

CHAPTER 136 ■ CELLULAR EFFECTS OF ANTIEPILEPTIC DRUGS

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INTRODUCTION

Antiepileptic drugs (AEDs) protect against seizures through interactions with a variety of cellular targets, which include various ion channels, a neurotransmitter transporter, a neurotransmitter metabolic enzyme, and a synaptic vesicle protein. AED actions on these targets can be categorized into four broad groups:

1. Modulation of voltage-dependent ion channels (mainly sodium [Na] but also calcium [Ca] channels)
2. Effects on γ -aminobutyric acid (GABA) systems, including alterations in the cellular disposition of GABA and enhancement of synaptic inhibition mediated by GABA_A receptors
3. Inhibition of synaptic excitation mediated by ionotropic glutamate receptors
4. Modulation of neurotransmitter release, particularly of glutamate, through presynaptic mechanisms.

A critical downstream effect of drugs that target voltage-dependent Na and Ca channels may be to selectively modulate glutamate release while only weakly affecting GABA release.¹³² Thus, group 1 and group 4 actions overlap in that they represent mechanisms for the presynaptic regulation of glutamate release. The ultimate effects of the interactions at these diverse targets 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, which is required for the expression of behavioral seizure activity in localization-related epilepsies. Generalized absence seizures, unlike other seizure types, are believed to result from thalamocortical synchronization. Interference with the intrinsic rhythm-generating mechanisms that underlie the synchronized activity in this circuit is necessary to abort these seizures. This chapter discusses the specific actions or combinations of actions that are believed to account for the anticonvulsant activity of marketed AEDs. Each of the AEDs has its own unique pharmacodynamic properties. In some cases, the uniqueness results because the biophysical parameters governing the drug's interaction with its target are distinct. For example, phenytoin and carbamazepine both interact with voltage-gated Na channels, but the kinetic properties of the interaction are subtly different. In other cases, the AEDs act selectively on unique targets. For example, ethosuximide targets T-type Ca channels, vigabatrin targets GABA transaminase, tiagabine targets the GAT-1 GABA transporter, gabapentin and pregabalin target $\alpha 2\text{-}\delta$ proteins, and levetiracetam targets the SV2A synaptic vesicle protein. Finally, in other cases still, AEDs such as phenobarbital, felbamate, and topiramate have mixed actions on various targets; their unique properties as anticonvulsants result from the combination of effects on these targets. These various diverse actions confer on each AED a characteristic and unique clinical profile.¹⁴⁷

MECHANISMS OF ACTION OF ESTABLISHED AEDs

Phenytoin and Carbamazepine

Phenytoin and carbamazepine interact with voltage-dependent Na channels at concentrations found free in plasma in patients being treated for epilepsy.⁹⁶ Both drugs are 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). This profile of activity is typical of AEDs that act as Na channel modulators. Na channels are composed of an α subunit (Na_v1.1–1.9) associated with auxiliary $\beta 1$ -, $\beta 2$ -, or $\beta 3$ -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.

Phenytoin and carbamazepine were demonstrated to reduce the frequency of sustained repetitive firing of action potentials.^{106,107} The characteristic property of these drugs is that they 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. The limitation of high-frequency repetitive firing is voltage-dependent, with limitation of firing increasing after depolarization and reducing after hyperpolarization. Once developed, the limitation of firing is prolonged, lasting several hundred milliseconds. The action of the AEDs appear to be due to a shift of Na channels to an inactive state from which recovery is delayed.

On mammalian myelinated nerve fibers, both phenytoin and carbamazepine produced a voltage-dependent block of sodium channels that could be removed by hyperpolarization, a shift of the steady-state sodium channel inactivation curve to more negative voltages, and a reduction in the rate of recovery of sodium channels from inactivation.¹⁵⁵ Sodium channels recovered from complete inactivation in a few milliseconds after a 500-ms depolarization to 25 mV. In the presence of 100 $\mu\text{mol/L}$ phenytoin or carbamazepine, however, recovery was prolonged to 90 or 40 ms, respectively. At 50 $\mu\text{mol/L}$, phenytoin and carbamazepine each produced a frequency-dependent block. However, the frequency-dependent block produced by carbamazepine was somewhat less pronounced than that produced by phenytoin. Of interest was the finding that phenytoin had a longer time-dependence for frequency-dependent block and for recovery from block than did carbamazepine, which would result in a more pronounced frequency-dependent block for phenytoin than for carbamazepine. Thus, although phenytoin and carbamazepine have qualitatively similar actions on sodium channels, their actions are quantitatively somewhat different. This may explain, at least in part, differences in efficacy for these two drugs in different patients.

In rat hippocampal neurons, phenytoin (200 $\mu\text{mol/L}$) produced a 20-mV negative shift in the steady-state inactivation

curve for Na channels and produced frequency-dependent block of Na channels.¹⁹¹ Frequency-dependent block was shown at frequencies as low as 1 Hz, and the block increased to 50% at 10 Hz.¹⁹¹ It has been suggested that unbinding of phenytoin from the Na channel is driven by channel deactivation, and that phenytoin may not stabilize the “normal” inactivation state.⁷⁸ The delay in recovery from apparent inactivation may be due to phenytoin blocking the Na channel by binding to a blocking site on the Na channel that is formed during activation and removed during deactivation and only slowly dissociating from the blocking site after deactivation. The phenytoin block is thus due to the voltage-dependency of deactivation. The slow dissociation, in part, accounts for phenytoin’s selective ability to block high-frequency firing: When recovery is slow, the block can accumulate during repetitive activation of the channel. Another important feature of the block of Na channels by phenytoin is its slow onset. Slow binding has two important implications. 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. In focal epilepsies, seizure discharges are associated with more sustained depolarizations than those occurring during interictal discharges. Only depolarizations that are as long as those occurring during ictal discharges provide the conditions required for drug binding and block.

Benzodiazepines and Barbiturates

Benzodiazepines and barbiturates enhance GABAergic inhibition at the free serum concentrations found in ambulatory patients⁹⁶ by interacting directly with GABA_A receptors. GABA_A receptors are formed by the assembly of multiple subunit subtypes ($\alpha 1$ – $\alpha 6$, $\beta 1$ – $\beta 3$, $\gamma 1$ – $\gamma 3$, δ , ϵ , π , θ , and $\rho 1$ – $\rho 3$) into a pentamer, although the most common and likely subunit composition has been determined to contain two α -subunits, two β -subunits, and a γ -subunit.¹⁰ The five subunits are arranged in a counterclockwise sequence (as seen from the synaptic cleft) $\gamma\beta\alpha\beta\alpha$.¹⁰ 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^{36,98} (see Chapter 23). GABA regulates gating (opening and closing) of the ion channel.^{96,186,197} Binding of GABA increases the probability of channel opening, and the open channel can close and rapidly reopen to create bursts of openings.

