Antiepileptic Drug Mechanisms of Action

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1) General principles:

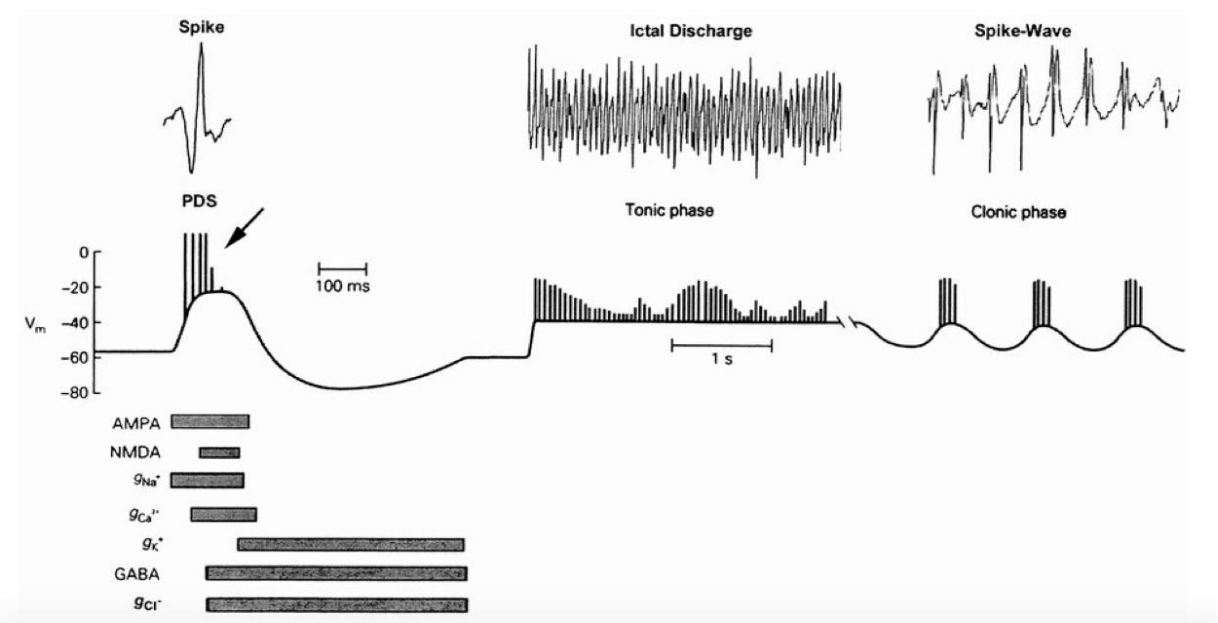
a) The goal of effective antiepileptic drug (AED) therapy is to eliminate or decrease seizure frequency while minimizing adverse effects.

b) Many mechanisms of action of AEDs have been identified through studies that are *in vitro*, *in vivo* in animal models and in humans with epilepsy. Some AED mechanisms of action are not well understood, and many AEDs have multiple relevant mechanisms.

c) Cellular events at the initiation of a seizure are depicted below showing prolonged depolarization with failure of inhibitory hyperpolarization. AMPA and NMDA channels open allowing influx of Na^+ and Ca^{++} during depolarization. This is followed by opening of K^+ channels and activation of GABA channels with Cl- entering the cell leading to hyperpolarization.[2]

d) Practical aspects of mechanism of action in the clinic

i) It has been proposed that when using AEDs in polytherapy, drug selection should focus on



combining AEDs with different mechanisms of action to reduce adverse effects and enhance efficacy. There is evidence from studies of lacosamide that adverse effects were enhanced when combining lacosamide (inhibition of slow sodium channels) with traditional fast sodium channel inhibitors.[7] Efficacy was increased when lacosamide was added to AEDs with a non-sodium channel mechanism. However, in clinical trials, adverse effects may limit doses achieved, therefore efficacy is closely tied to adverse effects. Thus the hypothesis that efficacy was improved due to higher dose cannot be disproven.

ii) A reasonable approach: 1. Optimize initial AED (maximum tolerable dose), 2. Add a second AED with multiple mechanisms of action, 3. Avoid combining similar mechanism of action drugs, 4. Titrate slowly, 5. Replace less effective drug if response is poor[5]

