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Antiepileptic Drug Mechanisms of Action

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Summary: Established antiepileptic drugs (AEDs) decrease membrane excitability by interacting with neurotransmitter receptors or ion channels. AEDs developed before 1980 appear to act on sodium channels, γ-aminobutyric acid type A ($GABA_A$) receptors, or calcium channels. Benzodiazepines and barbiturates enhance $GABA_A$ receptor–mediated inhibition. Phenytoin (PHT), carbamazepine (CBZ), and possibly valproate (VPA) decrease high-frequency repetitive firing of action potentials by enhancing sodium-channel inactivation. Ethosuximide (ESM) and VPA reduce a low threshold (T-type) calcium-channel current. The mechanisms of action of the new AEDs are not fully established. Gabapentin (GBP) binds to a high-affinity site on neuronal membranes in a restricted regional distribution of the central nervous system. This binding site may be related to a possible active transport process of GBP into neurons; however, this has not been proven, and the mechanism of action of GBP remains uncertain. Lamotrigine (LTG) decreases sustained high-frequency repetitive firing of voltage-dependent sodium action potentials that may result in a preferential decreased release of presynaptic glutamate. The mechanism of action of oxcarbazepine (OCBZ) is not known; however, its similarity in structure and clinical efficacy to CBZ suggests that its mechanism of action may involve inhibition of sustained high-frequency repetitive firing of voltage-dependent sodium action potentials. Vigabatrin (VGB) irreversibly inhibits GABA transaminase, the enzyme that degrades GABA, thereby producing greater available pools of presynaptic GABA for release in central synapses. Increased activity of GABA at postsynaptic receptors may underlie the clinical efficacy of VGB. **Key Words:** Anticonvulsants—Neuropharmacology—Benzodiazepines—Barbiturates—Phenytoin—Carbamazepine—Ethosuximide—Trimethadione—Valproate—Gabapentin—Lamotrigine—Vigabatrin.

A limited number of antiepileptic drugs (AEDs) are available for treatment of patients with epilepsy. Until recently, AEDs were limited primarily to phenytoin (PHT), carbamazepine (CBZ), barbiturates and primidone (PRM), benzodiazepines (BZDs), valproate (VPA), and ethosuximide (ESM). Recently, a number of additional AEDs have become available. Four promising new AEDs are gabapentin (GBP), lamotrigine (LTG), oxcarbazepine (OCBZ), and vigabatrin (VGB). Felbamate (FBM) was approved for prescription in the United States, but early experience was associated with an unacceptably high incidence of aplastic anemia (Pennell et al., 1995), and in August 1994, the manufacturer and the FDA recommended that patients be discontinued from FBM if clinically possible. Actions of the established and the new AEDs at neurotransmitter receptors or ion channels may be responsible for their clinical effects. Three primary neurotransmitter receptors or ion channels are targeted by the established AEDs and by some of the newly developed AEDs: $GABA_A$ receptor channels, voltage-dependent sodium channels, and voltage-dependent low-threshold (T-type) calcium channels. The interaction of the established and recently developed AEDs with specific neurotransmitter receptors or ion channels is discussed in this review.

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BZDs AND BARBITURATES

BZDs and barbiturates enhance γ-aminobutyric acid (GABA)-ergic inhibition at free serum concentrations found in ambulatory patients (Macdonald, 1989) (Table 1). At high concentrations achieved in patients during treatment of status epilepticus, both drugs also limit high-frequency repetitive firing of action potentials, presumably by interacting with voltage-gated sodium channels (McLean and Macdonald, 1988). Both BZDs and barbiturates interact with the $GABA_A$ receptor, which is a macromolecular protein containing binding sites at least for GABA, picrotoxin, neurosteroids, barbiturates, and BZDs, and a chloride ion-selective channel (DeLorey and Olsen, 1992). GABA receptors

TABLE 1. *Established antiepileptic drug actions*

	Sodium channels	$GABA_AR$ channels	T-Calcium channels
Carbamazepine	+ +	–	–
Phenytoin	+ +	–	–
Primidone	+	–	?
Valproate	+ +	?/+	?/–
Barbiturates	+	+	–
Benzodiazepines	+	+ +	–
Ethosuximide	–	–	+ +

(GABARs) appear to be composed of combinations of different subtypes (α1–α6, β1–β4, γ1–γ3, δ and ρ1–ρ2) of polypeptide subunits (Shofield et al., 1987; Pritchett et al., 1989*a*; Shivers et al., 1989; Cutting et al., 1991). There is a differential regional expression in the central nervous system and spinal cord of various subunit subtype mRNAs (Laurie et al., 1992; Wisden et al., 1992). Some subtype mRNAs are expressed only in specific cell types (α6 mRNA was demonstrated only in cerebellar granule cells), whereas other subtype mRNAs, such as for the β2 subtype, have a more widespread distribution. Thus, differential expression and assembly of various subunit subtypes could produce a multitude of GABAR isoforms.