Barbiturates enhance GABA_A receptor current by binding to an allosteric regulatory site on the receptor, but the specific residues that constitute the allosteric binding site are unknown.¹²⁶ Mutagenesis studies have demonstrated that a glycine residue in the first transmembrane domain²¹ and a tryptophan residue in the third transmembrane domain² of the β -subunit may be involved in barbiturate actions. All GABA_A receptor isoforms containing at least an α - and β -subunit have been shown to be sensitive to barbiturates; in general, only minor differences in sensitivity are noted for different isoforms. However, GABA_A receptors that contain a δ -subunit instead of the more common $\gamma 2$ -subunit and that are believed to be localized perisynaptically, where they mediate tonic inhibition, are more sensitive to barbiturates than are those containing $\gamma 2$ -subunits that are synaptically localized.¹ Single-channel record-

ings of barbiturate-enhanced single GABA_A receptor currents have directly demonstrated that barbiturates increase mean channel open duration but do not alter receptor conductance or opening frequency.^{96,185}

The sensitivity of GABA_A receptors to benzodiazepines requires the presence of a γ -subunit coexpressed with an $\alpha 1$ -, $\alpha 2$ -, $\alpha 3$ -, or $\alpha 5$ -GABA_A receptor subtype.¹³⁴ Expression of the $\alpha 4$ - or $\alpha 6$ -subtypes with $\beta 1$ - and $\gamma 2$ -subtypes results in receptors that are insensitive to benzodiazepines.²⁰³ Thus, benzodiazepine sensitivity of GABA_A receptors depends on both γ -subunit and α -subtypes. The single high-affinity binding site for benzodiazepines is located at the α/γ -subunit interface, whereas the two binding sites for GABA are at the α/β -interfaces. These two binding sites are allosterically coupled.¹²⁶ Benzodiazepines increase GABA_A receptor current, and single-channel recordings have demonstrated that they increase GABA_A receptor opening frequency without altering mean open time or conductance.^{148,189}

Ethosuximide and Trimethadione

Ethosuximide and trimethadione, which are effective in the treatment of generalized absence seizures, have been shown to interact with voltage-dependent T-type Ca channels (Table 1). The multiple Ca channel types^{22,122} are designated as L (Ca_v1.1–1.4), P/Q (Ca_v2.1), N (Ca_v2.2), R (Ca_v2.3), and T (Ca_v3.1–3.3), each with different voltage ranges and rates for activation and inactivation. Each channel type is composed of an ion conducting α -subunit (Ca_v1.1–1.4, Ca_v 2.1–2.3) and may include smaller accessory subunits, β - (Ca_v1–4) and $\alpha 2\delta 1$ –4, which are not required for function but do modify gating.^{81,22}

Generalized absence epilepsy is characterized clinically by brief periods of loss of consciousness and electrically by generalized 3-Hz spike-and-wave discharges recorded on the electroencephalogram. Thalamic relay neurons play a critical role in the generation of the abnormal thalamocortical rhythmicity that underlies the 3-Hz spike-and-wave discharge. Whole-cell voltage clamp recordings from acutely dissociated relay neurons from the rat thalamus have demonstrated the presence of low-threshold (T-type) and high-threshold Ca currents.¹⁷⁴ The T-type currents had properties such that channel activation was necessary and sufficient to cause the generation of low-threshold Ca spikes in thalamic relay neurons. Ethosuximide and dimethadione, the active metabolite of trimethadione, both reduced T-type Ca currents of thalamic neurons isolated from guinea pigs and rats^{27,28} at clinically relevant concentrations. Phenytoin and carbamazepine, which are ineffective in the control of generalized absence seizures, had minimal effects on T-type current. Dimethadione reduced T-type Ca current by a mechanism similar to that of ethosuximide. Another anticonvulsant succinimide, α -methyl- α -phenylsuccinimide, also reduced T-type currents, whereas a convulsant succinimide, tetramethylsuccinimide, only reduced the T-type current at very high concentrations.²⁹ These results suggest that anticonvulsant succinimides and dimethadione may have their primary action by reducing the T-type Ca current in thalamic relay neurons. More recent studies have largely confirmed these effects of ethosuximide in additional preparations, although variability in responsiveness occurs.^{55,184,183} It has been proposed that certain factors regulating pharmacologic sensitivity, such as the presence of accessory Ca channel subunits, may contribute to the variability. Recent studies with recombinant human T-type Ca channels indicated that the action of ethosuximide is more complex than previously appreciated.⁴⁵ There may be two binding sites, one with high-affinity (~ 0.1 mM) that accounts for $\sim 20\%$ of total channel blockade and a low-affinity site (~ 10 mM) that accounts for the remainder. Although

TABLE 1
MOLECULAR TARGETS OF ANTIEPILEPTIC DRUGS

Drug	Molecular target			
	Na channels	Ca channels	GABA system	Glutamate receptors
<i>Predominant Na (and Ca) channel activity</i>				
Phenytoin	I_{NaF} (↓) I_{NaP} (↓)			
Carbamazepine	I_{NaF} (↓)			
Oxcarbazepine	I_{NaF} (↓)			
Lamotrigine	I_{NaF} (↓)	HVA (↓)		
Zonisamide	I_{NaF} (↓)	T-type (↓)		
<i>Predominant Ca channel activity</i>				
Ethosuximide	? I_{NaP} (↓)	T-type (↓)		
<i>GABA systems</i>				
Benzodiazepines			GABA _A R (↑)	
Vigabatrin			GABA-T (↓)	
Tiagabine			GABA transporter (↓)	
<i>Mixed</i>				
Valproate	? I_{NaF} (↓) I_{NaP} (↓)	? T-type (↓)	GABA turnover (↑)	
Felbamate	I_{NaF} (↓)	HVA (↓)	GABA _A R (↑)	NMDA (↓)
Topiramate	I_{NaF} (↓) I_{NaP} (↓)	HVA (↓)	GABA _A R (↑)	KA/AMPA (↓)
Phenobarbital		HVA (↓)	GABA _A R (↑)	AMPA (↓)
<i>Novel targets</i>				
Gabapentin	$\alpha 2\delta$ protein (Ca channel subunit)			
Pregabalin	$\alpha 2\delta$ protein (Ca channel subunit)			
Levetiracetam	SV2A synaptic vesicle protein			

↑, Indicates increase in activity of target; ↓, indicates decrease in activity of target.
 Abbreviations: AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; GABA, γ -aminobutyric acid; GABA-T, GABA aminotransferase; GABA_AR, GABA_A receptor; HVA, high voltage activated; I_{NaF} , fast Na current; I_{NaP} , persistent Na current; KA, kainate; NMDA, N-methyl-D-aspartate.
 Adapted from Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs. *Nat Rev Neurosci.* 2004;5:553–564, with permission.¹⁴⁵

ethosuximide did not alter the voltage-dependency of steady-state inactivation or the time course of recovery from inactivation of the T-type Ca current, the drug did inhibit the current in a voltage-dependent manner, with current reduction most prominent at negative membrane potentials and less prominent at more positive membrane potentials.⁴⁵ Thus, 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.⁵⁵

Valproate

Valproate has many pharmacologic actions, none of which by itself can completely account for its clinical activity in epilepsy and the other conditions for which it is used, including bipolar disorder and migraine headache. It has therefore been proposed that valproate acts through a combination of neurophysiological and neurochemical actions.⁸⁸ Among these diverse actions, effects on GABA systems may play a leading role. Although the precise mechanism is obscure, in some specific brain regions thought to be involved in the control of seizure generation and propagation, valproate increases the turnover of GABA and presumably enhances GABAergic function. Indeed, valproate has actions in animal epilepsy mod-

els that overlap with drugs that are believed to act on GABA systems. Thus, valproate is especially active in genetic models of absence seizures, such as the genetic absence epilepsy rat from Strasbourg (GAERS).¹⁰⁰ It is also protective against seizures induced by methyl 6,7-dimethoxy-4-ethyl- β -carboline-3-carboxylate (DMCM)¹²⁹ and in the 6-Hz model, an alternative electroshock model that is sensitive to GABAergic agents.^{8,67} Valproate also 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.⁸⁸ In view of the activity of valproate in the MES model, which is shared with drugs like phenytoin, carbamazepine, and lamotrigine that are well recognized to modulate voltage-gated Na channels, it has been proposed that valproate might also have an action on Na channels. Indeed, valproate does block sustained high-frequency repetitive firing of neurons in culture.¹⁰⁶ However, detailed voltage clamp experiments of valproate actions on Na currents have not been performed; therefore, it cannot be concluded that valproate has a mechanism of action similar to that of the classical Na-channel AEDs.