2) **Antiepileptic Drugs by Mechanism of Action:**

a) **Blockers of repetitive action of sodium channels**

- Na channel exists in the resting, active and inactive states
- Cell membrane reaches threshold, Na channels open → rapid depolarization, conduction of action potential along the axon → reaches nerve terminal and releases neurotransmitter.
- After depolarization, Na channel enters inactive state. AEDs stabilize this inactive form by binding when it is firing, called "use dependent." Ideally, AEDs suppress abnormal repetitive firing in a seizure focus with little effect on normal neuronal activity.
- AEDs with Major Effect on Na channels: carbamazepine, phenytoin, lamotrigine, oxcarbazepine, eslicarbazepine, lacosamide; More minor effect: felbamate, valproate, topiramate, zonisamide, rufinamide
- Lacosamide has a higher affinity for the slow inactivation state of voltage gated sodium channels; unlike carbamazepine, phenytoin, lamotrigine which enhance the fast inactivation state
- Other points: Na channel AEDs should generally be avoided in Dravet syndrome due to the effect of the SCN1A gene mutation. Na channel AEDs (and some GABA enhancing AEDs) should be avoided in genetic generalized epilepsy patients due to possibility of worsening seizures (such as phenytoin, carbamazepine and gabapentin). Lamotrigine may exacerbate myoclonus.

b) **Calcium channel blockers:**

- T-calcium channel blockers. T-Ca channels are small, voltage dependent channels that act as "pacemakers for the brain". T-currents provide the neuron with a mechanism for automaticity, and generation of spike-waves in thalamocortical circuits. They specifically inhibit absence seizures.
- Examples: ethosuximide, zonisamide; minor effect of valproate
- N- and P/Q-Ca channel blockers. Examples: lamotrigine; minor effect levetiracetam

c) **GABA enhancers**
- Attachment of GABA to $GABA_A$ receptors allows passage of Cl- into the cell → hyperpolarization
- Barbiturates prolong the duration of Cl- channel opening while benzodiazepines increase the frequency of opening
- Two AEDs work by directly increasing the concentration of GABA at the synaptic cleft: Vigabatrin is an irreversible inhibitor of GABA-transaminase (interferes with GABA metabolism) and tiagabine blocks GABA reuptake.
- Clobazam is a 1,5 benzodiazepine derivative; metabolite is N-desmethyl-clobazam; $GABA_A$ receptor agonist with higher affinity for α2 subunit compared to traditional 1,4-benzodiazepines and less affinity for α1 subunit (thought to cause sedating properties of benzodiazepines)
- Examples: barbiturates, benzodiazepines, tiagabine, vigabatrin, clobazam, felbamate, topiramate; minor effect: valproate

d) **Glutamate modulators:**
- Excitation is produced by binding of glutamate to five receptors: NMDA, AMPA, kainate, glycine, metabotropic. Facilitates passage of Ca++ and Na+ into the cell and K+ out of the cell, destabilizing it.
- Examples: phenytoin and gabapentin (glycine), lamotrigine and phenobarbital (kainate), levetiracetam (kainate), felbamate (NMDA), perampanel (AMPA), topiramate (AMPA and kainate),
- Perampanel is an antagonist of glutamate at AMPA receptors

e) **Carbonic anhydrase inhibitors:**
- Increase the concentration of hydrogen ions intracellularly → decrease pH → K+ ions shift to extracellular space → hyperpolarization and increase in seizure threshold of cells
- Examples: topiramate, zonisamide, acetazolamide

f) **Unique binding sites:**
- levetiracetam, brivaracetam → binds SV2A (synaptic vesicle protein 2A, has a role in neurotransmitter release), facilitates GABA; brivaracetam higher affinity and more selective.
- gabapentin, pregabalin → bind and modulate at α2δ subunit of high-voltage-activated Ca++ channels

