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Antiepileptic Drug Mechanisms of Action

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Summary: Clinically used antiepileptic drugs (AEDs) decrease membrane excitability by interacting with ion channels or neurotransmitter receptors. Currently available AEDs appear to act on sodium channels, $GABA_A$ receptors, or calcium channels. Phenytoin, carbamazepine, and possibly valproate (VPA) decrease high-frequency repetitive firing of action potentials by enhancing sodium channel inactivation. Benzodiazepines and barbiturates enhance $GABA_A$ receptor–mediated inhibition. Ethosuximide and possibly VPA reduce a low-threshold calcium current. The mechanisms of action of AEDs currently under development are less clear. Lamotrigine may decrease sustained high-frequency repetitive firing. The mechanisms of action of felbamate are unknown. Gabapentin (GBP) appears to bind to a specific binding site in the central nervous system with a restricted regional distribution, but the identity of the binding site and the mechanism of action of GBP remain uncertain. **Key Words:** Anticonvulsants—Neuropharmacology—Neurotransmitters—GABA—Phenytoin—Carbamazepine—Ethosuximide—Trimethadione—Benzodiazepines—Barbiturates—Valproate—Felbamate—Gabapentin—Lamotrigine—Neural inhibition—Sodium—Calcium.

A limited number of antiepileptic drugs (AEDs) are available for use in the treatment of patients with epilepsy. In the United States, AEDs are limited primarily to phenytoin (PHT), carbamazepine (CBZ), barbiturates and primidone (PRM), benzodiazepines (BZDs), valproate (VPA), and ethosuximide (ESM). Three additional AEDs may be available in the United States in the near future: felbamate (FBM), gabapentin (GBP), and lamotrigine (LTG). It is likely that the currently used AEDs as well as the new AEDs have as their primary targets of action neurotransmitter receptors or ion channels. Three primary neurotransmitter receptor or ion channels are targeted by the currently prescribed AEDs and at least one of the newly developed ones: voltage-dependent sodium channels, voltage-dependent calcium channels, and $GABA_A$ receptor channels. Basic actions at these ion channels or neurotransmitter receptor channels may be responsible for the clinical actions of those AEDs. The interaction of clinically available AEDs and the three new AEDs FBM, GBP, and LTG with those specific neurotransmitter receptors or ion channels will be the subject of this review.

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PHENYTOIN AND CARBAMAZEPINE

PHT and CBZ have been shown to interact with sodium channels at concentrations found free in the plasma of patients being treated for epilepsy (Macdonald, 1989). These AEDs were shown to 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 that they did not reduce the amplitude or duration of single action potentials but reduced the ability of neurons to fire trains of action potentials at high frequency. The limitation of high frequency repetitive firing was voltage-dependent, limitation of firing being increased after depolarization and reduced after hyperpolarization. Once developed, the limitation of firing was prolonged, lasting several hundred milliseconds. The action of the AEDs appeared to be due to a shift of sodium channels to an inactive state that was similar to the normally occurring inactive state but from which recovery was delayed.

The actions of PHT and CBZ on mammalian myelinated nerve fibers have been studied (Schwarz and Grigat, 1989). Both AEDs produced a voltage-dependent block of sodium channels that could be removed by hyperpolarization. PHT produced a shift of the steady-state sodium channel inactivation curve to