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.⁷⁰ This effect occurred over a concentration range of 100 to 1,000 μ mol/L. However, the magnitude of block was modest, with a 16% reduction seen at 1 mmol/L. Whether this modest reduction in T-type Ca current is sufficient to

explain the effect of valproate on generalized absence seizures is unclear. Furthermore, the basis for the discrepancy between the results obtained in thalamic neurons and primary afferent neurons remains uncertain. Whether this is a relevant mechanism of action for valproate will have to be determined by future investigation.

MECHANISMS OF ACTION OF NEWER AEDs

Felbamate

Felbamate is a dicarbamate, which is an analog of the sedative-hypnotic drug meprobamate (2-methyl-2-propyl-1,3-propanediol dicarbamate). Despite its idiosyncratic toxicities, felbamate is a highly effective AED with a broad spectrum of activity, and is one of only three AEDs for which there is evidence, from a controlled clinical trial, of efficacy in the treatment of the Lennox-Gastaut syndrome.⁵ Felbamate has been reported to inhibit sustained repetitive action potential firing in cultured neurons, suggesting that it modulates voltage-gated Na channels.²⁰¹ Although an effect on recombinant Na channels is observed only at relatively high (1 mM) concentrations,¹⁷⁵ inhibition of Na-channel function could, at least in part, contribute to felbamate's anticonvulsant activity. Felbamate has also been reported to inhibit high voltage-gated Ca channels,^{167,168} but the significance of this action for seizure protection is uncertain. Like meprobamate, felbamate potentiates GABA_A receptor currents via an interaction with a site on the GABA_A receptor that is distinct from the benzodiazepine recognition site.^{77,137} The threshold concentration for felbamate modulation of GABA_A receptor currents is ~100 μ M, and the IC₅₀ value for allosteric inhibition of *t*-[³H]butylbicycloorthobenzoate binding to GABA_A receptors in rat brain slices is 250 μ M.⁷⁷ Because low therapeutic (anticonvulsant) serum concentrations of felbamate are in the range of 100 to 300 μ M, the action of felbamate on GABA_A receptors is probably relevant to its anticonvulsant activity. In addition, felbamate at a concentration of 100 μ M has been found to block *N*-methyl-D-aspartate (NMDA) receptor-mediated synaptic responses¹³⁵ and to inhibit NMDA-receptor currents in cultured neurons (K_d , ~1 mM^{137,171}). It has been proposed that felbamate may act as a competitive antagonist at the glycine recognition site of NMDA receptors,^{105,193} and studies in animal models seemed to support this concept.^{26,200} However, several studies directly examining the interaction between felbamate and the NMDA receptor have shown conclusively that felbamate does not act at the glycine site per se.^{73,135,137,171,181} On the basis of whole-cell and single-channel recordings, Subramaniam et al.¹⁷¹ concluded that felbamate acts both by a channel blocking mechanism and also by distinct effects on channel gating. Details of the effects on gating have been defined by Kuo et al.,⁷⁹ who found that low, submillimolar concentrations of felbamate more readily blocked the late sustained phase of NMDA receptor responses but not the initial onset of the response. This phenomenon was ascribed to an acceleration of the decay of responses. It can be speculated that this property would confer selectivity on felbamate to block seizures, because the prolonged pathologic activation that occurs during seizures would be suppressed more strongly than normal (rapid) synaptically generated NMDA responses. In addition, NMDA receptor blockade responses was greater with high concentrations of NMDA, another factor that would allow the drug to selectively block seizure discharges associated with strong activation of NMDA receptors. Kuo et al. further found that felbamate selectively binds with higher affinity to the desensitized state

of NMDA receptors (55 μ M) than to the resting or activated states (200 and 110 μ M, respectively), so that the allosteric blocking action relates to stabilization of the desensitized state.⁷⁹

Felbamate also selectively blocked currents from recombinant NMDA receptors composed of NR2B subunits at lower concentrations (IC₅₀, 0.5 mM) than it blocked currents from NMDA receptors formed from other subunit combinations.^{52,73} This selectivity could contribute to the relatively low neurobehavioral toxicity of felbamate in relation to other NMDA receptor antagonists. Unlike the NR2A subunit that is distributed ubiquitously in the central nervous system (CNS), expression of the NR2B subunit in the adult is largely restricted to the forebrain. Thus, felbamate may selectively target NMDA receptors in forebrain areas critical to seizure generation, with less effect on nonforebrain structures that could mediate side effects. The subunit selectivity could also account for the clinical utility of felbamate in seizure disorders affecting the immature brain, such as Lennox-Gastaut syndrome, because NR2B subunits are more abundant in the developing brain.

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. Although both gabapentin and pregabalin are based on a GABA backbone, bulky aliphatic substituents in the molecules preclude binding to the GABA recognition site on GABA_A receptors. The drugs also do not interact with other sites on GABA_A receptors, including the benzodiazepine recognition site.¹⁷² Although there are reports of agonist activity at GABA_B receptors, the preponderance of evidence indicates that GABA_B receptors are not a pharmacologic target.¹⁷⁸ Additional studies have shown that gabapentin does not inhibit GABA uptake or GABA catabolism, although it may enhance GABA turnover.⁹¹ Increases in GABA levels have been reported in humans using noninvasive spectroscopic techniques,^{80,131} but neither gabapentin nor pregabalin affect brain GABA levels in the rat,⁴⁰ and thus the significance of these alterations in GABA metabolism are uncertain. Nevertheless, there is little doubt that the therapeutic activities of gabapentin and pregabalin do not reside in effects on GABA systems. Indeed, the molecular targets of gabapentin and pregabalin are almost certainly α 2 δ -proteins, which are believed to be auxiliary subunits of voltage-activated Ca channels. Strong evidence for this concept is the observation that the binding affinities of gabapentin, pregabalin, and related structures to α 2 δ -subunits correlate in a stereoselective fashion with their anticonvulsant potencies.^{12,19} In addition, knockin of a mutation (R217A) in the α 2 δ -1 subunit in mice, which results in markedly reduced binding of gabapentin and pregabalin, reduces the anticonvulsant activity of pregabalin and eliminates its analgesic activity.¹⁴⁸ Because the anticonvulsant actions of phenytoin and the analgesic actions of morphine are not altered by the same mutation, it is likely that the α 2 δ -1 protein is a target for the pharmacologic effects of pregabalin. However, since the mutation does not completely eliminate the anticonvulsant activity of pregabalin, it is plausible that effects occur on targets other than α 2 δ -1. Because gabapentin and pregabalin also bind to α 2 δ -2, this is a logical second target; but until experiments with mice bearing mutations in both α 2 δ -1 and α 2 δ -2 are available, the possibility that the drugs confer anticonvulsant activity through interactions with non- α 2 δ targets cannot be eliminated.

