Mechanism of Action Overview

Sodium channel blockers

Action potentials are caused by an exchange of ions across the neuron membrane. A stimulus first causes sodium channels to open. Because there are many more sodium ions on the outside, and the inside of the neuron is negative relative to the outside, sodium ions rush into the neuron. Sodium has a positive charge, so the neuron becomes more positive and becomes depolarized. It takes longer for potassium channels to open. When they do open, potassium rushes out of the cell, reversing the depolarization. Also at about this time, sodium channels start to close. This causes the action potential to go back toward -70 mV (a repolarization).

Sodium channels (specifically, voltage-gated sodium channels) are responsible for the firing of neurons in the brain. Think of a neuron as a water hose. The hose is full of little gates that prevent the water from flowing through it. When the gates "sense" that water is coming, they open and allow the water to flow through. This is a rough analogy of how the voltage gated sodium channel work only instead of water they allow passage of positively charged ions (sodium) into the cell which allows the signal to carry on.
The firing of an action potential by an axon is accomplished through the sodium channel. Each sodium channel exists in three states:

1. **Resting** – Channel allows passage of sodium into the cell.
2. **Open** – Channel allows increased flux of sodium into the cell.
3. **Refractory (inactivation)** – Channel does not allow passage of sodium into the cell.

During the action potential these channels exist in the active state and then undergo fast inactivation. This inactivation prevents the channel from opening and ends the action potential and occurs within milliseconds. Many AEDs that target sodium channels prevent the return of the sodium channels to the active state by stabilizing them in the inactive state; however, drugs that target the fast inactivation (see below) selectively reduce the firing of all active cells.

In addition to fast inactivation these voltage-gated sodium channels may also undergo slow inactivation that occurs over seconds to minutes. Slow inactivation is believed to result from a structural rearrangement of the sodium channel and does not result in a complete blockade of voltage-gated sodium channels. Rather, these drugs only affect neurons that are depolarized or active for long periods of time. These are typically the neurons at the epileptic focus. *There appears to be synergy combining slow and fast sodium channel blocking agents together.*

**Enhanced Na Channel Inactivation**

Some antiepileptic drugs stabilize inactive configuration of sodium (Na⁺) channel, preventing high-frequency neuronal firing thus reducing the number of action potentials elicited.
- Fast channel sodium channel blockers: phenytoin, carbamazepine, oxcarbazepine, lamotrigine, felbamate, topiramate, valproic acid, zonisamide, rufinamide, eslicarbazepine

- Slow channel sodium channel blockers: lacosamide

**Calcium channel blockers**

Calcium channels function as the “pacemaker” of normal rhythmic brain activity. Calcium channels exist in three known forms in the brain: L, N, and T. T-calcium channels have been known to play a role in the three-per-second spike-and-wave discharges of absence seizures.

**Reduced Current through T-Type Calcium Channels**

Low-voltage calcium (Ca2+) currents (T-type) are responsible for rhythmic thalamocortical spike-and-wave patterns of generalized absence seizures. Some antiepileptic drugs lock these channels, inhibiting underlying slow depolarizations necessary to generate spike-wave bursts.

Ethosuximide, zonisamide, and valporate specifically block the T-type calcium channels.

**Reduced Current through L-Type Calcium Channels**
Gabapentin and pregabalin are both derivatives and structurally similar to the neurotransmitter GABA but they are not believed to act on the same brain receptors. Some of their activity may involve interaction with L-type voltage-gated calcium channels specifically the alpha2-delta protein, an auxiliary subunit of L-type voltage gated calcium channels throughout the central nervous system.

**GABA enhancers**

GABA is a neurotransmitter widely distributed throughout the central nervous system, and it exerts postsynaptic inhibition. GABA has two types of receptors, A and B. GABA-A has binding sites for GABA, benzodiazepines, and phenobarbital. Once this GABA-A receptor is activated, chloride passes through chloride channels resulting in an increased negativity of the cell. So the cell has greater difficulty reaching the action potential.

The GABA system can be enhanced by binding directly to GABA-A receptors, blocking presynaptic GABA uptake, inhibiting the metabolism of GABA by GABA transaminase, and increasing the synthesis of GABA.

**Enhanced GABA Activity**

Gamma-aminobutyric acid (GABA)-A receptor mediates chloride (Cl-) influx, leading to hyperpolarization of cell and inhibition. Antiepileptic drugs may act to enhance Cl-influx or decrease GABA metabolism.

GABA Enhancers = Benzodiazepines, phenobarbital, primidone, tiagabine, clobazam, topiramate (nonbenzodiazepine GABA (A) receptor)
Glutamate blockers

Glutamate is an excitatory amino acid neurotransmitter. When glutamate binds to the glutamate receptor, the receptor facilitates the flow of both sodium and calcium ions into the cell, while potassium ions flow out of the cell, resulting in excitation.

The glutamate receptor has five potential binding sites:

1. AMPA site
2. Kainate site
3. NMDA site
4. Glycine site
5. Metabotropic site

NMDA Receptor Site Blocking Agent = felbamate
AMPA/Kainate Site Blocking Agent = topiramate, perampanel (noncompetitive AMPA receptor antagonist)

Carbonic anhydrase inhibitors

Inhibition of the enzyme carbonic anhydrase increases the concentration of hydrogen ions intracellularly and decreases the pH. The potassium ions shift to the extracellular compartment
to buffer the acid-base status. This results in hyperpolarization and an increase in the seizure threshold of the cells.

Carbonic Anhydrase Inhibitors = acetazolamide, topiramate (weak), zonisamide (weak)

**SV2A binding agents**

Synaptic vesicle protein 2A (SV2A) is ubiquitously expressed in the brain, but the function is poorly understood. SV2A appears to be important for the availability of calcium-dependent neurotransmitter vesicles ready to release their content. The lack of SV2A results in decreased action potential-dependent neurotransmission, while action potential-independent neurotransmission remains normal.

**SV2A Binding Agents = levetiracetam**

**K channel opener**

Potassium channels with distinct subcellular localization, biophysical properties, modulation, and pharmacologic profile are primary regulators of intrinsic electrical properties of neurons and their responsiveness to synaptic inputs. An increase in membrane conductance to K+ ions causes neuronal hyperpolarization and, in most cases, reduces firing frequency, exerting a strong inhibitory function on neuronal excitability. Kv7.2 and Kv7.3 belong to the Kv7 (KCNQ) subfamily of K+ channel genes and have been shown to be involved in brain excitability control. M-type potassium currents are a species of subthreshold voltage-gated potassium current that control neuronal excitability through stabilizing membrane potentials. M-channels are composed of heteromeric or homologous assembly of the different subunits KCNQ1, KCNQ2, KCNQ3, KCNQ4, and KCNQ5.

The mechanism of action of ezogabine (EZG) increases the number of KCNQ channels that are open at rest and also primes the cell to retort with a larger, more rapid, and more prolonged response to membrane depolarization or increased neuronal excitability. In this way, EZG amplifies this natural inhibitory force in the brain, acting like a brake to prevent the high levels of neuronal action potential burst firing (epileptiform activity) that may accompany sustained depolarizations associated with the initiation and propagation of seizures. This action to restore physiologic levels of neuronal activity is thought to underlie the efficacy of EZG as an anticonvulsant in a broad spectrum of preclinical seizure models and in placebo-controlled trials in patients with partial epilepsy. EZG selectively enhances M-currents through KCNQ 2/3 channels and KCNQ3/5 channels as well a homomeric KCNQ5 channels. Selectivity of EZG is important for safety since KCNQ1 subunits are present in cardiac cells and KCNQ4 subunits in the auditory system.