Mechanism of Action of Antiepileptic Drugs

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Cellular targets of AEDs

✓ Modulation of voltage-dependent ion channels (mainly sodium [Na] but also calcium [Ca] channels)

✓ Effects on GABA systems, including alterations in the cellular disposition of GABA and enhancement of synaptic inhibition mediated by GABA_A receptors

✓ Inhibition of synaptic excitation mediated by ionotropic glutamate receptors

✓ Modulation of neurotransmitter release, particularly of glutamate, through presynaptic mechanisms
Phenytoin and Carbamazepine

✓ voltage-dependent Na channels at concentrations found free in plasma in patients being treated for epilepsy

✓ highly protective against tonic seizures in animal models (as in the maximal electroshock [MES] test), but do not protect against clonic seizures (as in the pentylenetetrazol [PTZ] test)

✓ Na channel modulators

  ✓ composed of an α subunit (NaV1.1–1.9) associated with auxiliary β1-, β2-, or β3-subunits.

  ✓ An α-subunit is sufficient to form the channel and allow functional expression, but the kinetic properties and voltage-dependence of channel gating are modulated by the β-subunits.
- reduce the frequency of sustained repetitive firing of action potentials
- do not reduce the amplitude or duration of single action potentials but reduce the ability of neurons to fire trains of action potentials at high frequency
- shift of Na channels to an inactive state from which recovery is delayed
- phenytoin had a longer time-dependence for frequency-dependent block and for recovery from block than did carbamazepine
  - more pronounced frequency-dependent block for phenytoin than for carbamazepine
- voltage-dependency of deactivation
Slow Binding of Phenytoin

- First, the time course of fast Na currents is not altered in the presence of the drug, and therefore, the kinetic properties of normal action potentials are not perturbed.
- Second, slow binding means that action potentials evoked by synaptic depolarizations of ordinary duration are not blocked.
- Even interictal discharges, characterized by depolarizations lasting 50 to 200 ms, are not sufficiently long for drug binding and block of Na channels.
- Consequently, the frequency of interictal discharges is unaffected by phenytoin.
- Only depolarizations that are as long as those occurring during ictal discharges provide the conditions required for drug binding and block.
Oxcarbazepine

- Dibenzazepine that is structurally similar to carbamazepine, except that it has a keto substitution at the 10 position of the dibenzazepine nucleus, which prevents the formation of the 10,11-epoxide.
- Oxcarbazepine is rapidly and nearly completely reduced to 10,11-dihydro-10-hydroxy carbamazepine (licarbazepine).
- Inhibiting the hind limb extension in rats and mice elicited by MES, but are approximately two to three times less effective against PTZ-induced seizures in mice.
- Poor anticonvulsant efficacy against picrotoxin- and strychnine-induced seizures in mice.
- Similar to that of carbamazepine, and depends on the modulation of voltage-dependent Na channels.
Topiramate

✓ sulfamate derivative of the naturally occurring monosaccharide D-fructose
✓ active against MES seizures in rats and mice, in amygdala-kindled seizures in rats, and sound-induced seizures in mice
✓ ineffective against seizures induced by PTZ, bicuculline, or picrotoxin

✓ effective in a rat genetic model of absence epilepsy and can also raise the threshold for clonic seizures induced by intravenous PTZ in mice
Several cellular mechanisms

(a) activity-dependent attenuation of voltage-dependent Na currents
(b) inhibition of high-voltage–activated Ca channels
(c) potentiation of GABA_A receptor-mediated currents
(d) inhibition of AMPA/kainate receptors (GluR5/6)
(e) inhibition of types II and IV carbonic anhydrase isoenzymes
(f) activation of a steady K current.
Benzodiazepines and Barbiturates

- enhance GABAergic inhibition at the free serum concentrations found in ambulatory patients by interacting directly with GABA$_A$ receptors
- GABA$_A$ receptors are formed by the assembly of multiple subunit subtypes ($\alpha_1$–$\alpha_6$, $\beta_1$–$\beta_3$, $\gamma_1$–$\gamma_3$, $\delta$, $\epsilon$, $\pi$, $\theta$, and $\rho_1$–$\rho_3$) into a pentamer
- Once assembled, GABA$_A$ receptors form chloride (Cl) ion channels, and the current carried by these channels can be modulated by a number of AEDs, including barbiturates and benzodiazepines.
- GABA$_A$ receptors have been shown to be involved in both phasic, inhibitory synaptic transmission and tonic, perisynaptic inhibition
Benzodiazepines and Barbiturates

- Barbiturates enhance GABA<sub>A</sub> receptor current by binding to an allosteric regulatory site on the receptor.
- Barbiturates increase mean channel open duration but do not alter receptor conductance or opening frequency.

