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Antiepileptic Drugs: Pharmacological Mechanisms and Clinical Efficacy with Consideration of Promising Developmental Stage Compounds

MICHAEL A. ROGAWSKI[1,*] AND ROGER J. PORTER[2]

[1]*Neuronal Excitability Section, Medical Neurology Branch, and* [2]*Office of the Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland*

* To whom requests for reprints should be addressed: NINDS, NIH, Building 10, Room 5N-248, Bethesda, MD 20892.

I. Introduction

Epilepsy is one of the most common afflictions of man. With a prevalence of approximately 1%, it is estimated that 50 million persons worldwide may have the disorder. Although many are well controlled with available therapies, perhaps one-quarter of the total continue to have seizures. Since the introduction of valproate in 1978, no new antiepileptic drug has been approved in the United States for the primary therapy of epilepsy. Nevertheless, there is cause for optimism. A large number of promising compounds are currently undergoing preclinical and clinical evaluation, and several of these will undoubtedly become meaningful additions to the neurologist's pharmacological armamentarium. Although many of these compounds were discovered by the time-honored approach of empirical drug screening, the creation of several were based on rational considerations of the pathophysiological mechanisms of the epileptic syndromes in conjunction with a detailed understanding of central excitability mechanisms and logical principles of drug design. In the future, it can be expected that such considerations will play an even greater role in the process of antiepileptic drug development.

Our purpose in this review is to consider the biological

mechanisms of action of currently marketed and developmental stage antiepileptic drugs in the context of the clinical syndromes they are designed to treat. Since the time of Hughlings Jackson more than 100 years ago, epileptic seizures have been known to represent "an occasional, excessive. . .discharge of nerve tissue. . . ." (Taylor, 1931). Seizures are divided fundamentally into two groups: partial and generalized (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). Partial seizures have clinical or EEG evidence of a local onset, but the word partial does not imply a highly discrete focus; such a focus often does not exist. The abnormal discharge usually arises in a portion of one hemisphere and may spread to other parts of the brain during a seizure. Generalized seizures, however, have no evidence of localized onset; the clinical manifestations and abnormal electrical discharge give no clue to the locus of onset of the abnormality, if indeed such a locus exists (Porter, 1989).

Partial seizures are divided into three groups: (*a*) simple partial seizures, (*b*) complex partial seizures, and (*c*) partial seizures secondarily generalized. Simple partial seizures are associated with preservation of consciousness and usually with unilateral hemispheric involvement. Complex partial seizures are associated with alteration or loss of consciousness and usually with bilateral hemispheric involvement. A partial seizure may become secondarily generalized, i.e., may progress to a generalized tonic-clonic seizure. If there is no evidence of localized onset, then the attack is a generalized seizure. The generalized seizures include: (*a*) generalized tonic-clonic seizures (grand mal), (*b*) absence seizures (petit mal), (*c*) myoclonic seizures, (*d*) atonic seizures, (*e*) clonic seizures, and (*f*) tonic seizures. Although the majority of seizures occur without any obvious precipitating factor, in some patients seizures are triggered by environmental stimuli such as flickering light. Visually evoked seizures are not uncommon in humans but are rare in animals. On the other hand, certain mice and rats are susceptible to audiogenic (sound-induced) seizures, whereas true audiogenic seizures (as opposed to music-induced or auditory startle-induced seizures) do not occur in humans (Niedermeyer, 1990). Seizures induced by a specific triggering factor are referred to as "reflex seizures."

Epilepsy, in contradistinction to seizures, is a chronic disorder characterized by recurrent seizures (Gastaut, 1973). The "epilepsies" consist of a variety of diverse syndromes characterized by different seizure types, etiologies, ages of onset, and EEG features; the classification of epileptic syndromes has recently been published (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). The first major division of the epileptic syndromes is the same as that for seizures, i.e., into the *partial* epilepsies or the *generalized* epilepsies. Each of these is further subdivided into idiopathic (i.e., cause unknown) or symptomatic (cause known) and then according to age of onset. When possible, specification of a patient's seizure disorder as a particular epileptic syndrome affords prognostic information that neither the seizure diagnosis nor the etiological diagnosis can provide and may assist in the selection of appropriate drug therapy.