GABA binds to $GABA_A$ receptors to regulate gating (opening and closing) of the chloride ion channel. The single-channel gating properties of the main conductance state of the native $GABA_A$ receptor in murine spinal cord neurons in culture have been characterized (Macdonald et al., 1989*a*; Weiss and Magleby, 1989; Twyman et al., 1990). Binding of GABA increases the probability of channel opening, and the open channel can close and rapidly reopen to create bursts of openings. To explain this complex gating behavior, the single-channel activity of the main conductance state has been modeled using a reaction scheme that incorporates two sequential GABA-binding sites, three open states, and 10 closed states (Macdonald et al., 1989*a*; Twyman et al., 1990).

Barbiturates and BZDs can modulate $GABA_A$ receptor current by regulating the single-channel properties of the receptor. To enhance the current, a drug may increase the channel conductance, increase the channel open and burst frequencies, and/or increase the channel open and burst durations. The kinetic model of the $GABA_A$ receptor has been used to study the mechanisms of action of AEDs that act on the $GABA_A$ receptor.

Barbiturates enhance the $GABA_A$ receptor current by binding to an allosteric regulatory site on the receptor (Olsen, 1987). Single-channel recordings 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 (Macdonald et al., 1989*b*; Twyman et al., 1989).

$GABA_A$ receptors have a high-affinity binding site for BZDs, and BZD and $GABA_A$ receptor-binding sites are allosterically coupled (Olsen, 1987). Single-channel recordings have demonstrated that BZDs increase $GABA_A$ receptor opening frequency without altering mean open time or conductance (Vicini et al., 1987; Rogers et al., 1989).

$GABA_A$ receptors expressed in *Xenopus* oocytes and Chinese hamster ovary cells formed from α1β1 subunits were insensitive to BZDs (Pritchett et al., 1989*b*; Moss et al., 1990). The basis for this insensitivity was determined when two forms of a third $GABA_A$ receptor subunit, the γ1 and γ2 subunits, were isolated from a human fetal brain cDNA library (Pritchett et al., 1989*b*). When the γ2 subunit was transiently coexpressed with α1 and β1 subunits in human embryonic kidney cells, fully functional $GABA_A$ receptors were formed that were sensitive to BZDs, β-carbolines, barbiturates, and picrotoxin.

Analysis of binding of various BZDs to purified GABARs from brain regions revealed the existence of two subclasses of BZD-binding sites, type I and type II BZD sites (Klepner et al., 1978; Braestrup and Nielsen, 1981; Lipa et al., 1981; Garret and Tabakoff, 1985; Eichinger and Sieghart, 1986). The identification of the multiple GABAR subunit families led to clarification of the basis for this heterogeneity. The molecular basis of type I and II BZD-binding sites was determined using transient expression of αx(x = 1–6)β1γ2 subunit combinations in HEK 293 cells (Pritchett et al., 1989*a*; Pritchett and Seeberg, 1990). The combination of α1β1γ2 GABAR subtypes produced type I BZD-binding sites and expression of α2β1γ2, α3β1γ2 or α5β1γ2 GABAR subtype combinations produced type II BZD-binding sites. These receptor isoforms were differentiated on the basis of binding of the type I BZD-selective compounds zolpidem and CL 218872. Expression of the α4 or α6 subtype with β1 and γ2 subtypes produced less characterized BZD-binding sites, thought previously to be an artifact (Wisden et al., 1991). These receptor isoforms did not bind the prototypical BZDs, diazepam (DZP) and flunitrazepam, or the β-carbolines, but did bind the "benzodiazepine receptor inverse agonst" Ro 15-4513 and the BZD antagonist flumazenil (Ro 15-1788). Binding of $GABA_A$ receptor agonists (muscimol) was not impaired. BZD receptor pharmacology was not altered by substituting any other β

subtype. Thus, BZD pharmacology of recombinant GABARs appeared to depend on the α subtype. The original type I and II BZD classification was further segregated into type I (α1), type IIA (α2 and α3), type IIB (α5), and type III (α4 and α6) BZD sites (Pritchett et al., 1989*a*; Doble and Martin, 1992). Therefore, despite the finding that the γ subunit confers BZD sensitivity to $GABA_A$ receptors, the α subunit appears to determine the type of BZD receptor expressed.