more negative voltages. Both PHT and CBZ reduced the rate of recovery of sodium channels from inactivation. In control solutions, sodium channels recovered from complete inactivation within a few milliseconds after 500-ms depolarization to 25 mV. In the presence of 100 μM PHT, recovery was prolonged to 90 ms. With 100 μM CBZ, recovery was prolonged to 40 ms. At 50 μM, PHT and CBZ each produced a frequency-dependent block. At 50 μM, PHT produced an initial block of 50%. With repetitive stimulation at 10 Hz, the block increased to approximately 80% over 2.5 s. Recovery from that block required approximately 2.5 s. At 100 μM, CBZ also produced a frequency-dependent block that was somewhat less pronounced than that produced by PHT. Thus, PHT and CBZ produced voltage- and frequency-dependent block of sodium channels. Because the concentration–response curves could be fitted assuming a first-order reaction, it was suggested that one drug molecule binds to one receptor near or at the sodium channel. The data also are consistent with PHT and CBZ binding with higher affinity to inactivated sodium channels rather 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 did CBZ. This difference would result in a more pronounced frequency-dependent block for PHT than for CBZ. Thus, although PHT and CBZ have *qualitatively* similar actions on sodium channels, the actions are *quantitatively* somewhat different. That fact may explain, at least in part, differences in the efficacy of the two AEDs among 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. PHT at 200 μM 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. Thus, the ability of PHT to enhance inactivation in neurons in cell culture and in mammalian myelinated nerve fibers also was 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 also were 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.

Thus, evidence from voltage-clamp experiments has 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. That stabilization of the inactive form of the receptor results in frequency-dependent block of sodium channels and blockade of sustained high-frequency repetitive firing of action potentials evoked from reduced membrane potentials. Of interest is the finding that PHT has a stronger slowing effect than CBZ, which would result in slightly different actions of those AEDs under different conditions of repetitive firing.

ETHOSUXIMIDE AND TRIMETHADIONE

A number of AEDs have been demonstrated to modify the properties of voltage-dependent calcium channels (Macdonald, 1989). PHT, barbiturates, and BZDs reduce calcium influx into synaptic terminals and block presynaptic release of neurotransmitter. However, those actions have been demonstrated only at high drug concentrations that are above therapeutic free serum concentrations. Thus, it has been concluded that AEDs do not have their primary actions on calcium channels. However, it has been shown that calcium channels are heterogeneous. In primary afferent neurons, at least four different types of channels have been described (Nowycky et al., 1985; Mintz et al., 1992). These channels have been called L channels, T channels, N channels, and P channels. These channel types have different voltage ranges for activation and inactivation and different rates of activation and inactivation. It also is likely that these are not the only types of calcium channels present on neurons. The finding that neurons express multiple calcium channels suggests that AEDs may act on specific subtypes of channels. This fact has been demonstrated for the AEDs ESM, trimethadione (TMO), and VPA, which are effective in the treatment of generalized absence seizures.

Generalized absence epilepsy is characterized clinically by brief periods of loss of consciousness and electrically by generalized 3-Hz spike and wave EEG discharges. 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 low-threshold T 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 shown that both ESM and dimethadione (DMO), the active metabolite of TMO, reduced the T-type calcium current of thalamic neurons isolated from guinea pigs or rats (Coulter et al., 1989*b,c*). The reduction of the T-type current was produced at concentrations of ESM and DMO that have clinical relevance. PHT and CBZ, which are ineffective in the control of generalized absence seizures, had minimal effects on the T-type calcium 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. DMO reduced the T-type calcium current by a mechanism similar to that of ESM. Another anticonvulsant succinimide, α-methyl-α-phenylsuccinimide, also reduced T-type calcium currents, whereas a convulsant succinimide, tetramethylsuccinimide, reduced the T-type calcium current only at very high concentrations (Coulter et al., 1990). These results suggest that anticonvulsant succinimides and DMO, compounds that are effective in the treatment of generalized absence epilepsy, may exert their primary action by reducing the low-threshold or T-type calcium current in thalamic relay neurons.

BENZODIAZEPINES AND BARBITURATES

The γ-aminobutyric acid$_A$ ($GABA_A$) receptor is a macromolecular protein containing binding sites for at least GABA, picrotoxin, neurosteroids, barbiturates and BZDs, and a chloride ion–selective channel (DeLorey and Olsen, 1992). The receptor appears to be composed of combinations of different isoforms of α, β, γ, δ, and ρ polypeptide subunits (Schofield et al., 1987; Pritchett et al., 1989*a*; Shivers et al., 1989; Cutting et al., 1991). $GABA_A$ receptors composed of only α and β subunits form chloride channels that are antagonized by picrotoxin and have an increased response in the presence of pentobarbital but lack sensitivity to BZDs; the presence of a γ subunit in addition to other subunits is necessary for full $GABA_A$ receptor pharmacology (Pritchett et al., 1989*b*). The subunit combinations that are expressed in vivo are uncertain.