In the absence of a specific etiological understanding in any of the human seizure disorders, rational approaches to drug therapy of epilepsy must necessarily be directed at the control of symptoms, i.e., the suppression of seizures. Antiepileptic drugs can control either the initiation and maintenance of the epileptic discharge or its spread within the brain. Recent advances in understanding the cellular mechanisms of epileptogenesis from the kindling model suggest that approaches designed to interdict development of epilepsy may also be possible. Although there are a wide variety of specific molecular targets, all anticonvulsant drugs ultimately must exert their actions by altering the activity of the basic mediators of neuronal excitability: voltage- and neurotransmitter-gated ion channels. In those cases in which drug mechanisms are reasonably well understood, three general themes encompass current views of antiepileptic drug action: (*a*) modulation of voltage-dependent ion channels involved in action potential propagation or burst generation, (*b*) enhancement of GABA†-mediated inhibition, and (*c*) suppression of acidic amino acid-mediated excitation. Because our understanding is incomplete, it must be recognized that these are not the only brain mechanisms by which currently available drugs could operate, nor are they the only mechanisms that ought to be targeted in the development of new drugs. Nevertheless, they do provide a useful framework for the classification of antiepileptic drugs and this struc-

† Abbreviations: CNS, central nervous system; NMDA, N-methyl-D-aspartate; GABA, γ-aminobutyric acid; CSF, cerebrospinal fluid; PTP, posttetanic potentiation; h_∞, steady-state inactivation; AMP, adenosine monophosphate; GTP, guanosine triphosphate; cDNA, complementary deoxyribonucleic acid; GABA-T, GABA-α-ketoglutarate transaminase; mRNA, messenger ribonucleic acid; THIP, 4,5,6,7-tetrahydroisoxazolo[4-*c*]pyridine-3-ol; EEG, electroencephalogram; i.p., intraperitoneal; p.o., oral; i.v., intravenous; s.c., subcutaneous; i.m., intramuscular; GABAmide, γ-aminobutyramide; APH or AP5, 2-amino-7-phosphonoheptanoic acid; APV or AP7, 2-amino-5-phosphonovaleric acid; CPP, 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid; PCP, phencyclidine; PCA, 1-phenylcyclohexylamine; MK-801, (+)-10,11-dihydro-5-methyl-5H-dibenzo[*a*,*d*]cyclohepten-5,10-imine or dizocilpine; ADCI, 5-aminocarbonyl-5H-dibenzo[*a*,*d*]cyclohepten-5,10-imine; LY201116, 4-amino-N-(2,6-dimethylphenyl) benzamide; MMP, N-monomethoxymethyl-phenobarbital; U-54494A, (±)-cis-3,4-dichloro-N-methyl{N-[2-(1-pyrrolidinyl)-cyclohexyl]benzamide}; D-19274, 3-({2-amino-6-[(4-flurophenyl)methyl]amino-3-pyridinyl}2-oxazolidinone HCl); AHR-12245, 2-(4-chlorophenyl)-3H-imidazo[4,5-*b*]pyridine-3-acetamide; CGS 19755, *cis*-4-phosphonomethyl-2-piperidine-carboxylic acid; NPC 2626, 2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid; D-CPP-ene, D-3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid; CGP 37849, 2-amino-4-methyl-5-phosphono-3-pentenoic acid; CI-966, [1-{2-[bis-4-(trifluoromethyl)phenyl]methoxy}ethyl]-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid.

ture allows the tentative categorization of the developmental stage compounds in the face of limited information regarding their pharmacological activity. Thus, in the following discussion, we often use the currently marketed drugs as prototypes and base our conclusions concerning the actions of the developmental stage compounds on the presumed mechanisms of the prototypes.

