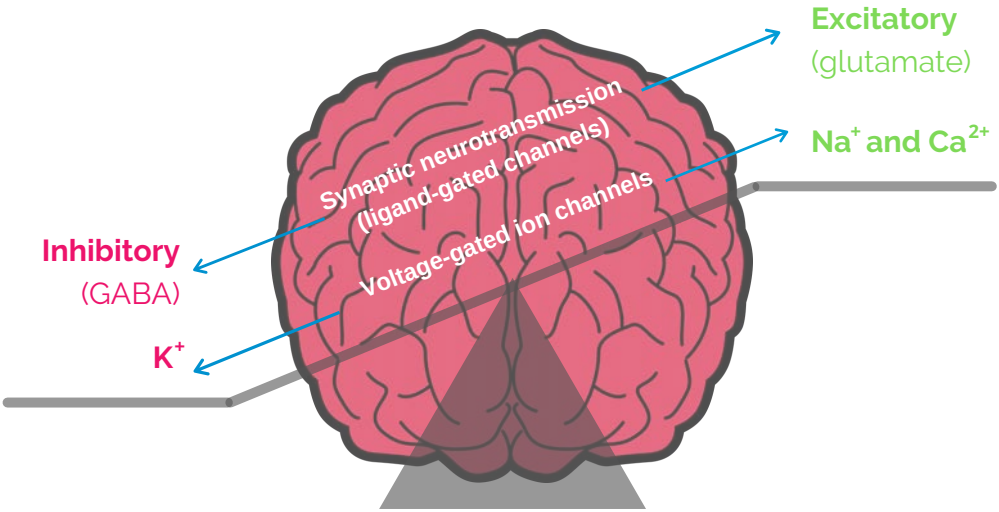
THE ROLE OF INHIBITION IN EPILEPTIC NETWORKS

Seizures arise when there is a **disruption** of brain mechanisms that normally create a **balance between neuronal inhibition and excitation**. Such imbalance may occur in a localized region of the brain, in multiple brain areas, or simultaneously throughout the whole brain.



Stafstrom CE (2010). Epilepsy : mechanisms, models, and translational perspectives. CRC Press Taylor & Francis Group. pp 3-19

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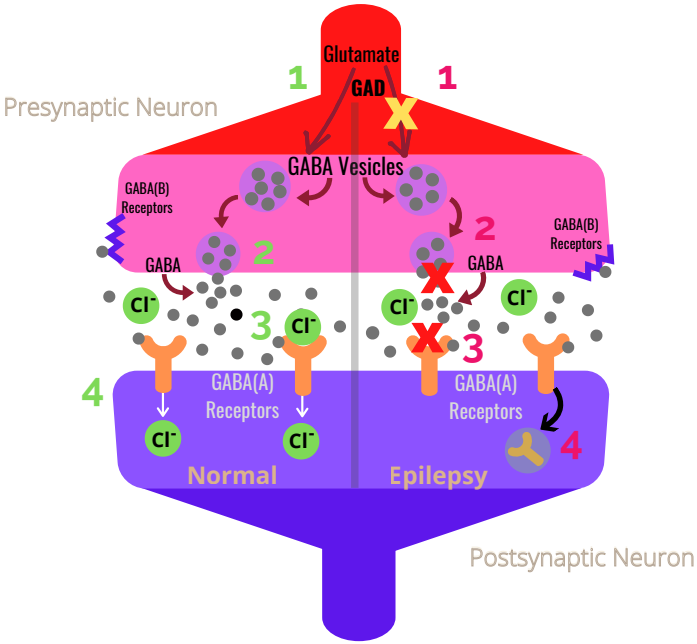
INHIBITORY SYNAPTIC NEUROTRANSMISSION



γ-aminobutyric acid (GABA) is a major inhibitory neurotransmitter

Normal

1 GABA is synthesized from glutamate by the enzime glutamic acid decarboxylase (GAD).

2 GABA is released prepackaged in vesicles from a presynaptic neuron into the synaptic cleft.

3 GABA binds to GABA(A) and GABA(B) receptors on postsynaptic membrane.

4 Upon activation in the adult brain, the GABA (A) receptors lead to Cl influx, which hyperpolarize the membrane and inhibits action potentials.

