

CHAPTER 43 ■ MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS

MICHAEL A. ROGAWSKI AND JOSÉ ENRIQUE CAVAZOS

Antiepileptic drugs (AEDs) protect against seizures through interactions with a variety of cellular targets. By affecting the functional activity of these targets, AEDs suppress abnormal hypersynchronous activity in brain circuits, leading to protection against seizures. The actions on these targets can be categorized into four broad groups: (i) modulation of voltage-gated ion channels, including sodium, calcium, and potassium channels; (ii) enhancement of GABA inhibition through effects on GABA_A receptors, the GAT-1 GABA transporter, or GABA transaminase; (iii) direct modulation of synaptic release through effects on components of the release machinery, including SV2A and $\alpha 2\delta$; and (iv) inhibition of synaptic excitation mediated by ionotropic glutamate receptors, including AMPA receptors (Table 43.1). The ultimate effects of these interactions are to modify the bursting properties of neurons and to reduce synchronization in localized neuronal ensembles. In addition, AEDs inhibit the spread of abnormal firing to distant sites. Some seizures, including typical generalized absence seizures, result from thalamocortical synchronization. AEDs effective in these seizure types interfere with the rhythm-generating mechanisms that underlie synchronized activity in the thalamocortical circuit. In this chapter, we consider each of the targets and discuss how AEDs affect the activity of these targets.

Many AED targets are ion channels, most notably voltage-gated sodium and potassium channels and GABA_A receptors. It is interesting to note that certain idiopathic epilepsy syndromes are believed to be the result of mutations in these same ion channels (see Chapter 4).

VOLTAGE-GATED ION CHANNELS

Voltage-Gated Sodium Channels

Voltage-gated sodium channels play an essential role in the initiation and propagation of action potentials in neurons. Neuronal depolarizations by a few millivolts, ordinarily as a result of synaptic activation of glutamate receptors (mainly AMPA receptors), activate sodium channels, causing opening of the channels and influx of sodium. The channels then inactivate within milliseconds. Influx of sodium ions during the brief time that sodium channels are open generates the depolarizing component of the action potential. Although the bulk of sodium channels inactivate, about 1% of the sodium current is noninactivating resulting in a small persistent sodium current (I_{NaP}), which is carried by the same channels as the fast transient current. I_{NaP} facilitates epileptic burst firing by reducing the threshold for action potential generation, sustaining repetitive firing, and enhancing depolarizing synaptic currents (1).

Some AEDs, most notably phenytoin, inhibit I_{NaP} , which is believed to contribute to their efficacy (2).

Voltage-gated sodium channels are multimeric protein complexes, composed of a large α subunit that forms four subunit-like homologous domains (designated I to IV) and one or more smaller β subunits (3). The ion-conducting pore is contained within the α subunit, as are the elements of the channel that mediate its fundamental physiologic properties including rapid inactivation. There are nine voltage-gated sodium channels, designated $Na_v1.1$ to $Na_v1.9$. $Na_v1.2$ is the predominant form in brain neurons, but $Na_v1.1$ and $Na_v1.6$ are also expressed in the brain. Mutations in each of these channels have been associated with various genetic epilepsies (4).

AEDs that protect against seizures through an interaction with voltage-gated sodium channels are commonly referred to as “sodium channel blockers.” They are among the most frequently used drugs in the treatment of focal and primary generalized tonic-clonic seizures and include phenytoin, carbamazepine, lamotrigine, oxcarbazepine (as well as its active metabolite licarbazepine), and lacosamide. AEDs that interact with voltage-gated sodium channels exhibit a characteristic “use-dependent” blocking action so that they inhibit high-frequency trains of action potentials much more potently than they inhibit individual action potentials or firing at low frequencies. Because they also exhibit a “voltage dependence” to their blocking action, sodium channel-blocking AEDs are more potent at inhibiting action potentials that ride on a depolarized plateau potential as characteristically occurs in seizures. Thus, sodium channel-blocking AEDs preferentially inhibit seizure discharges in relation to normal ongoing neural activity. By virtue of their ability to inhibit the action potential invasion of nerve terminals, sodium channel-blocking AEDs inhibit the release of diverse neurotransmitters including glutamate; whether this is responsible for the therapeutic activity of the drugs is uncertain (5).

The binding site on sodium channels for sodium channel-blocking AEDs is believed to overlap the binding site of local anesthetics, which is within the pore of the channel and is formed by the S6 segments of domains I, II, and IV. Sodium channel-blocking AEDs bind with higher affinity to this site when the channel is in the inactivated state, and, when such a drug is bound, the channel is stabilized in the inactivated state. When neurons are depolarized and firing rapidly, sodium channels spend a greater amount time in the inactivated state and are able to accumulate bound drug so that they become trapped in the inactivated state. This accounts for the use- and voltage-dependent blocking action that they exhibit. Phenytoin, carbamazepine, and lamotrigine are considered “classical” sodium channel-blocking AEDs. Lacosamide also is believed to exert its therapeutic effects by interacting with sodium channels (6). Unlike other sodium channel-blocking

TABLE 43.1

MOLECULAR TARGETS OF CLINICALLY USED AEDS

Molecular target	AEDs that act on target
<i>Voltage-gated ion channels</i>	
Voltage-gated sodium channels	Phenytoin, fosphenytoin, ^a carbamazepine, oxcarbazepine, ^b eslicarbazepine acetate, ^c lamotrigine, and lacosamide; possibly, topiramate, zonisamide, and rufinamide
Voltage-gated calcium channels	Ethosuximide
Voltage-gated potassium channels	Ezogabine
<i>GABA inhibition</i>	
GABA _A receptors	Phenobarbital, primidone, and benzodiazepines including diazepam, lorazepam, and clonazepam; possibly, topiramate and felbamate
GAT-1 GABA transporter	Tiagabine
GABA transaminase	Vigabatrin
<i>Synaptic release machinery</i>	
SV2A	Levetiracetam
α2δ	Gabapentin, gabapentin enacarbil, ^d and pregabalin
<i>Ionotropic glutamate receptors</i>	
AMPA receptor	Perampanel
<i>Mixed/unknown</i>	
	Valproate, felbamate, topiramate, zonisamide, rufinamide, and adrenocorticotropin

^aFosphenytoin is a prodrug for phenytoin.