For each drug considered in this review, we briefly describe its anticonvulsant profile in animal seizure models because this can often give insight into its cellular mechanism of action. A wide variety of animal models are used to screen potential antiepileptic drugs (see reviews by Reinhard and Reinhard, 1977; Porter et al., 1984; Meldrum, 1986; Jobe and Laird, 1987; Lothman et al., 1988; Kupferberg, 1989a; Fisher, 1989). These include spontaneous or reflex models of epilepsy in inbred animals, chemically induced seizures, and electrically induced seizures. In addition, various models utilize chemicals applied to the surface of the cortex or injected into the brain. Finally, the kindling model can be used to evaluate antiepileptic drugs. We consider the results of testing with these diverse models when it is available, but we particularly focus on the data obtained in the maximal electroshock seizure test and in the pentylenetetrazol test. These two models are widely used, are highly reproducible, and provide a basis for comparing different chemical entities under relatively well-standardized conditions. Results in these two models are especially apt to provide preliminary clues as to cellular mechanisms of action. The maximal electroshock test evaluates the ability of drugs to prevent electrically induced tonic hindlimb extension in mice and rats. Efficacy in this model has been shown to correlate with ability to prevent partial and generalized tonic-clonic seizures in man, and it is often stated that this model evaluates the capacity of a drug to prevent seizure spread. Drugs that are active in the maximal electroshock test often have a phenytoin-like effect on voltage-dependent Na^+ channels (table 1), although drugs that act specifically to block NMDA-type excitatory amino acid receptors or that increase synaptic norepinephrine levels (Burley and Ferrendelli, 1984; Przegalinski, 1985) are also effective in this test. On the other hand, the pentylenetetrazol test as most commonly performed evaluates the ability of potential antiepileptic drugs to prevent clonic seizures and may correlate with activity against absence seizures; there are, however, several drugs that are active in this test but are not useful in absence attacks, such as phenobarbital. Activity in this seizure model often indicates that a drug can affect GABAergic brain systems, either by enhancing brain GABA levels or by altering the sensitivity of postsynaptic GABA receptors. Specific antiabsence drugs, such as ethosuximide and trimethadione, which may act by blocking T-type voltage-dependent Ca^{2+} channels, are also effective in the pentylenetetrazol test. The pentylenetetrazol model also appears to correlate with ability to retard the development of kindled seizures (Albertson et al., 1984a; Schmutz et al., 1988). (When activity of the drug against pentyelenetetrazol-induced *tonic* seizures is reported, the significance is different and is more comparable to the maximal electroshock test.)

Following the discussion of drug activity in animal seizure models, we next consider data concerning the biochemical and cellular electrophysiological actions of the drug that may be relevant to its anticonvulsant activity in animals and man. Finally, we turn to a discussion of the clinical efficacy of the drug in human seizure disorders.

II. Drugs Used Primarily in the Treatment of Partial Seizures and Generalized Tonic-Clonic Seizures

A. Phenytoin

The ideal antiepileptic would prevent seizures without producing side effects that adversely affect the patient's quality of life. The discovery of phenytoin (fig. 1) demonstrated that this ideal was approachable. At normal therapeutic serum concentrations of 10–20 μg/ml (40–80 μM), phenytoin protects against seizures without causing sedation or otherwise interfering with normal CNS function in most patients. In addition to revolutionizing epilepsy therapy, the introduction of phenytoin set a standard against which to measure potential new antiepileptic agents. Phenytoin was the result of a search by Merritt and Putnam (1938) for a nonsedating analog of phenobarbital capable of suppressing electroshock-induced seizures in animals. The drug has very specific effects on the pattern of electroshock seizures in that it completely abolishes the tonic phase (usually scored as hindlimb extension; ED_{50}, 9.5 mg/kg, i.p., in mice) but may enhance or prolong the clonic phase of the seizure (Toman et al., 1946; Swinyard et al., 1989). In contrast, phenytoin is ineffective against seizures induced by chemoconvulsants such as pentylenetetrazol, bicuculline, picrotoxin, penicillin, and strychnine (Swinyard et al., 1989; see Eadie and Tryer, 1989, for additional references); it is weak in protecting against myoclonic responses in photosensitive baboons (Meldrum et al., 1975) and generalized seizures in alumina cream-lesioned cats (Majkowski et al., 1976); and it has variable effects against amygdaloid-kindled seizures in rats (Callaghan and Schwark, 1980; McNamara et al., 1989). Phenytoin has been shown to limit the propagation of epileptic activity from regions of epileptic cortex, even though it may actually increase the frequency of spiking in such foci (Morrell et al., 1959). As a consequence, it is often stated that phenytoin inhibits seizure spread but does not stop the initiation of epileptic discharges.

Phenytoin is known to exert a wide variety of pharmacological actions on neurons many of which are compatible with anticonvulsant activity. However, the chal-

TABLE 1

*Anticonvulsant potencies and proposed cellular mechanisms of action of prototype antiepileptic drugs**

Seizure type/ antiepileptic drug	Mouse anticonvulsant screen (mg/kg, i.p.)		Voltage-dependent Na^+ channels	T-type voltage-dependent Ca^{2+} channels	$GABA_A$-receptor mechanisms
	MES ED_{50}	PTZ ED_{50}			
Generalized tonic-clonic and partial seizures					
Phenytoin	9.5	No protection	+		
Carbamazepine	8.8	Potentiation	+		
Phenobarbital	21.8	13.2			+
Broad spectrum					
Clonazepam	92.7	0.18			+
Diazepam	19.1	0.17			+
Valproate	272	149	+		+
Absence seizures					
Ethosuximide	>1000	130		+	
Trimethadione	628	301		+†	

* Abbreviations: MES, maximal electroshock (tonic) seizure test; PTZ, pentylenetetrazol (clonic) seizure test; ED_{50}, median effective dose. Adapted from Porter et al. (1984) and Swinyard (1989).