The $\alpha 2\delta$ -subunits are highly glycosylated proteins having a molecular mass of ~ 150 kD (997 to 1150 amino acid residues). Four homologous forms exist, but only subtypes 1 and 2 bind gabapentin and pregabalin with high affinity.⁷⁵ Each of the $\alpha 2\delta$ -subunits are products of a single gene that is posttranslationally cleaved into $\alpha 2$ - and δ -peptides, which are then covalently linked by a disulfide bridge. Within the multimeric complex that forms the functional Ca channel, the $\alpha 2\delta$ -subunit is adjacent to or embedded in the pore forming $\alpha 1$ -subunit. The δ -subunit portion of $\alpha 2\delta$ is in close association with the channel and serves as an anchor for the $\alpha 2$ -subunit, which is located largely extracellularly.²⁰⁴ Mutagenesis experiments have shown that the gabapentin binding site is probably confined to the $\alpha 2$ -subunit protein and the external portion of the associated δ component.^{18,195} The $\alpha 2\delta$ -1 and $\alpha 2\delta$ -2 subunits are believed to form complexes with many voltage-dependent Ca channel types, but it is not yet clear which Ca channels are important for the therapeutic activity of gabapentin and pregabalin, nor is the functional role of the $\alpha 2\delta$ subunit complex fully understood. However, for some Ca channel types, the $\alpha 2\delta$ subunit complex has been shown to allosterically enhance current amplitude and also promote channel trafficking to the membrane.

Functional studies of the effects of gabapentin on Ca channel activity have yielded divergent results¹⁷⁸; however, the general consensus is that gabapentin and pregabalin reduce the release of neurotransmitters from neural tissue, with effects on glutamate release being of particular relevance in epilepsy.^{11,38} Thus, in various preparations, gabapentin and pregabalin have been shown to reduce the amplitude of evoked and spontaneous excitatory postsynaptic currents. Surprisingly, however, a reduction also occurs in the frequency of miniature excitatory synaptic currents.^{3,128} 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. Rather, it has been speculated that binding of the drugs to $\alpha 2\delta$ -subunits directly influences the release machinery,¹⁴⁷ possibly by affecting physical interactions between presynaptic Ca channels and proteins mediating exocytosis.¹⁶⁵

Gabapentin and pregabalin are absorbed in the gut and pass across the blood-brain barrier via the system L transporter, which is specialized for the transport of large, neutral amino acids.¹⁷⁰ The fact that these drugs are substrates for this transporter is essential to their anticonvulsant activity because it allows them to gain access to the CNS.¹² However, an interaction with the transporter is not responsible for seizure protection or other pharmacologic activities of the drugs.

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.^{20,178,202} 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.¹⁷⁸ Overall, the preferential activity against tonic seizures, in the MES test and other models, and lack of protective activity against absence seizures, is consistent with the presumed mechanism of action, which is to inhibit synaptic release. This conclusion is based on a comparison with other AEDs with a similar profile in animal seizure models, most notably Na-channel blocking AEDs. Although Na-channel blocking AEDs do not directly alter synaptic responses, as noted earlier, their inhibitory action on Na channels translates into

reduced transmitter output at synapses, with a preference for the release of glutamate.

Lamotrigine

Lamotrigine [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine] is a phenyltriazine with weak antifolate activity. Lamotrigine was developed after it was observed that the use of phenobarbital, primidone, and phenytoin resulted in reduced folate levels, and that folates could induce seizures in experimental animals.¹³⁶ It was proposed that antifolate activity may be related to the anticonvulsant properties of these AEDs; however, this has not been confirmed in structure-activity studies.¹⁴⁶ Lamotrigine has 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.¹¹⁰ Lamotrigine is also inactive in rat models of absence epilepsy.¹⁸⁸ Therefore, its profile in animal models is similar to that of Na-channel modulators such as phenytoin and carbamazepine.

Early studies of the mechanism of action of lamotrigine examined its effects on the release of endogenous amino acids from rat cerebral cortex slices in vitro. As is the case for AEDs that act on voltage-dependent Na channels,⁸⁷ lamotrigine 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.⁸⁵ At high concentrations, lamotrigine had no effect on spontaneous or potassium (K)-evoked amino acid release. These studies suggested that lamotrigine acts presynaptically on voltage-gated Na channels to decrease glutamate release. In radioligand studies, the binding of [³H]batrachotoxinin A 20- α -benzoate, a neurotoxin that binds to receptor site 2 on voltage-dependent Na channels, was inhibited by lamotrigine in rat brain synaptosomes.²⁵ Several electrophysiological studies have investigated the effects of lamotrigine on voltage-dependent Na channels. Lamotrigine blocked sustained repetitive firing in cultured mouse spinal cord neurons in a concentration-dependent manner at concentrations therapeutic in the treatment of human seizures.²⁵ In cultured rat cortical neurons, lamotrigine reduced burst firing induced by glutamate or K, but not unitary Na action potentials evoked at low frequencies.⁸⁶ In cultured hippocampal neurons, lamotrigine reduced Na currents in a voltage-dependent manner, and at depolarized potentials showed a small frequency-dependent inhibition.¹¹⁵ Lamotrigine increased steady-state inactivation of rat brain type IIA Na channel α -subunit currents expressed in Chinese hamster ovary cells¹⁸⁰ and produced both tonic and frequency-dependent inhibition of voltage-dependent Na channels in clonal N4TG1 mouse neuroblastoma cells, but had no effect on cationic currents induced by stimulation of glutamatergic receptors in embryonic rat hippocampal neurons.¹⁹⁴

In cultured rat cortical neurons, lamotrigine at high concentrations was able to inhibit peak high-threshold Ca currents and appeared to shift the threshold for inward currents to more depolarized potentials.⁸⁶ In clonal rat pituitary GH3 cells, lamotrigine at the same concentration did not inhibit high-threshold Ca currents, caused only slight inhibition of low-threshold Ca currents, reduced rapidly inactivating voltage-dependent K currents, and had no significant effect on Ca-activated K currents.⁸² In cultured rat cortical neurons, lamotrigine did not appear to mimic the effect of diazepam when tested on GABA-evoked Cl currents.⁸⁶

These results indicate that the antiepileptic effect of lamotrigine, like that of phenytoin and carbamazepine, is at least in part due to use- and voltage-dependent modulation of fast voltage-dependent Na currents. However, lamotrigine has a

broader clinical spectrum of activity than phenytoin and carbamazepine and is recognized to be protective against generalized absence epilepsy and other generalized epilepsy syndromes, including primary generalized tonic-clonic seizures, juvenile myoclonic epilepsy, and Lennox-Gastaut syndrome.^{16,41,133} The basis for the broader spectrum of activity of lamotrigine is unknown, but could relate to actions of the drug on voltage-activated Ca channels.¹⁴⁵ Lamotrigine blocks T-type Ca channels weakly, if at all.^{44,49} However, it does inhibit native and recombinant high-voltage-gated Ca channels (N- and P/Q/R-types) at therapeutic concentrations.^{49,167,196} Whether this activity on Ca channels accounts for lamotrigine's broader clinical spectrum of activity in comparison with phenytoin and carbamazepine remains to be determined.