^bOxcarbazepine serves largely as a prodrug for licarbazepine, mainly S-licarbazepine.

^cEslicarbazepine acetate is a prodrug for S-licarbazepine.

^dGabapentin enacarbil is a prodrug for gabapentin.

AEDs, lacosamide does not inhibit high-frequency repetitive spike firing on the time scale of 100s of milliseconds. It does, however, inhibit spike firing in long trains of spikes on the time scale of 1 to 2 seconds. It has been proposed that the very slow action of lacosamide is due to an enhancement of a distinct and poorly understood form of inactivation, referred to as “slow inactivation.” However, an alternative explanation is that lacosamide binds more slowly to fast inactivated sodium channels than do the other sodium channel–blocking AEDs. In any case, the unusually slow development of block produced by lacosamide during high-frequency activity could allow lacosamide to better discriminate between seizure-like pathologic firing and normal network activity.

T-Type Voltage-Gated Calcium Channels

Low voltage-activated (T-type) calcium channels play a role in the intrinsic thalamocortical oscillations that underlie the spike-and-wave discharges of generalized absence seizures (7–9). There are three T-type Ca²⁺ channel isoforms encoded by separate genes, denoted as Ca_v3.1 (α1G), Ca_v3.2 (α1H), and Ca_v3.3 (α1I). All three T-type calcium channel isoforms are expressed in thalamocortical circuits (10). Ca_v3.1 is prominently expressed in thalamic relay neurons in the dorsal thalamus, which plays a key role in absence seizures; Ca_v3.2 and to a lesser extent Ca_v3.3 are prominently expressed in thalamic reticular neurons. All three T-type calcium channel isoforms are expressed in the cortex, with Ca_v3.2 mainly localized to layer V. In non-REM sleep, including during delta waves, sleep spindles, and K complexes, the thalamocortical circuit switches from a tonic to oscillatory mode of firing, but in absence epilepsy, this switching can occur inappropriately,

even during wakefulness (11,12). T-type calcium channels in the thalamus and cortex contribute to the abnormal behavior of the circuit. These channels generate low-threshold spikes, leading to burst firing and oscillatory behavior (13). GABA-ergic neurons of the thalamic reticular nucleus are also critically involved in absence seizures as they hyperpolarize thalamic relay neurons, which deinactivate T-type calcium channels allowing the channels to generate burst firing and the propagation of spike-and-wave discharges in the thalamocortical circuit (14).

Ethosuximide, which is highly efficacious in the treatment of absence seizures but not other seizure types, seems to act by inhibition of T-type calcium channels in the thalamocortical circuit (15–17). At clinically relevant concentrations (20 to 40 μg/mL), some but not all investigators have observed a partial (20% to 30%) reduction of T-type calcium current by ethosuximide. However, studies with recombinant T-type calcium channels have confirmed that ethosuximide blocks all three channel types (18). The block increases when the current is activated from more depolarized potentials and when T-type calcium channels are inactivated as especially occurs during high-frequency activation, so that the drug has selectivity for pathologic behavior in the thalamocortical circuit, which is associated with neuronal depolarization and inactivation of T-type calcium channels. Effects on other membrane currents, including I_{NaP} and calcium-activated potassium current, may contribute to the efficacy of ethosuximide in absence epilepsy (17). Remarkably, results in animal models indicate that early treatment with ethosuximide can have disease-modifying (antiepileptogenic) effects, causing a persistent reduction in seizures and mitigation of behavioral comorbidities (19,20). These actions may be caused by epigenetic modifications. A study showing that children with absence epilepsy who

receive ethosuximide are more likely than those who receive valproic acid to achieve long-term remission is consistent with the disease-modifying actions observed in animal studies (21).

The efficacy of some other AEDs may also depend, at least in part, on actions at T-type calcium channels. Zonisamide, in addition to effects on voltage-activated sodium channels, may also block T-type calcium channels (11), thus accounting for its likely efficacy in absence epilepsy (22). Similarly, there is evidence that valproate, a drug of choice in absence epilepsy, may also inhibit T-type calcium channels (17).

K_v7 Voltage-Gated Potassium Channels

Voltage-gated potassium channels are a diverse and evolutionarily ancient group of ion channels that serve a variety of key functions in the nervous system. Opening of potassium channels drives the membrane potential toward a hyperpolarized level, which serves to repolarize depolarizing events (such as action potentials and synaptic potentials) and cause a generalized reduction in excitability. In 1998, the first genes for a human idiopathic epilepsy were identified (23). These genes, designated *KCNQ2* and *KCNQ3*, encoded novel brain potassium channel subunits, K_v7.2 and K_v7.3, respectively, that are homologous to a previously identified cardiac potassium channel K_v7.1, encoded by *KCNQ1* (*LQT1*). The novel brain potassium channels mediate the M-current, a potassium current that increases as the membrane potential in neurons approach action potential threshold. K_v7 channels, together with HCN (hyperpolarization-activated cyclic nucleotide-gated potassium channels) and KCa2/SK (small-conductance calcium-activated potassium channels), generate the medium after hyperpolarization, which is elicited by a burst of action potentials and serves to limit further firing (24). K_v7 potassium channels therefore contribute to spike-frequency adaptation and can be considered to serve as a “brake” on epileptic firing. The K_v7 family of potassium channels is now known to contain five members, including K_v7.1, which is expressed predominantly in the heart, and K_v7.2 to K_v7.5, which are expressed exclusively in the nervous system (25).