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, investigators have modeled the single-channel activity of the main conductance state using a reaction scheme incorporating 2 sequential GABA binding sites, 3 open states, and 10 closed states (Macdonald et al., 1989*a*; Twyman et al., 1990).

Barbiturate and BZD drugs can modulate the $GABA_A$ 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 through the $GABA_A$ receptor.

Barbiturates enhance the $GABA_A$ receptor current by binding to an allosteric regulatory site on the receptor (Olsen, 1987). Results from fluctuation analysis suggest that phenobarbital (PB) and pentobarbital increased the mean channel open duration of $GABA_A$ receptor currents without altering channel conductance (Study and Barker, 1981). Single-channel recordings of barbiturate-enhanced single $GABA_A$ receptor currents directly demonstrate 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).

For $\alpha_1\beta_1$ receptors expressed in *Xenopus* oocytes or Chinese hamster ovary (CHO) cells, currents were increased by pentobarbital (Moss et al., 1990; Verdoorn et al., 1990). Furthermore, the concentration dependence for the effect was the same for receptors with different α and β subunits coexpressed with γ_2 and with $\beta_2\gamma_2$ alone in *Xenopus* oocytes (Verdoorn et al., 1990). These results directly demonstrate that the α and β subunits contain the allosteric regulatory site for barbiturates.

$GABA_A$ receptors have a high-affinity binding site for BZDs, and BZD- and $GABA_A$ receptor–binding sites have been demonstrated to be coupled allosterically (Olsen, 1987). BZDs increase $GABA_A$ receptor current. Results from fluctuation analysis suggest that the BZD diazepam increases $GABA_A$ receptor current by increasing opening frequency without altering

channel conductance or open duration (Study and Barker, 1981). Single-channel recordings have confirmed that BZDs increase 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 CHO cells formed from $\alpha_1\beta_1$ subunits are 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 γ_1 and γ_2 subunits, were isolated from a human fetal brain cDNA library (Pritchett et al., 1989*b*). When the γ_2 subunit was coexpressed transiently with α_1 and β_1 subunits in human embryonic kidney cells, fully functional $GABA_A$ receptors were formed that were sensitive to BZDs, β-carbolines, barbiturates, and picrotoxin.

Benzodiazepine receptors are heterogeneous, with BZDI and BZDII receptors having been characterized (Klepner et al., 1978). The identification of the three specific subunits forming $GABA_A$ receptors led to clarification of the basis for this heterogeneity. Expression of $\alpha_1\beta_1\gamma_2$ $GABA_A$ receptors in human kidney cells produces receptors similar to BZDI receptors, whereas expression of $\alpha_2\beta_1\gamma_2$ and $\alpha_3\beta_1\gamma_2$ $GABA_A$ receptors produces receptors similar to BZDII receptors (Pritchett et al., 1989*a*). Thus, despite the finding that the γ subunit confers benzodiazepine sensitivity to $GABA_A$ receptors, the α subunit appears to determine the type of BZD receptor expressed. BZDII receptors are also heterogeneous, being formed from $\alpha_2\beta_1\gamma_2$ or $\alpha_3\beta_1\gamma_2$ subunit combinations. The physiological and pharmacological significance of the differential expression of α subunits remains to be determined.

