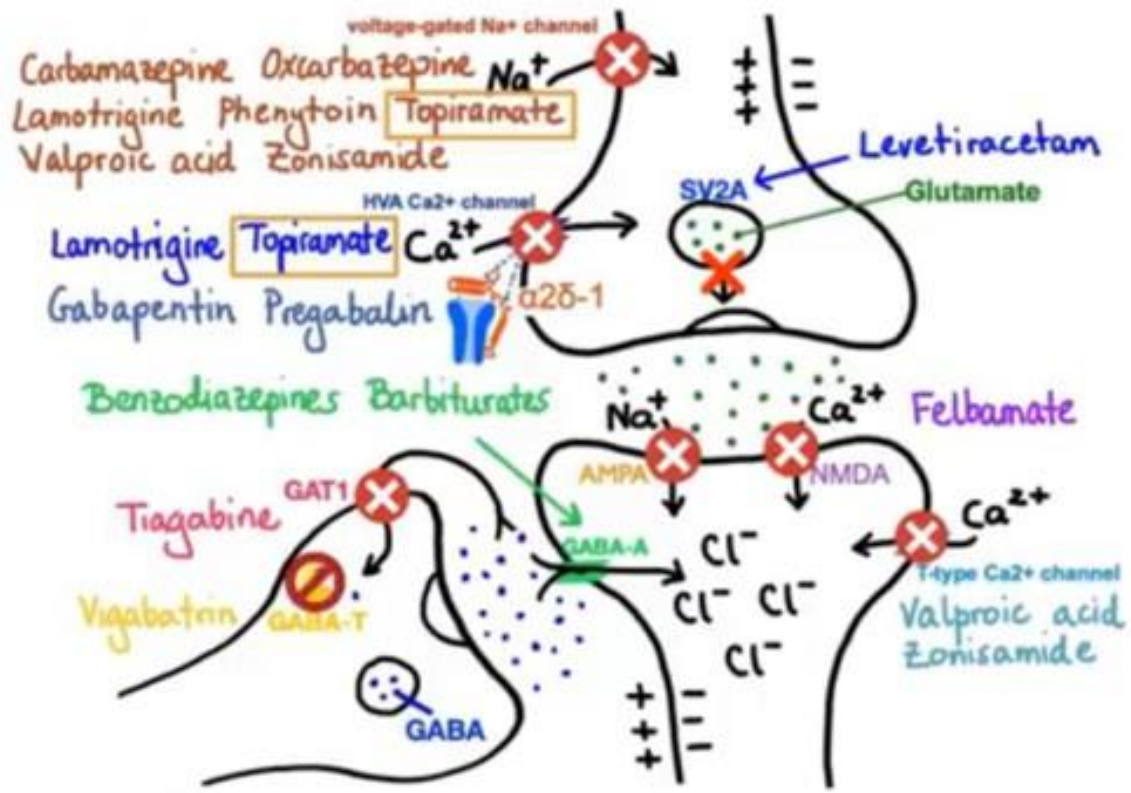


4.Inhibit N-type Ca^{2+} channels:

Inhibition of N-type Ca2+ channels →decrease synaptic release of glutamate(Lomotrigine, gabapentin)

5. Inhibition of T-type Ca^{2+} Channels:

Inhibits low threshold calcium current carried by T type calcium channels(Ethosuximide, Valproic acid)


voltage-gated Na+ channel
Carbamazepine Oxcarbazepine
Lamotrigine Phenytoin Topiramate
Valproic acid Zonisamide
Na+
Levetiracetam
SV2A
Glutamate
HVA Ca2+ channel
Lamotrigine Topiramate
Ca2+
Gabapentin Pregabalin
α2δ-1
Benzodiazepines Barbiturates
Na+
Ca2+
Felbamate
AMPA
NMDA
GAT1
Tiagabine
GABA-A
Cl-
Ca2+
T-type Ca2+ channel
Valproic acid
Zonisamide
Vigabatrin
GABA-T
GABA

Mechanisms of Drugs Used in Seizures

Phenytoin Carbamazepine Sodium valproate	• Inhibition of use dependent voltage gated Na^+ Channels
Benzodiazepine Phenobarbital Sodium valproate	• Enhancement of GABA action
Phenobarbital Sodium valproate Felbamate	• Inhibition of glutamate action
Ethosuximide Valproic Acid	• Inhibition of T-type Ca^{++} Channels

Mechanisms of Drugs Used in Seizures

GABA transaminase inhibitors	• Valproate, Vigabatrin
NMDA antagonist	• Felbamate
AMPA antagonist	• Topiramate

Phenytoin

- Oral
- Intravenous : Fosphenytoin is used which is rapidly converted to phenytoin in plasma
- Narrow therapeutic index : Therapeutic Drug Monitoring may be required
- Elimination : Zero order kinetics:
- Enzyme inducer

Note : Changing from one dosage of a particular brand to another can lead to suboptimal or toxic plasma levels

Therapeutic uses:

Antiepileptic use:

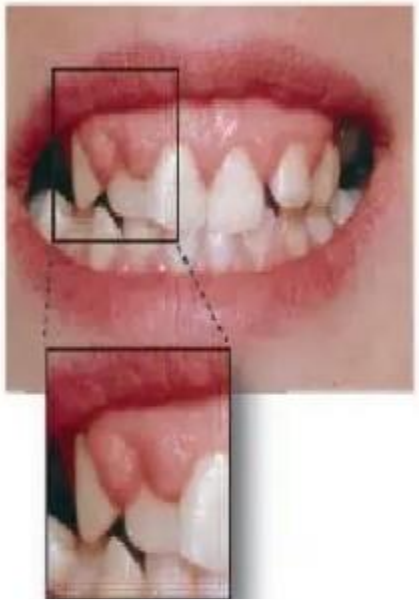
- Partial seizures (especially complex partial)- First choice
- Grand mal epilepsy (generalized tonic-clonic seizure) and status epilepticus- Second choice