Ezogabine, which is efficacious in the treatment of partial seizures, acts as a positive modulator of the nervous system K_v7 potassium channels (K_v7.2 to K_v7.5) but does not affect the cardiac member of the family (K_v7.1). Of particular relevance to the antiseizure action of ezogabine is its action on the M-current, which is predominantly carried by channels composed of K_v7.2 and K_v7.3, although K_v7.5 alone or in combination with K_v7.3 also contributes (26,27). Ezogabine causes a hyperpolarizing shift in the activation of K_v7 channels such that more M-current is generated near resting potential. It also causes a change in the kinetics of single KCNQ channels to favor channel opening, thus increasing the macroscopic M-current; ezogabine does not alter the single-channel conductance of individual K_v7 channels (28). Many K_v7 channels in the brain are believed to be K_v7.2/K_v7.3 heteromers, which are highly sensitive to ezogabine (EC₅₀, 1.6 μM) (27). Peak plasma levels of ezogabine range from 354 to 717 ng/mL (1.2 to 2.4 μM) (29), and plasma protein binding is 80% so that free plasma concentrations are estimated to be about 0.2 to 0.5 μM; brain concentrations are expected to be similar. Therefore, therapeutic concentrations likely only modestly potentiate the most sensitive K_v7 channels and do not affect less sensitive channels. The binding site for ezogabine in K_v7.2/K_v7.3 heteromers is in

a pocket formed by the pore-lining S5 membrane segment of one subunit and the pore-lining S6 membrane segment of the neighboring subunit (30,31). Channel opening may expose the pocket, permitting binding of ezogabine, which stabilizes the open-channel conformation.

GABA INHIBITION

GABA, the neurotransmitter of local inhibitory interneurons, acts through GABA_A receptors and GABA_B receptors. GABA_A receptors, which are Cys loop-type ligand-gated chloride channels, represent an important target for AEDs and will be considered here; GABA_B receptors, which are heterodimeric G protein-coupled receptors that activate potassium channels and inhibit calcium channels, are distinct in structure and function from GABA_A receptors and are not a target of any AED. Although only about one in five cortical neurons is GABA-ergic (32), these neurons play a critical role in controlling the firing rate and timing of principal (excitatory) neurons. In addition, they synchronize local neuronal ensembles and restrain the generation of abnormal epileptic behavior. Consequently, enhancement of GABA-ergic inhibition is a key mechanism of AED action.

GABA_A Receptors

GABA_A receptors are heteropentameric protein complexes localized to the postsynaptic membrane of inhibitory synapses where they mediate fast neuronal inhibition on a millisecond time scale. They are also located extrasynaptically where they respond to ambient GABA in the extracellular milieu and confer tonic (long-term) inhibition. There are 19 known GABA_A receptor subunits (α1 to 6, β1 to 3, γ1 to 3, δ, ε, θ, π, and ρ1 to 3). However, the bulk (60%) of synaptic GABA_A receptors are believed to have the α1β2γ2 configuration, and a considerable fraction of the remainder (15% to 20%) are α2β3γ2. Among the receptor subtypes that contribute to tonic signaling in the brain regions relevant to epilepsy are α4βxδ receptors, which are believed to mediate the tonic current in dentate granule cells and thalamocortical neurons, and α5-containing GABA_A receptors in CA1 pyramidal cells (33).

Benzodiazepines, such as diazepam, lorazepam, and clonazepam, and barbiturates, such as phenobarbital, are AEDs that act on GABA_A receptors as positive allosteric modulators. At higher concentration, barbiturates can directly activate GABA_A receptors in the absence of GABA (34), whereas benzodiazepines cannot. Benzodiazepines are specific for synaptic GABA_A receptors containing the γ2 subunit and act to allosterically modulate these receptors to increase the channel opening frequency resulting in enhanced synaptic inhibition. This confers a broad-spectrum anticonvulsant action. In most epilepsy syndromes, the specific cellular types that are involved in the anti-seizure activity of benzodiazepines are not known. However, in the case of absence epilepsy, it is believed that benzodiazepines desynchronize the thalamocortical oscillations underlying generalized spike-and-wave discharges by specific effects on α3-containing GABA_A receptors in the thalamic reticular nucleus (35). Barbiturates, presumably because they are not specific for α3-containing GABA_A receptors, are not active in absence epilepsy and may even aggravate absence seizures. In contrast to benzodiazepines, barbiturates do not appear

to increase the frequency of GABA-induced chloride channel opening, but instead increase the channel open time. In addition to effects on GABA_A receptors, barbiturates modulate other ion channel systems, including calcium and sodium channels, and these actions may contribute to therapeutic activity (36).

GAT-1 GABA Transporter

The action of neurotransmitter GABA is terminated by uptake into neurons and glial cell by membrane-bound GABA transporters, of which there are four types, termed GAT-1, BGT-1, GAT-2, and GAT-3. GAT-1 (encoded by the *SLC6A1* gene), the predominant form in the forebrain (including the neocortex and hippocampus), is localized to GABA-ergic terminals as well as to glial processes near GABA synapses. Tiagabine is a highly selective inhibitor of GAT-1 in neurons and glia (37). Inhibition of GAT-1 by tiagabine suppresses the translocation of extracellular GABA into the intracellular compartment, thus raising extracellular GABA levels. Functionally, tiagabine prolongs GABA-mediated inhibitory synaptic responses, and the marked elevation in extracellular GABA it produces may lead to activation of extrasynaptic GABA receptors.

GABA Transaminase

4-Aminobutyrate aminotransferase (GABA transaminase), an enzyme that catalyzes the conversion of GABA and 2-oxoglutarate into succinic semialdehyde and glutamate, is responsible for the metabolic inactivation of GABA. Inhibition of GABA transaminase with vigabatrin (γ -vinyl GABA), an irreversible suicide inhibitor of the enzyme, leads to marked increases in brain GABA levels. Although the antiseizure action of vigabatrin is believed to reflect inactivation of GABA transaminase, how this occurs is not straightforward and does not appear to be due to an enhancement of inhibitory synaptic transmission. In contrast to the action of tiagabine, vigabatrin does not elicit larger or more prolonged GABA_A receptor-mediated synaptic responses (38,39). Rather, preincubation of brain slices with vigabatrin irreversibly inhibited miniature and evoked inhibitory postsynaptic currents. Additional experiments suggested that the paradoxical effect resulted from a reduction in the GABA content of synaptic vesicles caused by GABA transaminase inhibition. In contrast to the effect on GABA-mediated synaptic transmission, vigabatrin caused an increase in nonsynaptic tonic GABA_A receptor current. This steady current is believed to be mediated by the action of GABA in the extracellular milieu acting on extrasynaptic GABA_A receptors. High levels of intracellular GABA cause a reversal of GABA transporters, resulting in a marked elevation in extracellular GABA, which is likely responsible for the increase in tonic GABA_A receptor current. It can be concluded that vigabatrin causes divergent effects on synaptic and extrasynaptic GABA-mediated inhibition, with seizure protection resulting from a predominance of the extrasynaptic action. Interestingly, in the early period after administration of vigabatrin to animals, there is a reduction in seizure threshold, whereas the anticonvulsant actions become evident only later (40,41). Thus, vigabatrin has a biphasic action with proconvulsant effects likely related to suppression of synaptic GABA-ergic neurotransmission and anticonvulsant effects due to spillover of GABA into the extracellular space and activation of extrasynaptic GABA_A receptors.