Levetiracetam

Levetiracetam [(S)- α -ethyl-2-oxo-pyrrolidine acetamide], the S-enantiomer of the ethyl analog of the nootropic agent piracetam, differs from other AEDs in its profile of activity in animal seizure models. Notably, levetiracetam is inactive against both the MES and subcutaneously administered PTZ seizures.^{74,89} Nevertheless, the drug does have activity in many acute seizure models. For example, it confers protection against sound-induced clonic seizures and also against clonic seizures induced by pilocarpine and DMCM, but not against seizures induced by other chemoconvulsants such as the GABA_A receptor antagonists bicuculline or picrotoxin or by intracerebroventricular injection of the excitatory amino acid agonists NMDA, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), or kainate.⁷⁴ Levetiracetam also confers protection against kindled seizures,⁸⁹ and it can inhibit the development of the seizure-prone state in various kindling models.^{47,90} Levetiracetam can also inhibit the developmental expression of tonic convulsions in a genetic epilepsy model.²⁰⁷ The anticonvulsant activity of levetiracetam is stereoselective (the R-enantiomer is very weak or inactive,⁴⁷ indicating an interaction with a structurally specific recognition site). In line with the atypical profile of levetiracetam in animal models, the drug also behaves distinctly in brain slice epilepsy models. Unlike conventional AEDs that inhibit high-frequency action potential firing, presumably through effects on Na channels, levetiracetam specifically suppresses synchronized network bursting, indicating an effect on synchronization mechanisms.¹²⁰ In this regard, it is noteworthy that levetiracetam has a much larger therapeutic window than do other AEDs (only very large doses \sim 1,000 mg/kg cause impairment of motor performance), which is consistent with a more specific action on epileptiform activity than that of other AEDs. The various differences between levetiracetam and other AEDs suggest that levetiracetam protects against seizures by a novel mechanism. However, until recently, a reasonable candidate was not at hand. Levetiracetam has been shown to inhibit voltage-activated Ca¹¹⁹ and K⁹⁹ currents at high concentrations. In addition, recognizing that levetiracetam is protective against seizures induced by the benzodiazepine receptor inverse agonist DMCM, it was observed that levetiracetam can reverse DMCM inhibition of GABA_A and glycine receptor responses in cultured neurons.¹⁴⁰ However, none of these actions has been convincingly linked to the anticonvulsant activity of the drug. In 1995, Noyer et al.¹²³ described a saturable and stereoselective specific binding site for [³H]levetiracetam in brain membranes. The binding site was found to be an integral membrane protein, having an apparent molecular mass of \sim 90 kDa, which is widely distributed in brain and localized to the synaptic vesicle membrane fraction in neurons. Although the binding site was only of moderate affinity (K_d , 0.8 μ M), a series of stereoisomer homologs of levetiracetam demonstrated a rank order of affin-

ity for the [³H]levetiracetam binding site that was highly correlated with their anticonvulsant activity, indicating that the binding was relevant for the anticonvulsant properties of levetiracetam and related structures. Further studies indicated that the binding protein is the ubiquitous synaptic vesicle protein SV2A.⁹⁵ Thus, levetiracetam has a target that is distinct from that of other AEDs. SV2A was originally described by Bajjalieh et al.⁶ as a 12-transmembrane domain glycoprotein homologous to membrane transporters. However, to date, a transporter activity for the protein has not been established. Rather, SV2A seems to interact with synaptotagmin, which is believed to be the Ca sensor in exocytosis.¹⁵³ It is now recognized that SV2A is a member of a small family of homologous proteins that also includes SV2B and SV2C; but only SV2A, the most ubiquitous form, binds levetiracetam. Studies with mice in which the SV2 proteins have been deleted by gene targeting are consistent with a possible role of SV2A in regulating seizure susceptibility, but they have not yet provided answers to the key questions of the function of SV2A and how levetiracetam binding confers seizure protection. In SV2A knockout mice, brain morphology—and indeed the morphology of synapses—is normal.^{30,60} However, homozygous SV2A knockout mice experience severe seizures and die between postnatal weeks (P)12 and P23; heterozygous animals are also susceptible to seizures but have nearly normal survival. The SV2 proteins do not appear to be required for synaptic transmission or for the uptake or storage of neurotransmitters, although they may play a subtle role in the release process during repetitive synaptic activation (as occurs during seizure activity) by regulating nerve terminal Ca dynamics.⁶⁰ Although there is still much to be learned about the mechanism of levetiracetam, it is now clear that its target is a component of the synaptic release machinery, which supports the unifying concept that the ultimate action of many AEDs, whatever their molecular targets, is to modulate neurotransmitter release. Levetiracetam is the first AED that targets the synaptic release machinery directly. Through this direct mechanism, the drug seems to be able to exert a protective action on seizures with a favorable side-effect profile.

Oxcarbazepine

Oxcarbazepine (10,11-dihydro-10-oxo-carbamazepine) is a dibenzazepine that is structurally similar to carbamazepine, except that it has a keto substitution at the 10 position of the dibenzazepine nucleus. The keto substitution prevents the formation of the 10,11-epoxide, which, in the case of carbamazepine has been hypothesized to contribute to toxicity. Rather, oxcarbazepine is rapidly and nearly completely reduced to 10,11-dihydro-10-hydroxy carbamazepine (licarbazepine; GP 47779; LIC477).³¹ Licarbazepine is a racemate, with the S(+)-enantiomer (BIA 2-093) about four times as abundant in the urine as the R(-)-enantiomer; both enantiomers have approximately equal anticonvulsant activity.^{13,154}

Oxcarbazepine and licarbazepine are effective in 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.⁷ In studies using rats at different developmental ages, oxcarbazepine, licarbazepine, and carbamazepine dose-dependently reduced the tonic phase of generalized seizures induced by PTZ and appeared to have identical anticonvulsant profiles in this model.⁷⁶ Oxcarbazepine and licarbazepine have relatively poor anticonvulsant efficacy against picrotoxin- and strychnine-induced seizures in mice.⁷ Oxcarbazepine was able to completely suppress seizures in rhesus monkeys in a chronic aluminum foci model of partial seizures. At comparable doses, licarbazepine was less effective in suppressing seizures in this model.⁶¹ Oxcarbazepine is effective in

the treatment of human partial seizures and generalized tonic-clonic seizures with and without secondary generalization.³³

In electrophysiologic studies in rat hippocampal slices, oxcarbazepine and licarbazepine enantiomers dose-dependently decreased epileptic-like discharges induced by penicillin.¹⁵⁴ In addition, the compounds reduced sustained high-frequency repetitive firing of voltage-dependent Na action potentials in mouse spinal cord neurons.¹⁹⁴ Oxcarbazepine is slightly more potent than carbamazepine in displacing [³H]batrachotoxinin A 20- α -benzoate from voltage-dependent Na channels in rat cortical synaptosomes and also slightly more potent in inhibiting ²²Na⁺ uptake.¹³ Together, these observations indicate that the anticonvulsant mechanism of oxcarbazepine is similar to that of carbamazepine, and depends on the modulation of voltage-dependent Na channels.

Tiagabine

Tiagabine [(*R*)-*N*-(4,4-di(3-methylthien-2-yl)but-3-enyl) nipecotic acid hydrochloride] is a nipecotic acid analog with an incorporated lipophilic anchor to facilitate crossing of the blood-brain barrier after oral administration.⁸⁴ Like nipecotic acid, tiagabine is a potent and specific competitive inhibitor of the neuronal and astrocytic GABA transporter GAT-1.¹⁷ Tiagabine binds with high affinity to the transporter, thus preventing GABA uptake without itself being transported. By slowing the reuptake of synaptically released GABA, tiagabine increases synaptic GABA levels and prolongs inhibitory postsynaptic potentials.^{39,59,150,169,182} The prolongation of inhibitory GABA-mediated synaptic responses by tiagabine may be enhanced with repetitive activation, such as occurs during the synchronous discharge of GABAergic interneurons during epileptic activity. This may minimize the behavioral depression that would accompany indiscriminate enhancement of GABA inhibition.