PHT AND CBZ

PHT and CBZ interact with voltage-dependent sodium channels at concentrations found free in plasma in patients being treated for epilepsy (Macdonald, 1989) (Table 1). These AEDs reduce the frequency of sustained repetitive firing of action potentials in neurons in cell culture (McLean and Macdonald, 1983, 1986*b*). The characteristic property of these AEDs was no reduction of the amplitude or duration of single action potentials but reduction of 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 increased after depolarization and reduced after hyperpolarization. Once developed, the limitation of firing is prolonged, lasting several hundred ms. The action of the AEDs appears to be due to a shift of sodium channels to an inactive state, which is similar to the normally occurring inactive state but from which recovery is delayed.

The actions of PHT and CBZ have also been studied on mammalian myelinated nerve fibers (Schwarz and Grigat, 1989). Both AEDs produce a voltage-dependent block of sodium channels that can be removed by hyperpolarization. PHT produces a shift of the steady-state sodium-channel inactivation curve to more negative voltages. PHT and CBZ both reduce the rate of recovery of sodium channels from inactivation. In control solutions, sodium channels recover from complete inactivation in a few ms after a 500-ms depolarization to 25 mV. In the presence of 100 μ*M* PHT or CBZ, recovery is prolonged to 90 or 40 ms, respectively. At 50 μ*M*, PHT and CBZ each produce a frequency-dependent block. At 50 μ*M*, PHT produces an initial block of 50%. With repetitive stimulation at 10 Hz, the block increases to about 80% over 2.5 s. Recovery from this block requires approximately 2.5 s. At 100 μ*M*, CBZ also produces frequency-dependent block which is somewhat less pronounced than that produced by PHT. Thus, PHT and CBZ produce voltage-dependent and frequency-dependent block of sodium channels. Because the concentration response curves could be fitted by assuming a first-order reaction, it has been suggested that one drug molecule binds to one receptor near or at the sodium channel. The data are also consistent with PHT and CBZ binding with higher affinity to inactivated sodium channels than to open or resting sodium channels. Of interest was the finding that PHT had a longer time dependence for frequency-dependent block and for recovery from block than CBZ. This would result in a more pronounced frequency-dependent block for PHT than for CBZ. Therefore, although PHT and CBZ have qualitatively similar actions on sodium channels, the actions are quantitatively somewhat different. This may explain, at least in part, differences in efficacy for these two AEDs in different patients.

Similar voltage-clamp experiments were performed on isolated mammalian brain neurons (Wakamori et al., 1989). Hippocampal pyramidal neurons from the CA1 region were obtained from 1- and 2-week-old rats. At 200 μ*M* PHT produced a 20-mV negative shift in the steady-state inactivation curve for sodium channels and produced frequency-dependent block of sodium channels. Frequency-dependent block was shown at frequencies as low as 1 Hz and the block increased to 50% at 10 Hz. Therefore, the ability of PHT to enhance inactivation in neurons in cell culture and in mammalian myelinated nerve fibers is also present in isolated mammalian neurons.

The effect of PHT on human sodium channels also has been examined (Tomaselli et al., 1989). Total mRNA was extracted from human brain and injected into *Xenopus* oocytes. The human brain sodium channels expressed in oocytes were also blocked by PHT in a voltage-, frequency-, and time-dependent fashion. The effects of PHT on human sodium channels were very similar to those on cultured mouse neurons, rat myelinated nerve, and rat hippocampal pyramidal neurons.

Evidence from voltage-clamp experiments has therefore confirmed the basic mechanism of action of PHT and CBZ. Both AEDs appear to stabilize the inactive form of the sodium channel in a voltage-dependent fashion, the effect being lessened at large negative membrane potentials and increased at less negative membrane potentials. Both AEDs slow the rate of recovery from sodium-channel inactivation and shift the steady-state sodium inactivation curve to more negative voltages. This stabilization of the inactive form of the receptor results in a frequency-dependent block of sodium channels and in the blockade of sustained high-frequency repetitive firing of action potentials evoked from re-

duced membrane potentials. Of interest is the finding that PHT has a stronger slowing effect than CBZ. This would result in slightly different actions of these drugs under different conditions of repetitive firing.