Interestingly, individuals with a rare genetic deficiency of GABA transaminase experience refractory seizures, supporting the view that inhibition of GABA transaminase is in fact the proconvulsant mechanism of vigabatrin (42).

SYNAPTIC RELEASE MACHINERY

SV2A

A variety of lines of evidence support the conclusion that SV2A, a membrane glycoprotein found in the secretory vesicles of neurons and endocrine cells and possibly immune cells, is the molecular target for levetiracetam (43,44). There is a strong correlation between the affinity of levetiracetam analogs for binding to SV2A and the potency of the analogs in several animal seizure models. Moreover, seizure protection conferred by levetiracetam and other SV2A ligands strongly correlates with the degree of SV2A occupancy in vivo. Finally, the anticonvulsant efficacy of levetiracetam but not valproate, which does not interact with SV2A, is reduced in SV2A^{-/-} mice that have one copy of SV2A disrupted by gene targeting. The precise way in which binding of levetiracetam to SV2A leads to seizure protection is not understood.

Indeed, the function of SV2A itself is obscure. Among the various functions proposed are roles in calcium-dependent exocytosis, neurotransmitter loading/retention in synaptic vesicles, and synaptic vesicle priming, as well as transport of vesicle constituents. SV2A is one of three homologous of SV2 proteins that belong to the major facilitator superfamily of 12-transmembrane domain transporters. Despite substantial effort, no transport function of these proteins has been identified, although studies with protein tomography have found that SV2A can adopt two alternate conformations consistent with a transporter role (45). Interestingly, however, levetiracetam binding does not cause a large-scale conformational change in SV2A or lock a specific conformational state of the protein as would an inhibitor of transport. Apparently, the drug has a more subtle effect on the protein. Although the function of SV2A is still poorly defined, SV2A^{-/-} knockout mice exhibit a lethal seizure phenotype demonstrating that SV2A in some way serves to restrain seizures.

A series of recent studies has examined the impact of levetiracetam on synaptic transmission in brain slice recordings (46). Although the drug had no effect on synaptic physiology with low-frequency activation, levetiracetam did reduce the synaptic release of both excitatory (glutamate) and inhibitory (GABA) neurotransmitters during high-frequency activation. The frequency dependence is compatible with the selective suppression of epileptic activity. Modulation of synaptic release is a common mechanism of many AEDs, including sodium channel blockers that indirectly inhibit release at both excitatory and inhibitory synapses by inhibiting action potential firing. It seems that drugs that suppress inhibition and excitation can effectively protect against seizures and they are not often proconvulsant. However, it is noteworthy that in some instances AEDs (notably phenytoin) can have proconvulsant effects.

$\alpha 2\delta$ -1

The gabapentinoids gabapentin and pregabalin act by binding to the $\alpha 2\delta$ -1 protein, which is an accessory subunit of voltage-gated calcium channels (47,48). $\alpha 2\delta$ -1 is located

heterogeneously in the brain, particularly at presynaptic sites on excitatory (glutamatergic) neurons. Dense expression is observed in areas relevant to epilepsy, including in excitatory hippocampal mossy fibers and in the neocortex and amygdala. In contrast, $\alpha 2\delta$ -1 has minimal expression in the thalamus, and it is noteworthy that gabapentinoids are not active in absence seizures, which as discussed above are dependent upon this brain structure. Four $\alpha 2\delta$ subunits have been identified, but gabapentinoids only bind to $\alpha 2\delta$ -1 and $\alpha 2\delta$ -2 owing to the presence of an RRR motif containing a critical arginine that is required for binding. Seizure protection conferred by gabapentinoids is eliminated in mice bearing a mutation in this motif (RRR mutated to RRA) in $\alpha 2\delta$ -1, demonstrating that $\alpha 2\delta$ -1 and not $\alpha 2\delta$ -2 is relevant for pharmacologic activity. Interestingly, deletion of $\alpha 2\delta$ -1 or $\alpha 2\delta$ -2 in mice is associated with absence epilepsy or enhanced seizure susceptibility (49,50).

The precise way in which binding of gabapentin and pregabalin to the $\alpha 2\delta$ -1 protein confers seizure protection is not well understood (51). Although some studies have found that the drugs inhibit calcium channel currents, most have not and it is generally believed that calcium channel inhibition is not the mechanism of action of gabapentinoids (52–54). Regardless of whether the drugs inhibit calcium channel function, they do seem to block the release of various neurotransmitters, including glutamate, and this may account for the antiseizure activity (55). There is some evidence that gabapentinoids cause internalization of calcium channels by reducing trafficking to the cell membrane (56,57). Whether this action could account for the rapid antiseizure effects of gabapentinoids in animal models is uncertain.

AMPA RECEPTORS

Perampanel is the first selective AMPA receptor antagonist approved for epilepsy treatment. Whereas $GABA_A$ receptors mediate fast synaptic inhibition, AMPA receptors are cation channels that serve as the main mediators of fast (millisecond time scale) synaptic excitation. It has been long appreciated that cascading excitation within networks of synaptically connected neurons is a key mechanism of epileptic synchronization, at least in the hippocampal CA3 region and possibly in other brain areas (58). Epileptic activity emerges from the network when GABA-mediated inhibition is deficient, and indeed chronic alterations in inhibition represent a leading hypothesis to explain some forms of epilepsy.