† The metabolite dimethadione was tested.

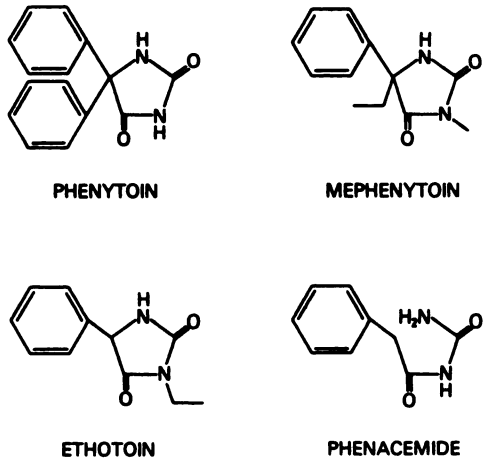


FIG. 1. Structures of succinamide anticonvulsants and phenacemide.

lenge for researchers has been to explain its relative lack of neurological side effects at therapeutic doses. For example, in mice, phenytoin's TD_{50} (dose at which 50% of animals exhibit toxicity) in the rotorod ataxia test is 66 mg/kg so that its protective index (TD_{50}/ED_{50}) is 6.9. Numerous excellent reviews of phenytoin's diverse neuronal actions have appeared (e.g., Yaari et al., 1986; Selzer et al., 1988; Eadie and Tryer, 1989; De Lorenzo, 1989) and the present account will focus on observations leading to a molecular understanding of its antiepileptic action. In recent years, it has been elegantly demonstrated that phenytoin can interact with the voltage-dependent Na^+ channels that are responsible for the action potential upstroke in a highly specific voltage- and frequency-dependent manner. This is the only known action of the drug that can easily explain its ability to suppress seizures without causing a generalized depression of the nervous system. Thus, the theory that Na^+ channel blockade is the mechanism underlying phenytoin's clinical efficacy is gaining widespread acceptance, although some investigators have also implicated effects on voltage-dependent Ca^{2+} channels. We will consider the experimental observations supporting the idea that phenytoin is a selective blocker of voltage-dependent Na^+ and Ca^{2+} channels. In addition, we will briefly consider data regarding the synaptic actions of phenytoin, including its ability to block neurally evoked excitatory transmitter release and its effects on excitatory amino acid-induced excitation and GABA-mediated inhibition. When evaluating any of the diverse pharmacological actions of phenytoin, one must always consider the data in light of the actual levels achieved in patients adequately treated by the drug. Although the usual therapeutic serum levels are 40–80 μM, phenytoin is highly protein bound so that only about 10% of the total is free and available to equilibrate with the CSF (Woodbury, 1989). Most investigators have considered the CSF levels to be a reasonable estimate of the drug concentration at the physiologically relevant acceptor site(s) because they are presumed to reflect the level in the extracellular compartment of the brain. We will follow this convention and focus on drug effects that occur at concentrations near the therapeutic CSF levels (approximately 4–8 μM). However, it is of interest to note that the brain concentration may be substantially higher than the CSF concentration, presumably because of binding to brain proteins and lipid (Goldberg and Crandall, 1978). Thus, the actual brain concentration is one to two times the *total* serum concentration (Woodbury, 1989) and the multitude of drug effects that occur at concentrations near the serum levels cannot therefore be discounted completely, although the physiologically relevant concentrations are presumed to be closer to the *free* brain concentration which is thought to be equivalent to CSF levels.