Epilepsy

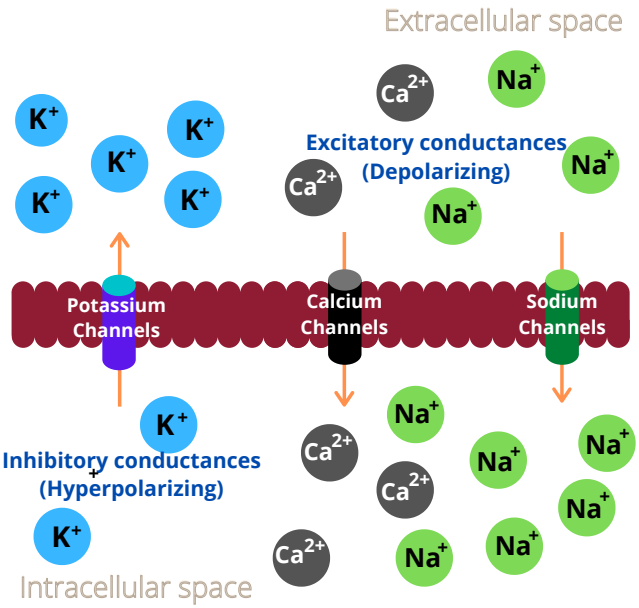
At the level of inhibitory cell networks, there are various pathophysiological events that underlie the development of epilepsy. Among them are the following (they do not occur sequentially):

- Decreased synthesis of GABA.
- Decreased release of GABA.
- Decreased sensitivity and efficacy of GABA receptors.
- Internalization (i.e., uptake inside the neuron) of GABA receptors.

It is important to note that under certain conditions, GABA can have excitatory effects. E.g. when the activity of the KCCN cotransporter (K^+/Cl^-) decreases, which normally maintains the hyperpolarization of GABAergic neurotransmission.

Olsen, R. W., & Avoli, M. (1997). GABA and Epileptogenesis. Epilepsia, 38(4), 399–407.
Di Cristo, G. et al (2018). KCC2, epileptiform synchronization, and epileptic disorders. Progress in Neurobiology, Volume 162, 1-16.

INHIBITORY ION CHANNELS



Normal

Voltage-gated **sodium (Na^+) and calcium (Ca^{2+})** channels **depolarize** the cell membrane toward the action potential threshold.

Voltage-gated **potassium (K^+) channels repolarize** the cell membrane or oppose depolarizing conductances to keep the membrane potential below threshold and dampen neuronal excitation

Membrane potential changes alter **conformation of the voltage-gated channels** and allow selective passage of charged ions through a pore.

Epilepsy

Mutations in genes coding for ion channel proteins **modify the kinetic and physicochemical properties of the channels**.

This **alters the transport and biogenesis of ions and neurotransmitters**, as well as the trafficking of receptors to the correct location in the membrane

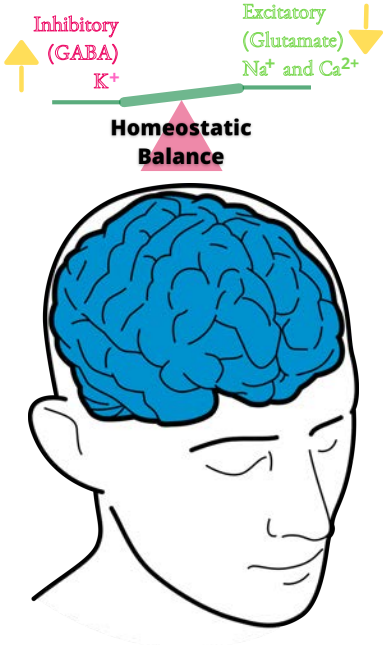
These mutations produce so-called epilepsy **channelopathies**

Wei F. et al., Ion Channel Genes and Epilepsy: Functional Alteration, Pathogenic Potential, and Mechanism of Epilepsy, Neurosci Bull. 2017 Aug; 33(4): 455–477.

EFFECTS OF ANTIEPILEPTIC DRUGS IN EPILEPTIC NETWORKS

Drugs that increase in GABAergic neurotransmission:

- Phenobarbital
- Phenytoin
- Valproate
- Clobazam
- Clonazepam
- Felbamate
- Gabapentin
- Topiramate
- Vigabatrin
- Tiagabine
- Zonisamide



Drugs that decrease glutamatergic neurotransmission:

- Felbamate
- Lamotrigine
- Levetiracetam
- Topiramate
- Brivaracetam
- Eslicarbazepine acetate
- Lacosamide.

Drugs that block sodium channels:

- Carbamazepine
- Phenytoin
- Valproate
- Felbamate
- Lacosamide
- Lamotrigine
- Levetiracetam
- Oxcarbazepine
- Topiramate
- Zonisamide
- Brivaracetam
- Carisbamate
- Eslicarbazepine acetate

Drugs that block calcium channels:

- Ethosuximide
- Valproate
- Gabapentin
- Lamotrigine
- Oxcarbazepine
- Topiramate
- Pregabalin
- Zonisamide
- Cannabidiol

Drugs activating potassium channels:

- Levetiracetam
- Topiramate

Sankaraneni R, Lachhwani D. Antiepileptic drugs--a review. Pediatr Ann. 2015 Feb;44(2):e36-42.

FOR MORE INFORMATION VISIT WWW.ILAE.ORG