Fast synaptic excitation is elicited by the exocytotic release of glutamate from excitatory principal neurons, which diffuses across the synaptic cleft and interacts with ionotropic glutamate receptors (iGluRs) of the AMPA and NMDA types to generate excitatory postsynaptic potentials (EPSPs). Summation of EPSPs leads to the firing of action potentials by the postsynaptic neuron. AMPA receptors have a special role in epileptic activity as epileptic synchronization cannot occur when AMPA receptors are blocked. In contrast, kainate receptors, which are iGluRs that have a similar structure to AMPA receptors, do not have a similarly essential role as kainate receptor knockout does not interfere with seizure generation (59). NMDA receptors are thought to contribute to epileptiform activity, but the blockade of NMDA receptors is insufficient to abolish epileptiform discharges in many seizure models (60). Pharmacologic blockade of AMPA receptors has broad-spectrum anticonvulsant activity in *in vitro* and animal seizure models.

Perampanel is a potent noncompetitive antagonist of AMPA receptors that does not affect NMDA receptor responses and has no known effects on other ion channels or molecular targets at therapeutically relevant concentrations (61). Therapeutic blood levels are expected to result in brain concentrations that would produce only low levels of inhibition of AMPA receptors. However, such low-level block of AMPA receptors is apparently sufficient to exert a clinical antiseizure action. Perampanel has a relatively low therapeutic window. Adverse central nervous system effects such as dizziness, irritability, and somnolence are common, particularly at higher-dose levels, emphasizing the importance of AMPA receptors in brain function.

MIXED/UNKNOWN ACTIONS

Valproate

Although valproate is one of the most valuable AEDs, the mechanism by which it protects against seizures is poorly understood. Valproate has multiple pharmacologic actions (62,63). Since it has been difficult to relate any one mechanism to the drug's broad spectrum of activity, it has been proposed that combined actions on several targets could account for its therapeutic properties. Although the actions of valproate on GABA systems are not straightforward, among the various pharmacologic effects that have been described, those related to GABA mechanisms are among the most likely to be relevant to valproate's antiseizure activity. For example, valproate increases the turnover of GABA, and this might be associated with enhanced synaptic or extrasynaptic inhibition. At high concentrations, valproate affects voltage-gated sodium channels, but recent studies in brain slice recordings have failed to provide support for sodium channel block as a relevant mechanism to explain clinical activity (64). Similarly, despite efficacy in absence epilepsy, there is little support for effects on T-type calcium channels. It is likely that valproate has pharmacologic actions relevant to its antiseizure activity that remain to be elucidated.

Felbamate

Felbamate, at concentrations within the therapeutic range, has been shown both to act as positive modulators of $GABA_A$ receptors and also to inhibit NMDA receptors (65). Felbamate potentiates GABA responses via an interaction with a site on the $GABA_A$ receptor that is distinct from the benzodiazepine recognition site. This action may be of relevance to felbamate's clinical activity. Although drugs that block NMDA receptors can exert antiseizure effects in certain animal models, there is doubt whether blockade of NMDA receptors is a useful strategy to treat epilepsy (66). Therefore, it is uncertain whether the NMDA receptor-blocking activity of felbamate is relevant to its clinical antiseizure activity.

Topiramate

As is the case for valproate and felbamate, the broad-spectrum anticonvulsant activity of topiramate is likely to result from mixed effects on several targets (67). Among topiramate's diverse pharmacologic actions, effects on voltage-activated

sodium channels, GABA_A receptor subtypes, AMPA or kainate receptors, and types II and IV carbonic anhydrase isoenzymes are potentially relevant to seizure protection. Unlike other AEDs, the effects on ion channels are unlikely to occur through direct modulation of channel gating. Rather, the pharmacologic actions of topiramate seem to be mediated indirectly, possibly through effects on channel phosphorylation.

The effects of topiramate on sodium channels occur at relatively low, therapeutically relevant concentrations and could be similar to the effects of other sodium channel-blocking AEDs (68). In addition to effects on fast sodium currents, topiramate, like phenytoin, blocks I_{NaP} at low concentrations. Effects of topiramate on GABA_A receptors could contribute to the broad spectrum of activity of topiramate. Topiramate is not active in animal models, such as the pentylenetetrazol test, that are typically sensitive to drugs that positively modulate GABA_A receptors. Nevertheless, the drug does have activity in an absence epilepsy model and can affect pentylenetetrazol threshold, which is consistent with effects on GABA_A receptors. There is evidence that topiramate may preferentially modulate a subset of GABA_A receptors and that drug sensitivity is dependent upon the β -subunit type (69).

Several authors have suggested that actions on fast glutamate-mediated excitatory neurotransmission could contribute to topiramate's antiseizure activity. In cultured neurons, the drug has been reported to inhibit responses to kainate, an agonist of AMPA and kainate receptors, leading to the conclusion that topiramate could be an antagonist of either AMPA or kainate receptors (70). Recently, kainate receptors have been found to be an unlikely target for an antiseizure agent (71). Whether actions of topiramate on glutamate-mediated neurotransmission contribute to its anticonvulsant activity remains to be determined.

The action of topiramate on carbonic anhydrase has been assumed not to contribute to its clinical efficacy because there is no cross-tolerance to the anticonvulsant activity of topiramate when tolerance occurs to the classical carbonic anhydrase inhibitor acetazolamide in mice. However, a recent review left open the possibility that carbonic anhydrase inhibition could, in part, play a role (67).

Zonisamide

There are some similarities between topiramate and zonisamide as they both contain a sulfur atom and both inhibit carbonic anhydrase. In addition, like topiramate, zonisamide may act on voltage-dependent sodium channels (72). Physiologic studies do not support an action on GABA_A receptors. Unlike topiramate, there are reports that zonisamide can inhibit T-type voltage-gated calcium channels (73), which may account for its activity in absence epilepsy.

Rufinamide

The unique spectrum of clinical activity of rufinamide in the treatment of the Lennox–Gastaut syndrome suggests that it has a distinct mechanism of action (26). However, to date, rufinamide has only been shown to interact with voltage-gated sodium channels, and the effects are subtle. Relevant concentrations of the drug may, at least for some subunit isoforms,

cause a depolarization in the activation voltage and slowing of recovery from inactivation, which would be expected to reduce neuronal excitability (74). Clearly, the effects on sodium channels cannot explain the special clinical activity of rufinamide.