1. Block of voltage-dependent Na^+ channels. Investigations of the cellular actions of phenytoin lagged by more than a decade the original accounts by Putnam and

Merritt (1937) of its ability to protect cats from electroshock-induced seizures (Merritt and Putnam, 1938). However, the first such report (Toman, 1949) was strikingly prescient in foretelling the conclusions of an additional 40 years of research. Frog sciatic nerve, when stimulated with a supramaximal shock, was shown to respond with an action potential followed by a second "rebound" spike. Phenytoin at near clinically effective concentrations (50 μM) prevented the rebound spike without altering the initial spike. Thus, phenytoin could produce a selective blockade of high-frequency repetitive neuronal firing; the obvious inference was that a similar action in the brain accounted for its ability to specifically block the spread of seizure discharges characterized by high-frequency neuronal activity. The lack of effect on the initial spike response was interpreted as reflecting the failure of phenytoin to cause a general depression of neuronal firing.

Blockade of PTP, one of the best documented and most robust physiological actions of phenytoin, may underlie the capacity of the drug to prevent seizure spread. PTP refers to the ability of high-frequency repetitive synaptic stimulation (tetanus) to transiently enhance the responsiveness of that pathway to a single stimulus. It has been suggested that PTP may be a mechanism that reinforces focal discharges by positive feedback and facilitates the spread of high-frequency impulses occurring in these foci to synaptically coupled cells in distant areas. In several preparations, phenytoin at low doses has been shown to prevent the augmentation of synaptic responses produced by a tetanizing stimulus (Esplin, 1957; Raines and Standaert, 1966; Selzer et al., 1985). For example, in the in vitro hippocampal slice preparation, PTP can be produced by high-frequency (100 Hz, 1–2 s) stimulation of the Schaffer collateral/commissural pathway to CA_1 pyramidal cells or by stimulation of the mossy fiber input to CA_3 cells (Griffith and Taylor, 1988a). Phenytoin (10–30 μM) accelerated the decay of PTP in both of these synaptic pathways. It should be noted, however, that phenytoin does not block all forms of synaptic plasticity. For example, long-term potentiation, a popular model of learning and memory, is unaffected by the drug (Stringer and Lothman, 1988). Neither the mechanism of PTP nor the way in which phenytoin attenuates it is well understood. Perhaps the most compelling hypothesis at present is that frequency-dependent block of voltage-dependent Na^+ channels by phenytoin leads to intermittent failure in the propagation of high-frequency action potential trains to nerve terminals, thus effectively reducing PTP (see Yaari et al., 1986, for references).

As in the early reports demonstrating a specific effect of phenytoin on repetitive firing in peripheral nerve preparations, more recent studies have confirmed that phenytoin inhibits high-frequency repetitive firing of mammalian central neurons in tissue culture at clinically relevant concentrations (McLean and Macdonald, 1983). It is of interest to note that spontaneous firing is only affected by higher concentrations of the drug, which is compatible with the idea that depression of normal neuronal firing only occurs under conditions of drug toxicity. The effect on high-frequency firing is thought to be a consequence of the unique voltage- and frequency-dependent manner in which phenytoin binds to Na^+ channels. Specific effects on Na^+ channels have been determined with three approaches: (*a*) displacement (binding) assays in membrane preparations using radiolabeled Na^+ channel toxins, such as [^{3}H]batrachotoxin (fig. 2), (*b*) toxin-stimulated $^{22}Na^+$ flux measurements in synaptosomes, and (*c*) voltage-clamp recordings of Na^+ currents in various cell types. In each assay, phenytoin fails to produce a substantial inhibitory effect at the usual therapeutic free serum (CSF) concentrations (5–10 μM), as expected, because this would cause a generalized depression of the nervous system. The drug does, however, depress Na^+ channel function at somewhat higher concentrations, i.e., those that are in the toxic range. Thus, the effective one-half inhibitory concentration is 40 μM in the batrachotoxin-binding assay (Willow and Catterall, 1982), 35 μM in the Na^+ flux assay (Willow et al., 1984), and 30–200 μM in voltage-clamp recordings (Lipicky et al., 1972; Schwarz and Vogel, 1977; Matsuki et al., 1984; Willow et al., 1985; Wakamori et al., 1989; Tomaselli et al., 1989; Schwarz and Grigat, 1989). However, in the voltage-clamp experiments, holding the cell for a prolonged period at depolarized potentials prior to presentation of the activating stimulus markedly enhanced the block produced by phenytoin (Willow et al., 1985) and, in fact, if the cell is continuously held at hyperpolarized potentials (−100 mV), the Na^+ channel block can be virtually eliminated (Schwarz and Vogel, 1977; Matsuki et al., 1984; Schwarz and Grigat, 1989).