Non-antiepileptic use:

- Trigeminal Neuralgia
- Ventricular arrhythmias due to digitalis toxicity

Adverse effects:

- Gingival hyperplasia and coarsening of facial features.
- Hirsutism and acne
- Pregnancy- Congenital malformation
- Hypersensitivity reactions
- Sudden withdrawal- seizures
- Deficiencies:
  - Folic acid (Megaloblastic anaemia)
  - Vitamin K (Haemorrhage)
  - Vitamin D (Rickets & Osteomalacia)- increases metabolism of calciferol



Drug interactions with phenytoin:

- Phenytoin being enzyme inducer, increases the metabolism of O C Pills, corticosteroids, folic acid, Vit. D, Vit. K etc.
- Carbamazepine, phenytoin, phenobarbital are enzyme inducers and increase each others metabolism

Carbamazepine

- Structurally related to tricyclic antidepressants (TCA)

Uses :

Antiepileptic use:

Effective in most forms of epilepsy (except absence seizures); particularly effective in psychomotor (simple & complex partial) epilepsy.

Non-epileptic use:

Trigeminal neuralgia

Maniac depressive psychosis

Adverse Effects:

- Drowsiness, dizziness, headache ataxia,diplopia
- Allergic reaction
- Aplastic anemia, leukopenia, hepatitis, SLE
- Water retention

Drug interaction:

- Strong enzyme inducing agent-therefore many drug interactions

Valproic Acid (Sodium Valproate)

- Enzyme inhibitor
- Highly protein bound

Therapeutic uses:

Antiepileptic use:

- Partial seizures
- Generalized seizures
  - Grand Mal : First Line
  - Petit Mal (Absence): First line
  - Myoclonic : First Line
  - Tonic, atonic & clonic seizures

Valproic Acid (Sodium Valproate)

Non-epileptic use:

- Maniac depressive psychosis
- Tardive dyskinesia
- Trigeminal neuralgia

Adverse effects:

Weight gain, tremors, alopecia, hepatotoxicity, pancreatitis, thrombocytopenia, use in pregnancy-neural tube defects(spina bifida)

Note: It is a broad-spectrum antiepileptic

Ethosuximide

- The main drug used to treat absence seizures (Petit Mal)
- Called ‘ Pure petit mal drug’

Adverse effects:

- GIT distress
- Mental disturbances- headache lethargy
- Skin rashes, eosinophilia, bone marrow depression

Benzodiazepine

- ❖ Remarkable antiseizure potency but has two important drawbacks that limit their usefulness as antiepileptic drugs
  - ✓ Pronounced sedative effect
  - ✓ Development of tolerance

- MOA : Benzodiazepines enhance the opening of GABA-mediated Cl^- channels (enhance GABA action).

- Lorazepam : preferred drug for status epilepticus
- Diazepam is preferred drug for Status epilepticus & febrile seizures
- Clonazepam: is effective in absence seizures, some cases of myoclonic seizures and akinetic seizures
- For febrile seizures in children diazepam is given rectally

Barbiturates

- Phenobarbital: is useful in the treatment of generalized tonic-clonic seizures and status epilepticus.
- It is an enzyme inducer
- Adverse effects: sedation, depression, drug interaction.

Newer antiepileptics

Gabapentin:

Mechanism:

- Close structural resemblance to GABA
- Increase release of GABA
- Inhibit N type calcium channels

Therapeutic uses:

- Used as adjuvant in partial and tonic clonic seizures
- Neuropathic pain
- Post herpetic neuralgia

Adverse effects:

Somnolence, dizziness, ataxia, headache, tremor

Drug Treatment: Key Concepts

- Monotherapy is preferred
- Anti-epileptic drugs suppress seizures but do not “cure” epilepsy.
- Accurate diagnosis and classification of seizure is critical to selection of appropriate pharmacotherapy.
- In general, the goal of treatment should be seizure freedom and no adverse effects. Patient-specific treatment goal(s) should be identified. Treatment goals may change over time.

Drug Treatment: Key concepts

- If the therapeutic goal (seizure freedom and no intolerable adverse effects) is not achieved with maximal monotherapy, a switch to an alternative single antiepileptic drug can be made or a second drug may be added (The second antiepileptic drug should have a different mechanism of action from the first)

- Many patients have to take medications throughout life. Some patients eventually can discontinue antiepileptic drug therapy.

Antiepileptic drug choice

Seizure Type	Preferred choice
Generalised tonic clonic seizures	Carbamezapine Phenytoin Sodium valproate
Partial (focal)Seizures	Carbamazepine Sodium valproate
Absence/Petit Mal	Ethosuximide, Sodium valproate
Myoclonic seizures	Sodium valproate
Status epilepticus (recurrent GTCS)	Lorezapam Diazepam
Febrile Seizures	Diazepam
Neuropathic pain	Carbamazepine, gabapentin

Summary

- Antiepileptics mainly act by blocking Na channel, Ca channel, glutamate, GABA transaminase and increase GABA action
- Phenytoin has narrow therapeutic index and has zero order kinetics
- Phenytoin, Phenobarbitone and carbamazepine are enzyme inducers
- Phenytoin causes gingival hyperplasia and coarsening of facial features
- Sodium valproate is a broad spectrum antiepileptic
- Gabapentin is used in neuropathic pain
- Some antiepileptic drugs have teratogenic effects

Thank you

s.hunaiti@ju.edu.jo