Adrenocorticotropin

The mechanism of adrenocorticotropin (ACTH) in the treatment of infantile spasms is not understood (75). ACTH stimulates glucocorticoid (cortisol) synthesis and release from the zona fasciculata of the adrenal cortex. The cortisol could produce an antiinflammatory action or have some other action in the brain to influence infantile spasms. Indeed, glucocorticoids are well recognized to themselves have therapeutic activity in the treatment of infantile spasms; whether ACTH is truly superior remains to be demonstrated conclusively. One possible additional action of ACTH that could contribute to enhanced activity is stimulation of neurosteroid synthesis. In addition to its actions with respect to glucocorticoids, ACTH also stimulates deoxycorticosterone (DOC) release from the zona glomerulosa of the adrenal cortex. DOC is, in part, converted to the anticonvulsant neurosteroid tetrahydro-DOC, which is a positive allosteric modulator of GABA_A receptors (76). It has been hypothesized that the tetrahydro-DOC could, at least in part, contribute to the ability of ACTH to terminate infantile spasms.

BASIS OF COMBINATIONAL TREATMENT

All clinically used AEDs protect against seizures in animal models as single agents. Studies with early AEDs suggested that the seizure protection conferred by drug combinations is simply additive (77). Since the use of more than one agent compounds the risk of side effects, these and other observations led to the recommendation that AEDs should be tried sequentially in monotherapy before combining agents. More recent experimental data suggest that combining drugs with complementary mechanisms of action might lead to synergism for efficacy (78). Observational studies of results obtained in clinical practice have shown that combining newer AEDs with different mechanisms of action may have greater effectiveness (a combination of efficacy and tolerability) than combining drugs with similar mechanisms of action (79). Consequently, an understanding of mechanism may impact clinical decision making in regard to the choice of drug combinations.

References

1. Stafstrom CE. Persistent sodium current and its role in epilepsy. *Epilepsy Curr.* 2007;7(1):15–22.
2. Mantegazza M, Curia G, Biagini G, et al. Voltage-gated sodium channels as therapeutic targets in epilepsy and other neurological disorders. *Lancet Neurol.* 2010;9(4):413–424.
3. Meldrum BS, Rogawski MA. Molecular targets for antiepileptic drug development. *Neurotherapeutics.* 2007;4(1):18–61.
4. Oliva M, Berkovic SF, Petrou S. Sodium channels and the neurobiology of epilepsy. *Epilepsia.* 2012;53(11):1849–1859. Erratum in: *Epilepsia.* 2013;54(3):570.
5. Waldmeier PC, Baumann PA, Wicki P, et al. Similar potency of carbamazepine, oxcarbazepine, and lamotrigine in inhibiting the release of glutamate and other neurotransmitters. *Neurology.* 1995;45(10):1907–1913.