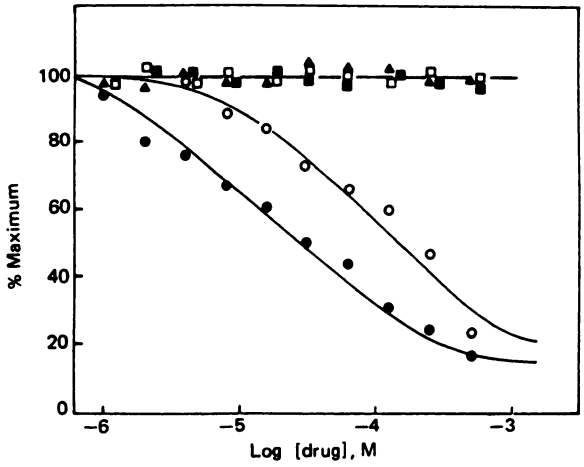


FIG. 2. Phenytoin and carbamazepine produce a concentration-dependent inhibition of the binding of [^{3}H]batrachotoxinin A 20-α-benzoate to synaptosomes from whole rat brain (in the presence of scorpion toxin). Phenytoin (●), carbamazepine (○), trimethadione (▲), ethosuximide (□), and sodium valproate (■). (From Willow and Catterall, 1982; used with permission.)

In a more quantitative sense, it can be stated that phenytoin shifts the steady state inactivation curve (h_∞) for Na^+ current to more hyperpolarized potentials. Repetitive pulsing also enhanced the inhibition produced by phenytoin so that the block of the Na^+ current only reached a steady state after a large number of depolarizations were delivered to the cell (Matsuki et al., 1984; Willow et al., 1985; Wakamori et al., 1989; Tomaselli et al., 1989; Schwarz and Grigat, 1989). Interestingly, depolarization to potentials negative to threshold (where the channels become inactivated without opening) was able to enhance block and, moreover, the degree of block could be shown to be dependent upon the duration at which the cell was held at the depolarized potential. In addition, recovery from inactivation that usually occurs very rapidly after hyperpolarization (within ~4 ms) was markedly slowed by phenytoin (~500 ms), as if the channels were prevented from leaving the inactivated state (Schwarz and Grigat, 1989). These observations strongly suggest that phenytoin binds preferentially to the *inactivated* (closed) state of the Na^+ channel (see also Courtney and Etter, 1983). Thus, although phenytoin binds poorly to Na^+ channels in their resting (closed) state, the drug also seems to have low affinity for *open* Na^+ channels and can only block the channels when they are inactivated. Although the exact way in which phenytoin blocks inactivated Na^+ channels in not known, this presumably occurs by stabilizing the channel in the inactivated state and preventing its transition to the resting state that it must reenter before it can open. A preliminary report describing the effects of phenytoin on single voltage-dependent Na^+ channels in outside-out membrane patches was generally consistent with the view developed from voltage-clamp experiments (Yaari and Carbone, 1985). Thus, phenytoin was shown to decrease the number of Na^+ channel openings after step depolarization but did not affect the single channel conductance or the mean open time; as in voltage-clamp recordings, the degree of block increased with more positive holding potentials.

2. Block of voltage-dependent Ca^{2+} channels. Phenytoin at relatively low concentrations (3–30 μM) can produce a voltage- and frequency-dependent block of low-threshold (T-type) Ca^{2+} channels in neuroblastoma cells that is very similar to its action on Na^+ channels in that the degree of block is enhanced by depolarization and by repetitive activation (Twombly et al., 1988). (The role of T-type Ca^{2+} channels in epileptogenesis is discussed in detail in section IV, A, 1.) Furthermore, in hippocampal neurons, phenytoin has been shown to selectively reduce a low-voltage-activated, inactivating (although not fully characterized) voltage-dependent Ca^{2+} current (Yaari et al., 1987). However, the drug failed to produce a significant block of T-type Ca^{2+} currents in thalamic neurons except at supratherapeutic concentrations (Coulter et al., 1989c). In addition, in a variety of neural tissues, relatively high concentrations of phenytoin (20–200 μM) have been shown to reduce Ca^{2+}-dependent action potentials (McLean and Macdonald, 1983), to inhibit the uptake of Ca^{2+} presumably via non-T-type Ca^{2+} channels (Pincus and Lee, 1973; Hasbani et al., 1974; Pincus and Hsiao, 1981; Messing et al., 1985; Sohn and Ferrendelli, 1976; Crowder and Bradford, 1987), and to competitively inhibit dihydropyridine Ca^{2+} channel antagonist binding to brain and cardiac membranes (Greenberg et al., 1984; Yatani et al., 1986). The relevance of these effects on Ca^{2+} channels to the antiepileptic action of the drug is uncertain.