- Benzodiazepines increase GABA<sub>A</sub> receptor current, and single-channel recordings have demonstrated that they increase GABA<sub>A</sub> receptor opening frequency without altering mean open time or conductance.
Ethosuximide and Trimethadione

- interact with voltage-dependent T-type Ca channels
- Thalamic relay neurons play a critical role in the generation of the abnormal thalamocortical rhythmicity that underlies the 3-Hz spike-and-wave discharge: presence of low-threshold (T-type) and high-threshold Ca currents
- reduced T-type Ca currents of thalamic neurons isolated from guinea pigs and rats
- Phenytoin and carbamazepine, which are ineffective in the control of generalized absence seizures, had minimal effects on T-type current
Specificity on Absence Seizures

✓ under conditions in which neurons are normally hyperpolarized (resting membrane potentials varying between –55 and –70 mV), the sensitivity of T-type Ca channels to succinimide block will be enhanced.

✓ In particular, these agents would be expected to block T-type Ca currents during slow, GABA-dependent network activity, as is believed to occur during absence seizures.
Valproate

- increases the turnover of GABA and presumably enhances GABAergic function
- especially active in genetic models of absence seizures, such as the genetic absence epilepsy rat from Strasbourg (GAERS).
- also protective against seizures induced by DMCM and in the 6-Hz model, an alternative electroshock model that is sensitive to GABAergic agents

- exhibits protective activity in virtually all other animal AED screening models including the MES and PTZ models, but its potency in any specific model varies depending on the species and route of administration
Issues on channel blocking

- block sustained high-frequency repetitive firing of neurons in culture
- detailed voltage clamp experiments of valproate actions on Na currents have not been performed

Although valproate is effective in the treatment of generalized absence seizures, studies in rat thalamic neurons did not demonstrate any effect on T-type Ca current, but subsequently, the drug was shown to reduce T-type currents in primary afferent neurons
**Gabapentin and Pregabalin**

- Gabapentin, the lipophilic 3-cyclohexyl analog of GABA, was originally synthesized in an attempt to develop a brain-penetrant GABA agonist.
- Pregabalin [S(+)-3-(aminomethyl)-5-methylhexanoic acid; S(+)-3-isobutyl GABA] is a congener of gabapentin with similar properties.
- Bulky aliphatic substituents in the molecules preclude binding to the GABA recognition site on GABA$_A$ receptors.
- Do not interact with other sites on GABA$_A$ receptors.
- Agonist activity at GABA$_B$ receptors.
- Gabapentin does not inhibit GABA uptake or GABA catabolism, although it may enhance GABA turnover.
α2δ-subunits of calcium channel

- binding affinities of gabapentin, pregabalin, and related structures to α2δ-subunits correlate in a stereoselective fashion with their anticonvulsant potencies.

- α2δ-subunits are highly glycosylated proteins having a molecular mass of ~150 kD (997 to 1150 amino acid residues) that form complexes with many voltage-dependent Ca channel types.

- reduce the release of neurotransmitters from neural tissue, with effects on glutamate release being of particular relevance in epilepsy.
Detailed mechanism

- reduce the amplitude of evoked and spontaneous excitatory postsynaptic currents
- a reduction also occurs in the frequency of miniature excitatory synaptic currents
- Because these events do not depend on Ca entry through voltage-sensitive Ca channels, gabapentin and pregabalin do not seem to be acting simply by inhibiting Ca channels in presynaptic terminals.
- binding of the drugs to α2δ-subunits directly influences the release machinery, possibly by affecting physical interactions between presynaptic Ca channels and proteins mediating exocytosis
Synaptic release (Glu) inhibition

- Both gabapentin and pregabalin are highly effective in the rat MES test and also are protective against tonic seizures induced by chemoconvulsants, with pregabalin being modestly more potent than gabapentin.
- Neither agent is as effective in the mouse, which is unusual, because most AEDs show the reverse species selectivity.
- Both drugs are effective in protecting against seizures in kindled rats, and are highly potent against audiogenic seizures in genetically susceptible mice.
- The drugs are only weakly active against chemoconvulsant-induced clonic seizures.
- They are not protective in models of absence epilepsy, and can even promote absence seizures at high doses.
Lamotrigine