6. Niespodziany I, Leclère N, Vandenplas C, et al. Comparative study of lacosamide and classical sodium channel blocking antiepileptic drugs on sodium channel slow inactivation. *J Neurosci Res*. 2013;91(3):436–443.
7. Avoli M, Rogawski MA, Avanzini G. Generalized epileptic disorders: an update. *Epilepsia*. 2001;42(4):445–457.
8. Huguenard JR. Block of T-type Ca^{2+} channels is an important action of succinimide antiabsence drugs. *Epilepsy Curr*. 2002;2(2):49–52.
9. Lambert RC, Bessaih T, Crunelli V, et al. The many faces of T-type calcium channels. *Pflügers Arch*. 2014;466(3):415–423.
10. Talley EM, Cribbs LL, Lee JH, et al. Differential distribution of three members of a gene family encoding low voltage-activated (T-type) calcium channels. *J Neurosci*. 1999;19(6):1895–1911.
11. Powell KL, Cain SM, Snutch TP, et al. Low threshold T-type calcium channels as targets for novel epilepsy treatments. *Br J Clin Pharmacol*. 2014;77(5):729–739.
12. Crunelli V, David F, Leresche N, et al. Role for T-type Ca^{2+} channels in sleep waves. *Pflügers Arch*. 2014;466(4):735–745.
13. Suzuki S, Rogawski MA. T-type calcium channels mediate the transition between tonic and phasic firing in thalamic neurons. *Proc Natl Acad Sci U S A*. 1989;86:7228–7232.
14. Danober L, Deransart C, Depaulis A, et al. Pathophysiological mechanisms of genetic absence epilepsy in the rat. *Prog Neurobiol*. 1998;55(1):27–57.
15. Coulter DA, Huguenard JR, Prince DA. Characterization of ethosuximide reduction of low-threshold calcium current in thalamic relay neurons. *Ann Neurol*. 1989;25:582–593.
16. Gören MZ, Onat F. Ethosuximide: from bench to bedside. *CNS Drug Rev*. 2007;13(2):224–239.
17. Broicher T, Seidenbecher T, Meuth P, et al. T-current related effects of antiepileptic drugs and a Ca^{2+} channel antagonist on thalamic relay and local circuit interneurons in a rat model of absence epilepsy. *Neuropharmacology*. 2007;53(3):431–446.
18. Gomora JC, Daud AN, Weiergräber M, et al. Block of cloned human T-type calcium channels by succinimide antiepileptic drugs. *Mol Pharmacol*. 2001;60(5):1121–1132.
19. Blumenfeld H, Klein JP, Schridde U, et al. Early treatment suppresses the development of spike-wave epilepsy in a rat model. *Epilepsia*. 2008;49(3):400–409.
20. Dezsi G, Öztürk E, Stanic D, et al. Ethosuximide reduces epileptogenesis and behavioral comorbidity in the GAERS model of genetic generalized epilepsy. *Epilepsia*. 2013;54(4):635–643.
21. Berg AT, Levy SR, Testa FM, et al. Long-term seizure remission in childhood absence epilepsy: Might initial treatment matter? *Epilepsia*. 2014;55(4):551–557.
22. Hughes JR. Absence seizures: a review of recent reports with new concepts. *Epilepsy Behav*. 2009;15(4):404–412.
23. Charlier C, Singh NA, Ryan SG, et al. A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. *Nat Genet*. 1998;18(1):53–55.
24. Gu N, Vervaeke K, Hu H, et al. Kv7/KCNQ/M and HCN/h, but not KCa2/SK channels, contribute to the somatic medium after-hyperpolarization and excitability control in CA1 hippocampal pyramidal cells. *J Physiol*. 2005;566(Pt 3):689–715.
25. Brown DA, Passmore GM. Neural KCNQ (Kv7) channels. *Br J Pharmacol*. 2009;156(8):1185–1195.
26. Rogawski MA. Diverse mechanisms of antiepileptic drugs in the development pipeline. *Epilepsy Res*. 2006;69(3):273–294.
27. Gunthorpe MJ, Large CH, Sankar R. The mechanism of action of retigabine (ezogabine), a first-in-class K^{+} channel opener for the treatment of epilepsy. *Epilepsia*. 2012;53(3):412–424.
28. Tatulian L, Brown DA. Effect of the KCNQ potassium channel opener retigabine on single KCNQ2/3 channels expressed in CHO cells. *J Physiol*. 2003;549(Pt 1):57–63.
29. Hermann R, Ferron GM, Erb K, et al. Effects of age and sex on the disposition of retigabine. *Clin Pharmacol Ther*. 2003;73(1):61–70.
30. Wuttke TV, Seebohm G, Bail S, et al. The new anticonvulsant retigabine favors voltage-dependent opening of the Kv7.2 (KCNQ2) channel by binding to its activation gate. *Mol Pharmacol*. 2005;67(4):1009–1017.
31. Lange W, Geissendörfer J, Schenzer A, et al. Refinement of the binding site and mode of action of the anticonvulsant Retigabine on KCNQ K^{+} channels. *Mol Pharmacol*. 2009;75(2):272–280.
32. Sahara S, Yanagawa Y, O'Leary DD, et al. The fraction of cortical GABAergic neurons is constant from near the start of cortical neurogenesis to adulthood. *J Neurosci*. 2012;32(14):4755–4761.
33. Walker MC, Kullmann DM. Tonic GABA_A receptor-mediated signaling in epilepsy. In: Noebels JL, Avoli M, Rogawski MA, et al., eds. *Jasper's Basic Mechanisms of the Epilepsies* [Internet]. 4th ed. Bethesda, MD: National Center for Biotechnology Information (US); 2012.
34. Rho JM, Donevan SD, Rogawski MA. Direct activation of GABA_A receptors by barbiturates in cultured rat hippocampal neurons. *J Physiol*. 1996;497(Pt 2):509–522.
35. Sohal VS, Keist R, Rudolph U, et al. Dynamic GABA_A receptor subtype-specific modulation of the synchrony and duration of thalamic oscillations. *J Neurosci*. 2003;23:3649–3657.
36. French-Mullen JM, Barker JL, Rogawski MA. Calcium current block by (–)-pentobarbital, phenobarbital, and CHEB but not (+)-pentobarbital in acutely isolated hippocampal CA1 neurons: comparison with effects on GABA-activated Cl^{-} current. *J Neurosci*. 1993;13(8):3211–3221.
37. Schousboe A, Madsen KK, Barker-Haliski ML, et al. The GABA synapse as a target for antiepileptic drugs: a historical overview focused on GABA transporters. *Neurochem Res*. 2014;39(10):1980–1987.
38. Overstreet LS, Westbrook GL. Paradoxical reduction of synaptic inhibition by vigabatrin. *J Neurophysiol*. 2001;86(2):596–603.
39. Wu Y, Wang W, Richerson GB. Vigabatrin induces tonic inhibition via GABA transporter reversal without increasing vesicular GABA release. *J Neurophysiol*. 2003;89(4):2021–2034.
40. Löscher W, Jäckel R, Müller F. Anticonvulsant and proconvulsant effects of inhibitors of GABA degradation in the amygdala-kindling model. *Eur J Pharmacol*. 1989;163(1):1–14.
41. Stuchlik A, Kubová H, Mares P. Single systemic dose of vigabatrin induces early proconvulsant and later anticonvulsant effect in rats. *Neurosci Lett*. 2001;312(1):37–40.
42. Medina-Kauwe LK, Tobin AJ, De Meirleir L, et al. 4-Aminobutyrate aminotransferase (GABA-transaminase) deficiency. *J Inherib Metab Dis*. 1999;22(4):414–427.
43. Kaminski RM, Gillard M, Klitgaard H. Targeting SV2A for discovery of antiepileptic drugs. In: Noebels JL, Avoli M, Rogawski MA, et al., eds. *Jasper's Basic Mechanisms of the Epilepsies* [Internet]. 4th ed. Bethesda, MD: National Center for Biotechnology Information; 2012.
44. Li G, Nowak M, Bauer S, et al. Levetiracetam but not valproate inhibits function of CD8⁺ T lymphocytes. *Seizure*. 2013;22(6):462–466.
45. Lynch BA, Matagne A, Brännström A, et al. Visualization of SV2A conformations in situ by the use of protein tomography. *Biochem Biophys Res Commun*. 2008;375(4):491–495.
46. Meehan AL, Yang X, Yuan LL, et al. Levetiracetam has an activity-dependent effect on inhibitory transmission. *Epilepsia*. 2012;53(3):469–476.
47. Dolphin AC. The $\alpha 2\delta$ subunits of voltage-gated calcium channels. *Biochim Biophys Acta*. 2013;1828(7):1541–1549.
48. Stahl SM, Porreca F, Taylor CP, et al. The diverse therapeutic actions of pregabalin: is a single mechanism responsible for several pharmacological activities? *Trends Pharmacol Sci*. 2013;34(6):332–339.
49. Davies A, Hendrich J, Van Minh AT, et al. Functional biology of the $\alpha 2\delta$ subunits of voltage-gated calcium channels. *Trends Pharmacol Sci*. 2007;28(5):220–228.
50. Ivanov SV, Ward JM, Tessarollo L, et al. Cerebellar ataxia, seizures, premature death, and cardiac abnormalities in mice with targeted disruption of the *Cacna2d2* gene. *Am J Pathol*. 2004;165(3):1007–1018.
51. Rogawski MA, Bazil CW. New molecular targets for antiepileptic drugs: $\alpha 2\delta$, SV2A, and K_v7/KCNQ/M potassium channels. *Curr Neurol Neurosci Rep*. 2008;8(4):345–352.
52. Stefani A, Spadoni F, Bernardi G. Gabapentin inhibits calcium currents in isolated rat brain neurons. *Neuropharmacology*. 1998;37(1):83–91.
53. van Hooft JA, Dougherty JJ, Endeman D, et al. Gabapentin inhibits presynaptic Ca^{2+} influx and synaptic transmission in rat hippocampus and neocortex. *Eur J Pharmacol*. 2002;449(3):221–228.
54. Brown JT, Randall A. Gabapentin fails to alter P/Q-type Ca^{2+} channel-mediated synaptic transmission in the hippocampus in vitro. *Synapse*. 2005;55(4):262–269.
55. Dooley DJ, Taylor CP, Donevan S, et al. Ca^{2+} channel $\alpha 2\delta$ ligands: novel modulators of neurotransmission. *Trends Pharmacol Sci*. 2007;28(2):75–82.
56. Hendrich J, Van Minh AT, Heblch F, et al. Pharmacological disruption of calcium channel trafficking by the $\alpha 2\delta$ ligand gabapentin. *Proc Natl Acad Sci U S A*. 2008;105(9):3628–3633.
57. Weissmann C, Di Guilmi MN, Urbano FJ, et al. Acute effects of pregabalin on the function and cellular distribution of $Ca_v2.1$ in HEK293t cells. *Brain Res Bull*. 2013;90:107–113.
58. Rogawski MA. AMPA receptors as a molecular target in epilepsy therapy. *Acta Neurol Scand Suppl*. 2013;197:9–18.
59. Fritsch B, Reis J, Gasior M, et al. Role of GluK1 kainate receptors in seizures, epileptic discharges, and epileptogenesis. *J Neurosci*. 2014;34(17):5765–5775.
60. Neuman R, Cherubini E, Ben-Ari Y. Epileptiform bursts elicited in CA3 hippocampal neurons by a variety of convulsants are not blocked by N-methyl-D-aspartate antagonists. *Brain Res*. 1988;459(2):265–274.
61. Hanada T, Hashizume Y, Tokuhara N, et al. Perampanel: a novel, orally active, noncompetitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy. *Epilepsia*. 2011;52(7):1331–1340.
62. Rogawski MA, Porter RJ. Antiepileptic drugs: Pharmacological mechanisms and clinical efficacy with consideration of promising developmental stage compounds. *Pharmacol Rev*. 1990;42:223–286.
63. Löscher W. Basic pharmacology of valproate: a review after 35 years of clinical use for the treatment of epilepsy. *CNS Drugs*. 2002;16(10):669–694.
64. Englund M, Hyllienmark L, Brismar T. Effect of valproate, lamotrigine and levetiracetam on excitability and firing properties of CA1 neurons in rat brain slices. *Cell Mol Neurobiol*. 2011;31(4):645–652.
65. Rho JM, Donevan SD, Rogawski MA. Mechanism of action of the anticonvulsant felbamate: opposing effects on N-methyl-D-aspartate and γ -aminobutyric acid_A receptors. *Ann Neurol*. 1994;35(2):229–234.
66. Rogawski MA. Revisiting AMPA receptors as an antiepileptic drug target. *Epilepsy Curr*. 2011;11(2):56–63.