ESM AND TRIMETHADIONE (TMO)

A number of AEDs can modify the properties of voltage-dependent calcium channels (Macdonald, 1989). PHT, barbiturates, and BDZ reduce calcium influx into synaptic terminals and block presynaptic release of neurotransmitter. However, these actions have been demonstrated only at high drug concentrations that are above therapeutic free serum concentrations in patients treated for epilepsy. Thus, it has been concluded that AEDs do not have their primary actions on calcium channels. Calcium channels, however, have been shown to be heterogeneous (Snutch et al., 1990, 1991; Hui et al., 1991; Mori et al., 1991; Starr et al., 1991; Williams et al., 1992). At least four different types of voltage-dependent calcium channels have been described and have been called L-type, T-type, N-type, and P-type channels (Nowycky et al., 1985; Mintz et al., 1992). These four calcium channels have different voltage ranges for activation and inactivation and different rates of activation and inactivation. Each channel type has been cloned and shown to be composed of several subunits (L-type channel: Campbell et al., 1988; Catterall, 1988; N-type channel: Williams et al., 1992; Fujita et al., 1993; P-type channel: Mori et al., 1991; and T-type channel: Soong et al., 1993). In addition, many subtypes of channels have been identified. It is also likely that these are not the only types of calcium channels present on neurons. In view of the finding that neurons express multiple calcium channels, it may be that AEDs act on specific types of channels. Indeed, this has been demonstrated for the AEDs ESM, TMO, and VPA, which are effective in the treatment of generalized absence seizures (Table 1). Generalized absence epilepsy is characterized clinically by brief periods of loss of consciousness and electrically by a generalized 3-Hz spike-and-wave discharge recorded on the electroencephalogram (EEG). It has been suggested that 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 calcium currents (Coulter et al., 1989*a*). The T-type currents had properties such that T-channel activation was necessary and sufficient to cause the generation of low-threshold calcium spikes in thalamic relay neurons. It was demonstrated the ESM and dimethidione, the active metabolite of TMO, both reduced the T-type current of thalamic neurons isolated from guinea pigs and rats (Coulter et al., 1989*b*,*c*). The reduction of the T-type current was produced at concentrations of ESM and dimethidione that have clinical relevance. PHT and CBZ, which are ineffective in the control of generalized absence seizures, had minimal effects on T-type current. The ESM-induced reduction of the T-type current was voltage-dependent. The reduction was most prominent at negative membrane potentials and less prominent at more positive membrane potentials. ESM did not alter the voltage dependency of steady-state inactivation or the time course of recovery from inactivation. Dimethidione reduced T-type current by a mechanism similar to that of ESM. Another anticonvulsant succinimide, α-methyl-α-phenylsuccinimide, also reduced T-type currents, whereas a convulsant succinimide, tetramethylsuccinimide, reduced only the T-type current at very high concentrations (Coulter et al., 1990). These results suggest that anticonvulsant succinimides and dimethidione, compounds effective in the treatment of generalized absence epilepsy, may exert their primary action by reducing the T-type calcium current in thalamic relay neurons.

VPA

The effect of VPA on sodium channels has been studied less extensively. It remains uncertain if VPA has the same mechanism of action as PHT and CBZ. Although VPA blocked sustained high-frequency repetitive firing of neurons in culture (McLean and Macdonald, 1986*a*) (Table 1), detailed voltage-clamp experiments of VPA actions on sodium currents have not been performed. It cannot be concluded that VPA has a mechanism of action similar to that of PHT and CBZ until these studies have been performed.

VPA is one of the most effective drugs against generalized absence seizures. Interestingly, initial studies of VPA did not demonstrate any effect on the T-type calcium current, but subsequently this agent was shown to reduce T-type currents in primary afferent neurons (Kelly et al., 1990) (Table 1). The effect was produced over a concentration range of 100–1,000 μ*M*. However, the magnitude of the effect was modest, with a 16% reduction seen at 1 m*M* VPA. Whether this modest reduction in T-type calcium current is sufficient to explain the effect of

VPA on generalized absence seizures is unclear. Furthermore, the basis for the discrepancy between the results obtained in rat thalamic neurons and rat primary afferent neurons remains uncertain. It may be that different neuron types have different sensitivities to these drugs or that the small effect is difficult to characterize. Whether this is a relevant mechanism of action for VPA will have to be determined by future investigation.

GBP

GBP, 1-(aminomethyl) cyclohexane-acetic acid, is a cyclic GABA analogue originally designed to mimic the steric conformation of GABA (Schmidt, 1989), to have high lipid solubility to penetrate the blood–brain barrier, and to be a centrally active GABA agonist with potential therapeutic value (Rogawski and Porter, 1990). GBP has been shown to have anticonvulsant activity in a variety of animal seizure models (Bartoszyk et al., 1986) and is effective in the treatment of human partial and generalized tonic–clonic seizures.