Tiagabine has a unique spectrum of activity in animal seizure models. The drug is highly potent against tonic and also clonic seizures induced by PTZ and DMCM,³² and is also effective against various types of kindled¹¹³ and reflex seizures.¹⁶³ It is only weakly active, if at all, against tonic hindlimb extension in the MES model.^{32,118} In addition, tiagabine is effective against status epilepticus (SE) in cobalt-lesioned rats but also produced a hyporeactive state associated with a rhythmic EEG pattern suggesting a generalized convulsant action.¹⁹² In fact, in patients who were not previously recognized as having epilepsy, tiagabine use has rarely been associated with new-onset seizures and SE. Interestingly, tiagabine was also shown to exert an antepileptogenic effect in amygdala kindling³² and to prevent seizures and neuronal damage in experimental SE.⁵⁰

Topiramate

Topiramate (2,3:4,5-*bis*-*O*-[1-methylethylidene]- β -*D*-fructopyranose sulfamate) is a sulfamate derivative of the naturally occurring monosaccharide *D*-fructose. The drug is active against MES seizures in rats and mice, in amygdala-kindled seizures in rats, and sound-induced seizures in mice.¹⁵⁹ It is ineffective against seizures induced by PTZ, bicuculline, or picrotoxin.^{42,159} It therefore has a profile of activity in animal models that is similar to that of Na channel-blocking AEDs¹⁴³; the profile also resembles that of glutamate receptor antagonists.⁹³ However, the drug has several properties that are atypical for Na channel-blocking AEDs in that it is effective in a rat genetic model of absence epilepsy¹¹⁷ and can also raise the threshold for clonic seizures induced by intravenous PTZ in mice.¹⁹⁸ Several cellular

mechanisms have been proposed to underlie the therapeutic activity of topiramate: (a) activity-dependent attenuation of voltage-dependent Na currents^{177,212}; (b) inhibition of high-voltage-activated Ca channels²¹⁰; (c) potentiation of GABA_A receptor-mediated currents^{46,68,198,199}; (d) inhibition of AMPA/kainate receptors^{43,162,164}; (e) inhibition of types II and IV carbonic anhydrase isoenzymes³⁷; and (f) activation of a steady K current.⁵³ The effects on Na channels occur at relatively low, therapeutically relevant concentrations (25–30 μ M). Trough serum concentrations of topiramate associated with antiepileptic activity in clinical trials range from 6 to 35 μ M. The biophysical details of the modulation of fast Na currents are similar to that of classical Na-channel blocking anticonvulsants, particularly phenytoin. Thus, the degree of block is enhanced with the long membrane depolarizations as are believed to occur during epileptiform activity. However, the unblock upon membrane hyperpolarization is more rapid than with phenytoin (comparable to carbamazepine and lamotrigine). It has been suggested that the faster recovery is desirable because it would allow ongoing neuronal activity to resume quickly after epileptiform activity is aborted. In addition to effects on fast Na currents, topiramate, like phenytoin, blocks persistent Na currents at low concentrations. Because persistent Na current may contribute to the initiation and maintenance of epileptiform activity,¹⁵⁶ this could represent an important factor in topiramate's anticonvulsant properties. The pharmacologic effect of topiramate on high-voltage-activated Ca current is of uncertain relevance, because the drug was specific for L-type Ca currents²¹⁰ and L-type Ca channel blockers are not effective as anticonvulsants.

Effects of topiramate on GABA_A receptors could contribute to the broad spectrum of activity of topiramate, but the evidence is imperfect. Topiramate is not active in those animal models, such as the PTZ 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 on PTZ threshold, consistent with effects on GABA_A receptors.³⁴ However, the ability of the drug to enhance GABA_A receptor currents within in vitro systems is inconsistent and variable among preparations and does not show ordinary concentration-dependence,^{46,53} making the effect difficult to study. The variability could be due in part to subunit selectivity, inasmuch as some GABA_A receptor subunit combinations expressed in *Xenopus* oocytes were potentiated, whereas others were inhibited.⁴⁶ The potentiation, when it occurs, is independent of an interaction with the GABA or benzodiazepine recognition sites of the GABA_A receptor, and effects on slow desensitization kinetics are more substantial than on the peak amplitude.^{46,199} Modulation of slow GABA_A receptor desensitization could influence seizure susceptibility,¹⁵ but the way in which this might occur with topiramate has yet to be defined. Evidence suggests that topiramate may alter the activity of the various receptors and ion channels with which it interacts by affecting their phosphorylation state.¹⁵⁹ Phosphorylation does influence the kinetic properties of GABA_A receptors,⁵⁴ raising the possibility that this mechanism could be relevant to their modulation by topiramate.

As noted, the activity of topiramate in animal models is compatible with effects on glutamate receptors, including NMDA and AMPA/kainate receptors.¹⁴³ There is no evidence that topiramate blocks NMDA receptors.⁴⁴ However, in cultured neurons, it does inhibit responses to kainate, an agonist of AMPA and kainate receptors.⁴⁴ Recently, topiramate was found to be a more potent and efficacious inhibitor of GluR5 kainate receptor currents in basolateral amygdala principal neurons than of AMPA receptor currents.⁴⁸ AMPA receptors are crucial for excitatory synaptic transmission throughout the CNS, and drugs that substantially block AMPA receptors produce dramatic neurobehavioral impairment.²⁰⁶ Thus, the finding

that topiramate is weak and has low efficacy as an AMPA receptor antagonist corresponds with the clinical observation that the drug is reasonably well tolerated. Kainate receptors represent a new potential anticonvulsant drug target.¹⁴⁵ Blockade of GluR5 kainate receptors is not associated with the side effects associated with blockade of AMPA receptors and, in fact, transgenic mice that lack GluR5 are grossly normal neurologically. The inhibitory action of topiramate on GluR5 kainate receptors develops slowly, suggesting that it acts indirectly. Recently, it has been found that topiramate inhibits phosphorylation of serine 845 of the AMPA receptor GluR1 subunit,⁴ suggesting that the effect of the drug on AMPA and perhaps kainate receptors is due to an alteration in the phosphorylation state of the protein. The relevance of the GluR5 kainate receptor–blocking activity of topiramate was confirmed using *in vivo* experiments in mice with selective glutamate receptor antagonists, in which anticonvulsant doses of topiramate blocked clonic seizures induced by a selective GluR5 kainate receptor agonist but not by an agonist of AMPA receptors.⁶⁷ In addition to effects on GluR5 kainate receptors, the drug may also affect the more abundant GluR6-containing kainate receptors.⁶⁶

The action of topiramate on carbonic anhydrase has been assumed not to contribute to its clinical efficacy because cross-tolerance to the anticonvulsant activity of topiramate does not occur with the classical carbonic anhydrase inhibitor acetazolamide in mice.¹⁶⁰ Moreover, topiramate is only a moderate-potency inhibitor of carbonic anhydrase isoenzymes.¹²¹ However, it is noteworthy that acetazolamide, like topiramate, has a preferential activity against MES seizures.³ Recently, evidence supporting a role for carbonic anhydrase inhibition in the action of topiramate has come from studies of GABA_A receptor-mediated depolarizing responses, which can be elicited by high-frequency stimulation of GABAergic synapses.⁵³ Such depolarizing GABA currents may promote the generation of seizure discharges. The efflux of intracellular bicarbonate formed by carbonic anhydrase is believed to be a major factor underlying depolarizing GABA currents.^{62,166} Topiramate at clinically relevant concentrations strongly inhibited depolarizing GABA currents without affecting hyperpolarizing GABA-mediated inhibitory postsynaptic currents. This effect is assumed to be due to carbonic anhydrase inhibition, because it was mimicked by acetazolamide.