- cannabinoids (cannabidiol=CBD) → mechanism not well understood; unlike THC, CBD has a low affinity for CB1 and CB2 endocannabinoid receptors which modulate neuronal excitability. Possible effect on TRPV1, voltage gated potassium and sodium channels, and GPR55[6]
- ezogabine → acts at K channel, no longer available in the U.S.
- tacrolimus, everolimus → mTOR inhibitor (use in tuberous sclerosis)

g) **AEDs with multiple relevant mechanisms of action**

- Valproic acid: effect on Na+ channels, T-type Ca++ currents, and enhances GABAergic neurotransmission
- Felbamate: effect on Na+ channels, GABA and inhibits NMDA
- Topiramate: effect on Na+ channels, inhibitory of kainate on glutamate receptors, enhance GABA, effect on carbonic anhydrase
  Zonisamide: effects Na+ channel, T-type Ca++ channels, modulates GABA, inhibits brain carbonic anhydrase

	Sodium Channel	**GABA**	**Excitatory Transmission**	**Other**
gabapentin pregabalin		**+/-**		**α2δ of Calcium channel**
tiagabine vigabatrin		**++**		
lamotrigine	**++**		**+ (kainate)**	**H current**
valproic acid	**+**	**+**		**Calcium**
topiramate	**+**	**+**	**+ (AMPA, kainate)**	**Calcium, carbonic anhydrase**
zonisamide	++			**Calcium, carbonic anhydrase**
carbamazepine oxcarbazepine eslicarbazepine phenytoin	**++**			
lacosamide	++ slow			
rufinamide	++			

levetiracetam, brivaracetam				**SV2A**
clobazam		+ BDZ		
~~ezogabine~~		+/-		Potassium channel
perampanel			AMPA receptor antagonist	
felbamate	+	+	NMDA receptor antagonist	Calcium

- AED and Associated Mechanisms Phenytoin and carbamazepine → block voltage-dependent sodium channels at high firing frequencies
- Oxcarbazepine → active metabolite licarbazepine (10-monohydroxy derivative (MGD)), blocks voltage-dependent sodium channels at high firings frequencies; also K+ channel effect
- Eslicarbazepine → metabolized to S-isomer of MHD
- Lamotrigine → blocks voltage-dependent sodium channels at high firing frequencies, enhances H current
- Zonisamide → blocks voltage-dependent sodium channels and T-type calcium channels; mild carbonic anhydrase inhibitor
- Rufinamide → unclear, possibly stabilization of Na+ channel inactive state
- Lacosamide → enhances slow inactivation of voltage gated sodium channels
- Topiramate → blocks voltage-dependent Na channels at high firing frequencies; increases frequency at which GABA opens Cl- channels; antagonizes glutamate action at AMPA/kainate receptor; inhibition of carbonic anhydrase
- Valproate → enhance GABA transmission, blocks voltage-dependent Na channels, modulates T-type Ca channels
- Felbamate → blocks voltage-dependent Na+ channels at high firing frequencies; modulates NMDA receptor (blocks) and GABA receptors (enhances)
- Levetiracetam → binding of reversible saturable specific binding site SV2A (a synaptic vesicle protein)
- Brivaracetam→ SV2A protein binding, facilitates GABA release, high affinity, more selective
- Barbiturates (phenobarbital, primidone) → prolong GABA-mediated chloride channel openings
- Benzodiazepines (clonazepam, diazepam, lorazepam, midazolam) → increase frequency of GABA-mediated chloride channel openings
- Tiagabine → interferes with GABA re-uptake
- Vigabatrin → irreversibly inhibits GABA-transaminase (interferes with GABA metabolism)

- Gabapentin → blocks Ca++ channels, enhances H current, suppressed presynaptic vesicle release, suppresses NMDA receptor at glycine site
- Pregabalin → increases glutamic acid decarboxylase; suppresses Ca++ current, binds alpha 2 delta subunit
- Ezogabine (no longer in use) → enhances transmembrane K+ current
- Perampanel → noncompetitive antagonist of postsynaptic AMPA receptors
- Ethosuximide → blocks low threshold "transient" (T-type) Ca channels in thalamic neurons
- clobazam → 1,5 benzodiazepine derivative, metabolite N-desmethyl-clobazam, $GABA_A$ receptor agonist with higher affinity for α2 subunit compared to traditional 1,4-benzodiazepines, low affinity for α1 subunit
- Acetazolamide → reversible inhibition of carbonic anhydrase

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