Early work with GBP suggested that it may act on GABAergic neurotransmitter systems, as it protected mice from tonic extension in chemical convulsion models using inhibitors of GABA synthesis (3-mercaptopropionic acid, isonicotinic acid, semicarbazide) or antagonists acting at the $GABA_A$ receptor complex (bicuculline, picrotoxin) (Bartoszyk et al., 1983; Bartoszyk and Reimann, 1985). However, subsequent work has not clearly demonstrated a specific effect of GBP on GABAergic neurotransmitter systems. Inhibition of monoamine release by GBP in electrically stimulated rabbit caudate nucleus (Reimann, 1983) and rat cortex (Schlicker et al., 1985) was not modified by GABA, baclofen, or bicuculline, suggesting that GBP did not act at $GABA_A$ or $GABA_B$ receptors. Binding experiments in rat brain and spinal cord have shown that GBP has no significant affinity for the $GABA_A$- or $GABA_B$-binding sites measured by [^{3}H]muscimol and [^{3}H]baclofen displacement, respectively. GBP did not significantly inhibit the binding of [^{3}H]diazepam, had only a weak inhibitory effect on the GABA-degrading enzyme GABA-aminotransferase, did not elevate GABA content in nerve terminals, and did not affect the GABA uptake system (Bartoszyk et al., 1986). However, GBP has been shown to increase GABA turnover in several regions of rat brain (Löscher et al., 1991). Recent work has shown that GBP binds to a novel high-affinity site in the central nervous system (Hill et al., 1993; Suman-Chauhan et al., 1993) and is potently displaced by the anticonvulsant 3-isobutyl GABA (Taylor et al., 1993), but the identity of this binding site remains uncertain. In addition, GBP has been shown to be a substrate for a saturable L-amino acid transport system in rat gut tissues (Stewart et al., 1993) and GBP appears to be concentrated from brain interstitial fluid into brain tissue by an active process (Welty et al., 1993). The results of these studies raise the possibility of a specific binding site of GBP for active transport across neuron membranes. This hypothesis remains to be tested.

In electrophysiologic studies, GBP did not affect depolarizations elicited by iontophoretic application of GABA on cultured mouse spinal cord neurons (Taylor et al., 1988; Rock et al., 1993). In addition, GBP appeared to act by GABAR-independent mechanisms in studies with rat hippocampal slices (Haas and Wieser, 1986) and the feline trigeminal nucleus (Kondo et al., 1991). GBP has been shown to decrease inhibition evoked by paired-pulse orthodromic stimulation of pyramidal neurons in the hippocampal slice preparation (Dooley et al., 1985; Taylor et al., 1988); however, the specific effect of GBP in this model is not known.

GBP protected mice from convulsions caused by strychnine, a glycine receptor antagonist, but was unable to displace [^{3}H]strychnine in binding studies at the highest concentrations tested (Bartoszyk et al., 1986). Electrophysiologic studies showed no effect of GBP on the response of spinal cord neurons to iontophoretically applied glycine (Rock et al., 1993).

GBP has been tested in animal seizure models in which seizures are induced by administration of excitatory amino acids. GBP prolonged the onset latency of clonic convulsions and tonic extension and death in mice after intraperitoneal injections of NMDA, but not kainic acid or quinolinic acid. GBP did not have a clear effect on convulsions when these compounds or glutamate were injected into the lateral ventricle of rats (Bartoszyk, 1983). Intraperitoneal injections in mice of GBP or the NMDA receptor competitive antagonist 3-((±)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP) antagonized tonic seizures. The effect of GBP, but not of CPP, was dose-dependently antagonized by the administration of serine, an agonist at the glycine receptor on the NMDA receptor complex, suggesting an involvement of the strychnine-insensitive glycine site of the NMDA receptor in the anticonvulsant activity of GBP (Oles et al., 1990).

In unpublished studies, GBP reportedly antagonized NMDA-induced, but not kainate-induced, depolarizations in thalamic and hippocampal slice

preparations, and antagonized NMDA-induced currents in the presence of glycine in cultured striatal neurons, an effect that was reversed by the addition of serine or increased glycine (Chadwick, 1992). Other studies did not show a significant effect of GBP on neuronal responses to iontophoretic application of glutamate or on membrane depolarizations and single-channel currents evoked by NMDA with or without coapplication of glycine (Rock et al., 1993). These results, in part, are similar to the findings of others in which GBP had no effect on spinal cord neuron depolarizations elicited by iontophoretically applied glutamate (Taylor et al., 1988; Rock et al., 1993) or pressure-ejected NMDA (Wamil et al., 1991*a*). In addition, in extracellular recordings from rat hippocampal slice preparations, GBP had no effect on long-term potentiation, making it unlike NMDA receptor antagonists (Taylor et al., 1988).