Overall, topiramate's broad spectrum of anticonvulsant activity is likely to result from effects on multiple target sites, including Na channels, kainate receptors, and possibly also GABA_A receptors and carbonic anhydrase isoenzymes. The effects on ion channels are complex and are unlikely to occur through direct effects on channel gating, but are more likely to be mediated indirectly, possibly through inhibition of channel phosphorylation.

Vigabatrin

Vigabatrin (γ -vinyl GABA; 4-amino-hex-5-enoic acid) is a structural analog of GABA that acts as an enzyme-activated ("suicide") inhibitor of GABA-transaminase (γ -aminobutyrate- α -oxoglutarate aminotransferase; GABA-T), a pyridoxal-5'-phosphate-dependent enzyme localized to mitochondria that is the main degradative enzyme for GABA. The drug initially binds reversibly to the pyridoxal-5'-phosphate cofactor and then binds irreversibly to the enzyme.⁵⁵ Because GABA-T inhibition is irreversible, recovery of GABA transaminating activity requires resynthesis of the enzyme. Vigabatrin is a racemic mixture of *S*(+)- and *R*(-)-enantiomers; only the *S*(+)-enantiomer inhibits GABA-T.⁸³ There is a corresponding stereoselectivity for the anticonvulsant activity of vigabatrin.¹⁰⁸ Administration of vigabatrin leads to large elevations in brain

GABA levels in animals⁹² and humans.¹³⁰ In addition, the drug causes a dose-dependent increase in cerebrospinal GABA in human subjects with epilepsy, without affecting the levels of other neurotransmitters, including monoamines.^{139,152} The extent to which vigabatrin increases GABA concentrations differs among brain regions, depending on the density of GABAergic neurons.²⁴ Although GABA-T is present in both neurons and glia,²³ the increase in brain GABA levels is predominantly due to inhibition of GABA-T in neurons.¹⁴⁹

The antiepileptic properties of vigabatrin have been attributed to enhanced GABA-mediated inhibition. Paradoxically, however, vigabatrin does not lead to larger GABA_A receptor-mediated synaptic responses, and it has generally been found to inhibit spontaneous and evoked synaptic GABA currents.^{58,127,205} In contrast to the effects on synaptic GABA responses, vigabatrin potently increases tonic current resulting from the action of ambient GABA on extrasynaptic GABA_A receptors.^{138,205} The increased extracellular GABA levels are attributed to efflux of GABA from neurons via GABA transporters operating in a reverse fashion due to high intracellular GABA. The enhanced activation of extrasynaptic GABA_A receptors produced by the elevated extracellular GABA is believed to produce an anticonvulsant effect through reduced network excitability, although the details of how this occurs remain to be defined. An alternate hypothesis is that vigabatrin prevents the fading of GABA responses during repetitive activation of inhibitory pathways, through reduced function of release-regulating presynaptic GABA_B receptors.⁵⁸ Such fading is believed to be an important factor that permits focal epileptiform activity to develop into a full-blown seizure.

Vigabatrin is indicated primarily for the treatment of partial seizures and is also a first-line treatment for infantile spasms. Therefore, its clinical indications differ from other drugs, such as benzodiazepines, that act on GABA systems. No uniform agreement exists on the profile of vigabatrin in animal epilepsy models. The variability in efficacy that has been observed can be attributed in part to differences in dosing and route of administration, because in some studies the drug was administered directly into the brain. The preponderance of evidence indicates that systemically administered vigabatrin is active against seizures induced by chemoconvulsants including strychnine, PTZ, picrotoxin, and isoniazid.^{14,33,71,94} It is also effective against sound-induced seizures in mice,¹⁰⁹ epileptic responses in photosensitive baboons,¹⁰⁸ and against amygdala-kindled seizures.^{64,161} In fact, as with other drugs that enhance GABAergic function, vigabatrin retards the development of kindled seizures, indicating that it has antiepileptogenic properties, at least in the kindling model.¹⁶¹ Despite the clinical efficacy against partial seizures, systemically administered vigabatrin has generally been found to be inactive in the MES test.¹⁴ It is also ineffective in genetic absence epilepsy models,¹⁰⁰ which corresponds with its lack of clinical antiabsence activity. Overall, vigabatrin has a unique profile of activity in animal models and in clinical use, which is not surprising because its mechanism of action differs from other marketed AEDs.

Zonisamide

Zonisamide (1,2-benzisoxazole-3-methanesulfonamide) is an AED with a unique chemical structure consisting of an aromatic fused benzene-isoxazole ring structure and a sulfonamide side chain. Zonisamide has a 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. Like these AEDs, zonisamide is protective in the MES test and inactive against subcutaneous PTZ seizures in both mice and rats^{102,179,202}; it is also inactive against seizures induced by bicuculline and picrotoxin. Zonisamide has activity

in various kindling models,^{51,63,65,190} and is also effective against tonic-clonic and myoclonic seizures in the Mongolian gerbil, a genetic animal model of reflex epilepsy.⁹ In a strain of spontaneously epileptic rats, it suppressed tonic, but not absence-like seizures, and inhibited sound-induced seizures in DBA/2 mice.¹¹⁷ However, zonisamide did not completely suppress spontaneous seizures in the EL mouse.¹¹⁶

Zonisamide prevented spread of epileptiform activity in the cortex of experimental animals, suppressing focal seizure activity induced by direct electrical stimulation of the cat visual cortex and increasing afterdischarge threshold¹⁹⁰; following unilateral injection of kainic acid into the amygdala of the rat, it reduced the spread of seizures to the contralateral side.¹⁷⁶ Zonisamide also suppressed epileptogenic focal activity induced in the cortex of experimental animals. Zonisamide reduced spiking activity induced by cortical freezing in cat cortex and interictal spikes induced by tungstic acid gel in rat cortex.^{56,57}

Multiple mechanisms of action for zonisamide have been proposed. These include (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, and (e) inhibition of carbonic anhydrase. Although some experimental data demonstrate pharmacologic activity relating to all these mechanisms, the effects on voltage-dependent Na channels and T-type Ca channels may be most relevant to the anticonvulsant activity of zonisamide.

The first study of the effects of zonisamide on Na channels was carried out in voltage-clamped *Myxicola* giant axons.¹⁵¹ Zonisamide had no effect on Na channel activation but produced a shift in the steady-state fast inactivation curve to more negative voltages, and it slowed recovery from both fast and slow inactivation. The effect of zonisamide was only produced with intracellular zonisamide; extracellular zonisamide did not affect Na channel inactivation. The zonisamide effect on fast inactivation occurred at relatively low concentrations (1 to 100 μM) with a half-maximal concentration of 12 μM producing a 20 mV shift in the steady-state inactivation curve. The effect of zonisamide to slow recovery from slow inactivation occurred at even lower concentrations (0.1 to 10 μM). Thus, this early study demonstrated that zonisamide directly affects Na channels at low concentrations.