- phenyltriazine with weak antifolate activity
- anticonvulsant activity against tonic seizures in the MES test and also against tonic seizures induced by PTZ, but it is not active in the conventional PTZ test in which clonic seizure activity is the end-point

- also inactive in rat models of absence epilepsy

- its profile in animal models is similar to that of Na-channel modulators such as phenytoin and carbamazepine
Presynaptic actions

- inhibited the release of glutamate and aspartate evoked by the Na-channel activator veratrine and was less effective in the inhibition of acetylcholine or GABA release
- no effect on spontaneous or potassium (K)-evoked amino acid release
- acts presynaptically on voltage-gated Na channels to decrease glutamate release
Broader clinical spectrum of activity

- broader clinical spectrum of activity than phenytoin and carbamazepine and is recognized to be protective against GAE and other IGE, including primary GTCSz, JME, and LGS

- blocks T-type Ca channels weakly

- inhibit native and recombinant high-voltage–gated Ca channels (N- and P/Q/R-types) at therapeutic concentrations
Levetiracetam

✓ S-enantiomer of the ethyl analog of the nootropic agent piracetam
✓ inactive against both the MES and subcutaneously administered PTZ seizures
✓ protection against sound-induced clonic seizures and also against clonic seizures induced by pilocarpine and DMCM and also against kindled seizures
✓ not against seizures induced by other chemoconvulsants such as the GABA$_A$ receptor antagonists bicuculline or picrotoxin or by icv injection of the NMDA, AMPA, or kainate
✓ suppresses synchronized network bursting, indicating an effect on synchronization mechanisms
SV2A binding

- homozygous SV2A knockout mice experience severe seizures and die between P12 and P23; heterozygous animals are also susceptible to seizures but have nearly normal survival
- SV2A seems to interact with synaptotagmin, which is believed to be the Ca sensor in exocytosis
- required for synaptic transmission or for the uptake or storage of neurotransmitters
- Levetiracetam is the first AED that targets the synaptic release machinery directly.
Vigabatrin

- structural analog of GABA that acts as an enzyme-activated (“suicide”) inhibitor of GABA-transaminase localized to mitochondria that is the main degradative enzyme for GABA

- Because GABA-T inhibition is irreversible, recovery of GABA transaminating activity requires resynthesis of the enzyme

- increase in brain GABA levels is predominantly due to inhibition of GABA-T in neurons
enhanced GABA-mediated inhibition

- does not lead to larger GABA$_A$ receptor-mediated synaptic responses
- inhibit spontaneous and evoked synaptic GABA currents
- increases tonic current resulting from the action of ambient GABA on extrasynaptic GABA$_A$ receptors
- increased extracellular GABA levels: efflux of GABA from neurons via GABA transporters operating in a reverse fashion due to high intracellular GABA.
- produce an anticonvulsant effect through reduced network excitability
GABA mechanism

- active against seizures induced by chemoconvulsants including strychnine, PTZ, picrotoxin, and isoniazid
- retards the development of kindled seizures, indicating that it has antiepileptogenic properties, at least in the kindling model

- inactive in the MES test

- ineffective in genetic absence epilepsy models, which corresponds with its lack of clinical anti-absence activity
Zonisamide

- aromatic fused benzene-isoxazole ring structure and a sulfonamide side chain
- profile of activity in animal seizure models that is similar to that of AEDs that modulate voltage-dependent Na channels, including phenytoin, carbamazepine, and lamotrigine
- protective in the MES test, kindling and inactive against subcutaneous PTZ seizures in both mice and rats
- inactive against seizures induced by bicuculline and picrotoxin
- effective against tonic–clonic and myoclonic seizures in the Mongolian gerbil, a genetic animal model of reflex epilepsy
- suppressed tonic, but not absence-like seizures, and...
Cellular mechanism

(a) modulation of voltage-dependent Na channels

(b) inhibition of T-type voltage-dependent Ca channels

(c) presynaptic inhibition or facilitation of neurotransmitter release

(d) alteration in neurotransmitter turnover and metabolism

(e) inhibition of carbonic anhydrase
modulation of voltage-gated Na channels to limit sustained, high-frequency, repetitive action potential firing
inhibits the release of glutamate and other neurotransmitters through a presynaptic action
complex actions on dopamine, serotonin and acetylcholine metabolism
complex cellular actions of zonisamide, including its effects on T-type Ca channels, likely account for its broader clinical spectrum of activity than conventional Na channel blocking AEDs