GBP had no effect on sustained repetitive firing of action potentials in mouse spinal cord neurons (Taylor et al., 1988; Rock et al., 1993). In other experiments using the same neuron preparation, prolonged times of exposure (12–48 h) and/or application of GBP resulted in a voltage- and frequency-dependent limitation of sustained repetitive firing of sodium action potentials at therapeutically relevant concentrations (Wamil et al., 1991*b*). However, GBP had no effect on rat brain type IIA sodium channel α subunit currents expressed in Chinese hamster ovary cells after 24-h bath application of GBP or when GBP was delivered by blunt pipette or the recording electrode (Taylor, 1993). The results of these different studies suggest that the antiepileptic activity of GBP is not due to a direct interaction with voltage-dependent sodium channels limiting sustained repetitive firing of action potentials.

Although most effective in the treatment of human partial and generalized tonic–clonic seizures, the effect of GBP on absence seizures has been studied in both animal models of absence seizures and as add-on therapy in patients with epilepsy that is AED-resistant. In animal studies using pentylenetetrazol-induced clonic seizures, GBP protected mice from clonic convulsions in both the s.c. metrazol test and the i.v. threshold test (Bartoszyk et al., 1986). However, in a rat genetic model of absence epilepsy, GBP increased EEG spike-and-wave bursts in a dose-dependent manner (Foot and Wallace, 1991). In human studies, GBP reduced more than 50% of absence seizures in half of the patients in one study (Bauer et al., 1989), and in another study GBP reduced absence seizures and generalized spike-and-wave complexes in patients undergoing 24-h EEG monitoring (Rowan et al., 1989). In studies of mouse spinal cord neurons, GBP blocked responses to Bay K 8644, an agonist at the dihydropyridine binding site of the L-type calcium channel (Wamil et al., 1991*a*). In other electrophysiologic studies, however, GBP did not significantly affect any calcium-channel current subtype (T, N, or L), suggesting that its basic mechanism of action was not on voltage-dependent calcium channels (Rock et al., 1993).

In summary, the results of several studies have not demonstrated a major effect of GBP on ligand- or voltage-gated channels (Table 2). Further work on the high-affinity binding site of GBP and the possibility of active transport of GBP across neuronal membranes should contribute significantly to understanding its mechanism of action.

LTG

LTG, 3,5,-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, is a phenyltriazine with weak antifolate activity. LTG was developed after observations that PB, PRM, and PHT resulted in reduced folate levels and that folates could induce seizures in experimental animals (Reynolds et al., 1966). It was proposed that antifolate activity may be related to anticonvulsant activity. However, this has not been demonstrated by structure–activity studies (Rogawski and Porter, 1990). LTG has anticonvulsant activity in several animal seizure models, including hindlimb extension in maximal electroshock and maximal pentylenetetrazol seizures in rodents (Miller et al., 1986). LTG has been effective as add-on therapy in the treatment of human partial and generalized tonic–clonic seizures.

The action of LTG on the release of endogenous amino acids from rat cerebral cortex slices in vitro has been studied. LTG potently inhibited release of glutamate and aspartate evoked by the sodium-channel activator veratrine and was much less effective in inhibition of release of acetylcholine or GABA. At high concentrations, LTG had no effect on spontaneous or potassium-evoked amino acid release. These studies suggested that LTG acted at voltage-dependent sodium channels, resulting in decreased presynaptic release of glutamate (Leach et al., 1986). In radioligand studies, the binding of

TABLE 2. *New antiepileptic drug actions*

	Sodium channels	$GABA_AR$ channels	T-Calcium channels	NMDAR channels
Gabapentin	+/?	+/?	–	–
Lamotrigine	+ +	–/?	–/?	?
Oxcarbazepine	+/?	?	?	?
Vigabatrin	?	+	?	?

[^{3}H]batrachotoxinin A 20-α-benzoate, a neurotoxin that binds to receptor site 2 on voltage-dependent sodium channels, was inhibited by LTG in rat brain synaptosomes (Cheung et al., 1992). Several electrophysiologic studies have tested the effects of LTG on voltage-dependent sodium channels. LTG blocked sustained repetitive firing in cultured mouse spinal cord neurons in a dose-dependent manner at concentrations therapeutic in the treatment of human seizures (Cheung et al., 1992). In cultured rat cortical neurons, LTG reduced burst firing induced by glutamate or potassium, but not unitary sodium action potentials evoked at low frequencies (Lees and Leach, 1993). In cultured hippocampal neurons, LTG reduced sodium currents in a voltage-dependent manner, and at depolarized potentials showed a small frequency-dependent inhibition (Mutoh and Dichter, 1993). LTG increased steady-state inactivation of rat brain type IIA sodium channel α subunit currents expressed in Chinese hamster ovary cells (Taylor, 1993) and produced both tonic- and frequency-dependent inhibition of voltage-dependent sodium 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 (Wang et al., 1993).