VALPROATE

The effect of VPA on sodium channels has been studied less extensively. It remains uncertain whether 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*), detailed voltage-clamp experiments on VPA actions on sodium currents have not been performed. It cannot be determined whether 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 low-threshold calcium current. A later study, however, demonstrated that VPA reduced T-type calcium currents in primary afferent neurons (Kelly et al., 1990). The effect was produced over a concentration range of 100–1,000 μM. However, the magnitude of the effect was modest, with a 16% reduction seen at 1,000 μM 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 those obtained in rat primary afferent neurons remains uncertain. It may be that different cell types have different sensitivities to those drugs or that the small effect is difficult to characterize. Whether this is a relevant mechanism of action for VPA remains to be determined.

FELBAMATE

FBM, 2-phenyl-1,3-propanediol dicarbamate, is a dicarbamate that has a structure similar to meprobamate, an antianxiety agent. In experimental animals, FBM was effective in blocking seizures induced by maximal electroshock, pentylenetetrazol, and picrotoxin (Swinyard et al., 1986). FBM inhibited bicuculline-induced seizures at high concentrations but was ineffective against strychnine-induced seizures (Sofia et al., 1991). These results suggest that FBM can both increase seizure threshold and prevent the electrical spread of seizure activity (Swinyard et al., 1986). In clinical studies, FBM has been effective against complex partial seizures in adults and the Lennox–Gastaut syndrome in children.

FBM has been tested for interaction with the $GABA_A$ receptor complex, a possible mechanism of its anticonvulsant activity. In rat brain cortical membranes, FBM did not affect ligand binding to the GABA-, BZD-, or picrotoxin-binding sites of the $GABA_A$ receptor complex. In addition, in radiolabeled Cl^- influx studies in cultured mouse spinal cord neurons, FBM did not affect GABA-induced $^{36}Cl^-$ influx (Ticku et al., 1991). These results suggest that FBM may not have a direct effect on the $GABA_A$ receptor complex. However, FBM in subprotective doses enhanced the protective effects of DZP against seizures induced by maximal electroshock, pentylenetetrazol, and isoniazid but not by bicuculline, suggesting that FBM may have indirect effects on the $GABA_A$ receptor complex or may be involved in other mechanisms of action (Gordon et al., 1991). FBM also has been tested for a possible effect on excitatory amino acid receptors. FBM inhibited *N*-methyl-D-aspartate (NMDA)- and quisqualate-induced seizures in mice but did not significantly inhibit MK-801 binding (Sofia et al., 1991). The significance of these results remains to be determined. Despite these early studies, the anticonvulsant mechanism of action of felbamate remains unknown.

GABAPENTIN

GBP, 1-(aminomethyl)-cyclohexaneacetic 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.

Despite demonstrated efficacy of GBP against a variety of seizures, the anticonvulsant mechanism of action is not known. Early research suggested that GBP may act on GABAergic neurotransmitter systems because it protected mice from tonic extension in chemical convulsion models using inhibitors of GABA synthesis (e.g., 3-mercaptopropionic acid, isonicotinic acid, semicarbazide) or antagonists acting on the $GABA_A$ receptor complex (e.g., bicuculline, picrotoxin) (Bartoszyk et al., 1983; Bartoszyk and Reimann, 1985). However, subsequent research 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 on $GABA_A$ 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]DZP, 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 (Loscher et al., 1991), and recent research has shown that GBP binds to a novel high-affinity site in partially purified synaptic plasma membranes from rat neocortex and is potently displaced by the anticonvulsant drug 3-isobutyl GABA (Taylor et al., 1993).

In electrophysiological studies, gabapentin did not affect depolarizations elicited by iontophoretic application of GABA on cultured mouse spinal cord neurons (Taylor et al., 1988; Rock et al., unpublished data). In addition, GBP appeared to act by GABA receptor–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 rat hippocampal slice preparation (Dooley et al., 1985; Taylor et al., 1988); however, the specific effect of GBP 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). Electrophysiological studies showed no effect of GBP on the response of spinal cord neurons to iontophoretically applied glycine (Rock et al., unpublished data).