67. Shank RP, Maryanoff BE. Molecular pharmacodynamics, clinical therapeutics, and pharmacokinetics of topiramate. *CNS Neurosci Ther.* 2008;14(2):120–142.
68. Avoli M, Kawasaki H, Zona C. Effects induced by topiramate on sodium electrogenesis in mammalian central neurons. *Epilepsia.* 1996;37(suppl 4):S1–S2.
69. Simeone TA, Wilcox KS, White HS. Topiramate modulation of β_1 - and β_2 -homomeric GABA_A receptors. *Pharmacol Res.* 2011;64(1):44–52.
70. Gibbs JW III, Sombati S, DeLorenzo RJ, et al. Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. *Epilepsia.* 2000;41(suppl 1):S10–S16.
71. Fritsch B, Reis J, Gasior M, et al. Role of GluK1 kainate receptors in seizures, epileptic discharges, and epileptogenesis. *J Neurosci.* 2014;34(17):5765–5775.
72. Biton V. Clinical pharmacology and mechanism of action of zonisamide. *Clin Neuropharmacol.* 2007;30(4):230–240.
73. Matar N, Jin W, Wrubel H, et al. Zonisamide block of cloned human T-type voltage-gated calcium channels. *Epilepsy Res.* 2009;83(2–3):224–234.
74. Gilchrist J, Dutton S, Diaz-Bustamante M, et al. Nav1.1 modulation by a novel triazole compound attenuates epileptic seizures in rodents. *ACS Chem Biol.* 2014;9(5):1204–1212.
75. Stafstrom CE, Arnason BG, Baram TZ, et al. Treatment of infantile spasms: emerging insights from clinical and basic science perspectives. *J Child Neurol.* 2011;26(11):1411–1421.
76. Reddy DS, Rogawski MA. Stress-induced deoxycorticosterone-derived neurosteroids modulate GABA(A) receptor function and seizure susceptibility. *J Neurosci.* 2002;22(9):3795–3805.
77. Leppik IE, Sherwin AL. Anticonvulsant activity of phenobarbital and phenytoin in combination. *J Pharmacol Exp Ther.* 1977; 200(3):570–575.
78. Deckers CL, Czuczwar SJ, Hekster YA, et al. Selection of antiepileptic drug polytherapy based on mechanisms of action: the evidence reviewed. *Epilepsia.* 2000;41(11):1364–1374.
79. Margolis JM, Chu BC, Wang ZJ, et al. Effectiveness of antiepileptic drug combination therapy for partial-onset seizures based on mechanisms of action. *JAMA Neurol.* 2014;71(8):985–993.