In cultured rat cortical neurons, LTG at high concentrations was able to inhibit peak high-threshold calcium currents and appeared to shift the threshold for inward currents to more depolarized potentials (Lees and Leach, 1993). In clonal rat pituitary GH3 cells, LTG at the same concentration did not inhibit high-threshold calcium currents, caused only slight inhibition of low-threshold calcium currents, reduced rapidly inactivating voltage-dependent potassium currents, and had no significant effect on calcium-activated potassium currents (Lang and Wang, 1991). In cultured rat cortical neurons, LTG did not appear to mimic the effect of diazepam when tested on GABA-evoked chloride currents (Lees and Leach, 1993).

These results suggest that the antiepileptic effect of LTG is due to a specific interaction at the voltage-dependent sodium channel that results in voltage- and frequency-dependent inhibition of the channel (Table 2). These results are similar to those found for PHT and CBZ. It remains to be determined whether this action results in a significant preferential decreased release of presynaptic glutamate.

OCBZ

OCBZ (10,11-dihydro-10-oxo-carbamazepine) is a derivative of the dibenzazepine series and is structurally very similar to CBZ. OCBZ differs from CBZ by a keto substitution at the 10,11 position of the dibenzazepine nucleus. The keto substitution causes a different biotransformation and greater tolerability in humans compared to CBZ. OCBZ is rapidly and almost completely metabolized to 10,11-dihydro-10-hydroxy carbamazepine (GP 47779; HCBZ), the active metabolite that is responsible for the antiepileptic activity of OCBZ (Jensen et al., 1991). HCBZ is a racemate with both enantiomers having approximately equal anticonvulsant activity (Schmutz et al., 1993). Metabolism of OCBZ does not result in the formation of 10,11-epoxy carbamazepine.

OCBZ and HCBZ are effective in inhibiting hindlimb extension in rats and mice elicited by maximal electroshock, but are approximately two to three times less effective against pentylenetetrazol-induced seizures in mice (Baltzer and Schmutz, 1978). In studies using rats at different developmental ages, OCBZ, HCBZ, and CBZ dose-dependently reduced the tonic phase of generalized seizures induced by pentylenetetrazol and appeared to have identical anticonvulsant profiles in this model (Kubova and Mares, 1993). OCBZ and HCBZ have relatively poor anticonvulsant efficacy against picrotoxin- and strychnine-induced seizures in mice (Baltzer and Schmutz, 1978). OCBZ was able to completely suppress seizures in rhesus monkeys in a chronic aluminum foci model of partial seizures. At comparable doses, HCBZ was less effective in suppressing seizures in this model (Jensen et al., 1991). OCBZ is effective in the treatment of human generalized tonic–clonic seizures and partial seizures with and without secondary generalization (Dam and Jensen, 1989).

In electrophysiologic studies of rat hippocampal slices, OCBZ and HCBZ enantiomers dose-dependently decreased epileptic-like discharges induced by penicillin. In addition, the drugs' ability to suppress discharges was decreased by 4-aminopyridine, a potassium-channel blocker (Schmutz et al., 1993). Because OCBZ and HCBZ are similar to CBZ in both structure and clinical efficacy, it is tempting to speculate that their mechanism of action may be similar to that of CBZ, i.e., inhibition of sustained high-frequency repetitive firing of voltage-dependent sodium action potentials (Table 2). However, this has not been demonstrated by electrophysiologic testing, and the mechanism of action of OCBZ remains unknown.

VGB

VGB [(γ-vinyl GABA) 4-amino-hex-5-enoic acid] is a synthetic derivative and structural analogue of

GABA. VGB was developed to be an enzyme-activated, irreversible inhibitor of GABA-transaminase (GABA-T), the primary presynaptic degradative enzyme of GABA. VGB's selective inhibition of GABA-T was intended to have potential therapeutic value by increasing GABA levels in the brain and thereby enhance GABAergic transmission. VGB is a racemic mixture of S(+)- and R(−)-enantiomers. The S(+)-enantiomer potently inhibits GABA-T whereas the R(−)-enantiomer has minimal activity (Larsson et al., 1986). The molecular mechanism of action of VGB's inhibition of GABA-T has been proposed by Lippert et al. (1977). VGB is accepted as a substrate of GABA-T by forming a Schiff base with pyridoxal phosphate in the active site of the enzyme, which abstracts a proton from the Schiff base. The resulting charge stabilization by the pyridine ring induces the aldimine to ketimine tautomerism that occurs in the normal transamination process. The reactive unsaturated ketimine forms a stable bond with a nucleophilic residue of GABA-T's active site, resulting in irreversible inhibition of the enzyme and eliminating its ability to transaminate new substrate.