3. Synaptic actions. Phenytoin has been reported to depress excitatory transmission by both pre- and postsynaptic mechanisms and to augment synaptic inhibition. The presynaptic effects, i.e., depression of excitatory transmitter release (Gage et al., 1980), has been hypothesized to relate to the inhibition of Ca^{2+} entry into presynaptic terminals (Yaari et al., 1979; Crowder and Bradford, 1987), although more recently the emphasis has been on the presumed intermittent block of impulse conduction in presynaptic fibers consequent to the interaction with Na^+ channels (Yaari et al., 1986). Reports that iontophoretically applied phenytoin can inhibit the postsynaptic effects of excitatory amino acid neurotransmitters (Sastry and Phillis, 1976; Matthews and Connor, 1977) have been discounted because of the high concentrations required when attempts were made to replicate the experiments under conditions with controlled drug concentrations (Nicoll and Wojtowicz, 1980; McLean and Macdonald, 1983).

As considered in detail in section II, D, 1, potentiation of GABA-mediated inhibition can be an important mechanism of anticonvulsant action. There have been a number reports that phenytoin can enhance GABA-mediated synaptic inhibition or responses to exogenously applied GABA (Raabe and Ayala, 1976; Ayala and Johnston, 1977; Deisz and Lux, 1977; Aickin et al., 1981; McLean and Macdonald, 1983; Kaneko et al., 1988). However, other investigators have failed to observe such an action of the drug (Hershkowitz and Ayala, 1981; Connors, 1981; Nicoll and Wojtowicz, 1980; Gallagher et al., 1981). McLean and Macdonald (1983) pointed out that when effects on GABA responses occur it is only at concentrations substantially higher than those that block sustained repetitive firing. In any case, because phenytoin has a different spectrum of anticonvulsant activity from the benzodiazepines (section III, C, 1) and vigabatrin (section V, C, 1) for which the evidence for a GABA-dependent mechanism is much stronger, it is unlikely that effects of phenytoin on GABA systems are significant factors in its anticonvulsant activity.

4. Special considerations applicable to the epileptic brain. Although the bulk of evidence supports the view that voltage-dependent Na^+ channels are the critical target at which phenytoin exerts its antiepileptic action,

consideration of several additional factors relating to the pathophysiology of the epileptic brain can help to refine our understanding of the therapeutic action of the drug (Yaari et al., 1986). As discussed above, repetitive activation of excitatory synapses can facilitate the efficacy of synaptic transmission as a result of phenomena like PTP. In contrast, there is no evidence that inhibitory synapses in the vertebrate CNS undergo such plasticity and, in fact, synaptic depression is more commonly the rule (Alger, 1985). Thus, during the evolution of a seizure discharge characterized by sustained, high-frequency neuronal firing, endogenous inhibitory mechanism are progressively depressed while recurrent synaptic excitation is enhanced: a sure recipe for an explosive (regenerative) discharge. In the same way that phenytoin-induced conduction block would limit recurrent excitation, the drug would favor the maintenance of intact inhibitory systems, thus stabilizing the neuronal network.

Another factor that has been emphasized by Yaari et al. (1986) is the ability of high external K^+ to facilitate the frequency-dependent block produced by phenytoin (Adler et al., 1986). [High K^+ depolarizes neurons and reduces the amplitude of K^+-dependent hyperpolarizing potentials, such as the spike afterhyperpolarization, and these authors have proposed that the more positive membrane potential facilitates the Na^+ channel block produced by phenytoin and acts to prevent removal of inactivation; changing external K^+ does not appear to have a direct effect on Na^+ channels (Selzer et al., 1988).] Continuous high-frequency firing of neurons during epileptic seizures is known to lead to a slow accumulation of K^+ in the extracellular space (to levels as high as 8–12 mM; see review by Somjen, 1984). This elevation of extracellular K^+ could selectively enhance the action of phenytoin in epileptic brain regions. However, such an effect would only occur with prolonged seizure events because the increase in K^+ is slower in time course than the electrographic seizure event, so that the general applicability of this idea is uncertain.