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 the mice were given intraperitoneal injections of NMDA but not kainic acid or quinolinic acid. GBP did not have a clear effect on convulsions when those compounds or glutamate was 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 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 antiepileptic activity of GBP (Oles et al., 1990).

In unpublished studies, GBP reportedly antagonized NMDA-induced, but not kainate-induced, depolarizations in rat 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 (Kelly et al., 1991). Those 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) 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., unpublished data). In other experiments using the same neuronal preparation, high concentrations of GBP (100 μM) reduced sustained repetitive firing of action potentials. After overnight exposure of the cultures to GBP, sustained repetitive firing of action potentials was reduced by GBP (1 μM) (Wamil et al., 1991*b*). The different results of these studies done on mouse spinal cord neurons suggest that the antiepileptic activity of GBP is not due to inhibition of sustained repetitive firing of sodium action potentials.

Although GBP is most effective in the treatment of human partial and generalized tonic–clonic seizures, the effect of GBP on absence seizures has been studied both in animal models of absence seizures and as add-on therapy in patients whose epilepsy is drug resistant. In animal studies using pentylenetetrazol-induced clonic seizures, GBP protected mice from clonic convulsions in both the subcutaneous pentylenetetrazol test and the intravenous 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 one human study, GBP reduced >50% of absence seizures in half of the patients (Bauer et al., 1989), and in another human 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 electrophysiological studies, however, GBP did not significantly affect any calcium channel current subtype tested (i.e., T, N, or L), suggesting that the basic mechanism of action was not on voltage-dependent calcium channels (Kelly et al., 1991).

The results of several studies have not shown GBP to have a major effect on ligand- or voltage-gated channels. Further study of the high-affinity binding site of GBP and the AED 3-isobutyl GABA may contribute significantly to our understanding of the mechanism of action of GBP.

LAMOTRIGINE

LTG, 3,5,-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, a phenyltriazine with weak antifolate activity, was developed after the observation that PB, PRM, and PHT resulted in reduced folate concentrations 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, that relationship has not been demonstrated in 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 shown to be 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 the release of glutamate and aspartate evoked by the sodium-channel activator veratrine and was much less effective in the 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 [^{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. In electrophysiological studies, 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). These results suggest that the antiepileptic effect of LTG is due to a specific interaction at the voltage-dependent sodium channel that may result in a preferential decrease in presynaptic glutamate release.

CONCLUSION

Currently available AEDs appear to have only three major mechanisms of action. 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 inactivation. AEDs that are effective against generalized absence seizures appear to reduce low-threshold (T-type) calcium channel current. Finally, AEDs that are effective against myoclonic seizures generally enhance $GABA_A$ receptor inhibition. Although currently available AEDs have been shown to be effective, there clearly are a number of patients, especially those with complex partial seizures, whose epilepsy is refractory to available AEDs. FBM, LTG, and GBP have shown promise in clinical trials and may be of some help in managing some patients with refractory epilepsy. Although the mechanisms of action of those AEDs is unclear, at least GBP and FBM may have novel mechanisms of action. Furthermore, it is likely that additional new AEDs that are under devel-

opment will have actions on different neurotransmitter receptors or channels. For example, considerable effort has been directed toward developing compounds that are antagonists of excitatory amino acid transmission. It is to be hoped that new AEDs that act on different neurotransmitter receptors or channels will permit patients whose seizures are currently untreatable to be treated pharmacologically.

To date, approaches to the investigation of the mechanisms of action of AEDs have been fairly descriptive. With the recent development and application of new molecular biological techniques to the study of CNS function and the cloning of cDNAs for specific neurotransmitter receptors and ion channels that are targets of AEDs, it may be possible to study in more detail the interactions of AEDs with their target receptors or channels. That investigative research will assist in the elucidation of channel and receptor structure and perhaps also clarify the interactions of AEDs with receptors and channels. Insights gained from such studies may be helpful in the design of improved AEDs that may act on presently known receptors or channels but have more specific or selective actions.

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