A number of animal studies have described the effects of VGB's inhibition of GABA-T. VGB inhibited mouse whole-brain GABA-T activity and increased whole-brain GABA concentrations (Jung et al., 1977; Schechter et al., 1977). These actions were seen in all brain areas assayed and were quantitatively different, corresponding to the relative regional distribution of GABAergic neurons (Chapman et al., 1982). In rat cortex, VGB markedly increased the synaptosomal GABA pool compared with nonsynaptosomal GABA (Sarhan and Seiler, 1979), suggesting a greater effect of VGB on neuronal GABA-T rather than glial GABA-T. This effect is consistent with the finding that neurons have a high-affinity GABA uptake system, whereas astrocytes have a low-affinity system (Schousboe et al., 1986).

In human studies, VGB dose-dependently increased cerebrospinal fluid levels of free and total GABA (Grove et al., 1981; Schechter et al., 1984; Ben-Menachem, 1989) but did not significantly affect other neurotransmitter systems (Schechter et al., 1984; Riekkinen et al., 1989). In recent studies with healthy subjects, nuclear magnetic resonance spectroscopy showed that occipital lobe GABA concentrations were elevated after the subjects received VGB (Petroff et al., 1993).

VGB has been shown to be an effective anticonvulsant in a variety of animal models of epilepsy. In studies with rodents, VGB inhibited strychnine-induced and audiogenic seizures (Schechter et al., 1977). Other studies showed that only the active S(+)-enantiomer of VGB was effective in inhibiting audiogenic seizures in mice (Meldrum and Murugaiah, 1983). VGB inhibited epileptic responses in photosensitive baboons (Meldrum and Horton, 1978) and inhibited the development of kindling (Shin et al., 1986; Löscher et al., 1987), as well as fully developed generalized seizures in the amygdala-kindled rat (Kalichman et al., 1982). VGB was less effective in inhibiting seizures caused by bicuculline and picrotoxin (Schechter and Tranier, 1977). VGB has been effective in the treatment of human partial seizures with or without becoming secondarily generalized.

In summary, VGB is a selective irreversible inhibitor of GABA-T, the main degradative enzyme of GABA. Inhibition of GABA-T produces greater available pools of presynaptic GABA for release in central nervous system synapses. Increased activity of GABA at postsynaptic GABA receptors can cause increased inhibition of neurons important in controlling the abnormal electrical activity of seizures (Table 2). These actions probably account for the clinical antiepileptic effects of VGB.

CONCLUSIONS

The established AEDs appear to have only three major mechanisms of action (Table 1). AEDs that are effective against generalized tonic–clonic and partial seizures appear to reduce sustained high-frequency repetitive firing of action potentials by delaying recovery of sodium channels from activation. Drugs that are effective against generalized absence seizures appear to reduce low-threshold (T-type) calcium currents. Finally, AEDs that are effective against myoclonic seizures generally enhance $GABA_A$ receptor inhibition. Although the established AEDs have been shown to be effective, there are clearly a number of patients, especially those with complex partial seizures, whose seizures are refractory to these AEDs. The new AEDs have shown considerable promise in clinical trials and may be of significant help in managing some refractory patients. Although the mechanisms of action of these AEDs are not fully established (Table 2), it is likely that additional new AEDs now under development will have actions on new neurotransmitter receptor or ion channels. For example, considerable effort has been directed toward developing compounds that are antagonists of excitatory amino acid transmission. It can be hoped that new AEDs acting on different neurotransmitter receptors or ion channels will lead to improved control of seizures in patients refractory to presently available AED therapy.

Approaches to the investigation of the mechanisms of action of AEDs to date have been fairly descriptive. With the recent development of new molecular biologic techniques for the study of central nervous system function and the cloning of cDNAs for specific neurotransmitter receptors and ion channels that are targets of AEDs, it may be possible to study the interaction of AEDs with their molecular targets in more detail. Insights gained from these studies may assist in the design of improved AEDs that act on the same receptors or ion channels but may have more specific and selective actions.

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