Recordings from cultured mouse spinal neurons have further indicated that zonisamide modulates voltage-dependent Na channels.¹⁴² Concentrations above 2 μM caused a concentration-dependent limitation of high frequency action potential firing, with half-maximal inhibition at 17 μM . The minimum effective plasma concentration of zonisamide that is protective in the MES test is 10 $\mu\text{g}/\text{mL}$ (47 μM), whereas concentrations greater than 70 $\mu\text{g}/\text{mL}$ (330 μM) are associated with neurotoxicity.¹⁰⁴ In clinical studies, therapeutic serum concentrations of zonisamide are in the range 20 to 30 $\mu\text{g}/\text{mL}$ (94–141 μM).¹⁵⁸ Zonisamide readily crosses the blood-brain barrier, and cerebrospinal fluid concentrations are similar to the free fraction in serum. Because zonisamide is approximately 50% bound to human serum albumin, minimum therapeutic brain concentrations are estimated to be in the range of 50 μM . Thus, the effect of zonisamide to limit the sustained, high-frequency, repetitive firing of action potentials occurred at concentrations that are therapeutically relevant. Although voltage-clamp studies have not been carried out in mammalian neurons, it can be inferred that zonisamide acts on voltage-dependent Na channels in a similar fashion to other Na-channel-modulating AEDs. That is, the drug likely produces use- and voltage-dependent blockade by binding to Na channels in the inactive state and slowing the rate of recovery of these channels from inactivation.

Unlike other Na-channel blocking AEDs, zonisamide also has specific effects on T-type Ca channels that are similar

to those of ethosuximide. Thus, in cultured fetal rat cortical neurons, zonisamide produced a concentration-dependent inhibition of T-type Ca current without affecting L-type Ca current.¹⁷³ The zonisamide reduction in peak T-type Ca current occurred in a concentration-dependent fashion with zonisamide concentrations in the range of 1 to 500 μM . T-type Ca currents were inhibited 10% to 25% at therapeutic concentrations of 10 to 50 μM , and the maximum inhibition obtained was 60%. Zonisamide also reduced the T-type Ca current recorded from cultured neuroblastoma cells, producing a 38% reduction in current at a concentration of 50 μM and a shift in the inactivation curve to more negative potentials by 20 mV.⁷² It seems plausible that the broader clinical spectrum of activity of zonisamide, including its activity in generalized absence seizures,¹⁵⁷ could relate to this action on T-type Ca current.

As is the case for other Na-channel modulating AEDs, the ability of zonisamide to modulate voltage-dependent Na channels is expected to reduce the action potential-evoked release of glutamate through a presynaptic action. In fact, recordings from hippocampal neurons in rat brain slices demonstrated that 20 μM zonisamide suppressed the amplitude of spontaneous action potential-dependent excitatory postsynaptic currents without affecting action potential-independent (miniature) synaptic currents.¹⁴⁴ Thus, these electrophysiologic studies demonstrate that zonisamide is able to block glutamate release through a presynaptic action, and they suggest that this occurs through an interaction with Na channels, and not through downstream components of the vesicular release machinery.

Studies with microdialysis in freely moving rats have indicated that zonisamide has complex actions on the release of various neurotransmitters, and that these effects could be mediated through actions distinct from the interaction with Na channels. The transmitters studied have included GABA, dopamine, serotonin, and acetylcholine. Zonisamide in some cases was found to increase release and in other cases to inhibit it.^{69,124,211} The extent to which these effects could contribute to the anticonvulsant activity of zonisamide is not well understood. However, it is interesting that zonisamide can enhance the basal release of GABA.²⁰⁸ Another observation suggesting that zonisamide could influence GABA systems is that chronic treatment of rats with zonisamide leads to downregulation of the GAT-1 GABA transporter.¹⁸⁷ In addition, there is evidence from radioligand binding suggesting that zonisamide could directly interact with GABA_A receptors. Thus, reports from one research group demonstrated that zonisamide displaced [³H]flunitrazepam and [³H]muscimol binding in rat brain, albeit at relatively high concentrations (100–1,000 μM).^{111,112} In addition, [³H]zonisamide was found to bind to a stereospecific binding site in a crude synaptosomal fraction of whole rat brain with a K_d of 90 nM.¹¹² Clonazepam reduced and GABA increased [³H]zonisamide binding, suggesting that the zonisamide binding site was coupled to benzodiazepine receptors. However, in spinal cord neurons in cell culture, zonisamide did not affect electrophysiologic responses to GABA.¹⁴² Overall, it seems unlikely that effects on GABAergic systems contribute in a major way to the anticonvulsant actions of zonisamide.

In a large number of additional studies, zonisamide has been reported to have various effects on monoamine turnover and metabolism (reviewed by Macdonald⁹⁸). Effects on dopamine systems have been particularly well studied, with several reports that zonisamide enhances dopamine turnover at therapeutic concentrations¹²⁵ but it is unlikely that these effects contribute to the therapeutic activity of zonisamide in epilepsy.¹¹⁴

Zonisamide has a sulfonamide side chain that is a common element of many carbonic anhydrase inhibitors, including acetazolamide, and zonisamide is well recognized to inhibit carbonic anhydrase isoenzymes.¹⁰¹ At least 15 human carbonic

anhydrase isoenzymes have been described, including forms that are cytoplasmic (I, II, III, and VII), mitochondrial (VA and VB), secreted (VI), and membrane-associated (IV, IX, XII, and XIV). Although zonisamide is a very weak inhibitor of membrane-associated isoenzyme XII, it inhibits isoenzyme IX with high affinity (K_1 , 5.1 nM).¹²¹ Given the emerging evidence that carbonic anhydrase regulates GABA signalling,¹⁴¹ this effect is intriguing. However, a role for carbonic anhydrase inhibition in the anticonvulsant mechanism of zonisamide has been discounted on the basis of structure-activity studies. Thus, both zonisamide and its 7-methyl analog have similar carbonic anhydrase inhibitory activity, but only zonisamide was protective in the mouse MES test.¹⁰³ This observation indicates that carbonic anhydrase inhibition is not the sole or major mechanism underlying the anticonvulsant activity of zonisamide; whether it is a contributory factor remains to be determined.

SUMMARY AND CONCLUSIONS

In summary a key action of zonisamide that likely contributes to its anticonvulsant activity is the modulation of voltage-gated Na channels to limit sustained, high-frequency, repetitive action potential firing. In addition, and in distinction with conventional Na-channel blocking AEDs, zonisamide can inhibit T-type Ca channels. Both effects occur at clinically effective free serum concentrations. By virtue of its action on Na channels, zonisamide inhibits the release of glutamate and other neurotransmitters through a presynaptic action. In addition, zonisamide has complex actions on dopamine, serotonin and acetylcholine metabolism; the relationship of these actions to anticonvulsant activity is obscure. Finally, zonisamide is a potent inhibitor of some carbonic anhydrase isoenzymes, but this action has not yet been linked to its therapeutic activity. The 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.²⁰⁹ The multiple mechanisms may extend its range of clinical utility not only to generalized absence seizures, but also to myoclonic seizures (including those in juvenile myoclonic epilepsy), infantile spasms, and the Lennox-Gastaut syndrome.

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1444 Section VI: Antiepileptic Drugs

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