5. Clinical efficacy. Phenytoin is an old, safe compound that rarely causes serious side effects. The main dose-related toxicities of the drug are nystagmus, ataxia, and incoordination, but these are not often a problem with serum levels in the usual therapeutic range. Disadvantages of phenytoin use include hirsutism, gingival hyperplasia, coarsening of the features, rarely peripheral neuropathy, and a teratogenic potential, including the fetal hydantoin syndrome. Phenytoin was marketed before controlled clinical trials were required. Its effectiveness against partial seizures and generalized tonic-clonic seizures is only anecdotally documented, although in a number of well-controlled studies phenytoin has been shown to be as effective as carbamazepine or valproate in the treatment of generalized tonic-clonic and partial seizures (Wilder and Rangel, 1989). In a large multicenter trial, phenytoin and carbamazepine were determined to be the two drugs of choice for the treatment of partial seizures (Mattson et al., 1985). Phenytoin is not efficacious in the treatment of absence or myoclonic seizures.

B. Other Hydantoins and Phenacemide

Following the discovery of phenytoin, a large number of hydantoins were synthesized and tested for anticonvulsant activity. Only two of these, mephenytoin and ethotoin, are currently marketed today, and these are used infrequently. Mephenytoin (3-methyl-5-ethyl-5-phenylhydantoin; fig. 1) is generally believed to be useful for the same clinical seizure types as phenytoin, although it has a somewhat different spectrum of anticonvulsant activity in animal seizure models (Kupferberg, 1989b). Like phenytoin, mephenytoin is active against tonic seizures in the maximal electroshock test. In addition, however, it can also increase the threshold for pentylenetetrazol-induced seizures, and, at high doses, it inhibits clonic seizures induced by bicuculline and picrotoxin. Mephenytoin is transformed into a number of metabolites, one of which, 5-ethyl-5-phenylhydantoin (Nirvanol), is more potent as an anticonvulsant than the parent (Kupferberg et al., 1978). Mephenytoin shares with phenytoin the dose-related side effects of nystagmus, diplopia, and ataxia but apparently does not cause hirsutism, gingival hyperplasia, or peripheral neuropathy (Troupin et al., 1976). Nevertheless, because of the high incidence of skin rashes and fatal aplastic anemia (Robins, 1962) as well as other idiosyncratic toxicities, its use is rarely warranted (Porter, 1989).

Ethotoin (3-ethyl-5-phenylhydantoin; fig. 1) has a similar anticonvulsant profile to mephenytoin in animal seizure models (Kupferberg, 1989b). Also like mephenytoin, ethotoin does not cause gingival hyperplasia or hirsutism and is generally well tolerated. The main disadvantage of the drug is its relatively low potency compared with phenytoin, although in uncontrolled trials the drug has shown promise (Carter et al., 1984).

Phenacemide (phenylacetylurea; fig. 1) is a ring-opened analog of phenytoin originally introduced as an antiepileptic by Gibbs et al. (1949). The use of phenacemide has been limited by the belief that it causes frequent idiosyncratic toxic reactions, including organ toxicity and personality changes (Troupin et al., 1976). However, in a recent study in 13 patients with refractory complex partial seizures, the drug was well-tolerated and efficacy results were encouraging (Coker et al., 1987). It remains to be determined whether control of plasma levels will prove to be useful in reducing the prominent toxic reactions to this drug so that it can be more widely used.

C. Carbamazepine

The iminostilbine carbamazepine (fig. 12) was the product of a structure-activity study carried out in the late 1950s to maximize the anticonvulsant activity of a series of iminodibenzyl derivatives (Kutt, 1989).

Carbamazepine and phenytoin have a similar spectrum of anticonvulsant activity in animal seizure models: both drugs selectively prevent tonic hindlimb extension in maximal electroshock seizures and both are ineffective against tonic seizures induced by pentylenetetrazol. At high doses (30 mg/kg, i.p.), carbamazepine reduces the severity and duration of amygdaloid-kindled seizures in rats (Höner, 1989; however, see Wada, 1977). The ED_{50} for carbamazepine in the mouse maximal electroshock test is 8.8 mg/kg, i.p. (Swinyard et al., 1989) and the rotorod TD_{50} is 72 mg/kg, giving a protective index (TD_{50}/ED_{50}) of 8.1, which is slightly higher than that of phenytoin. Also like phenytoin, carbamazepine is highly effective at protecting against the spread of activity from experimental spike foci and is less effective against the initiation of epileptic discharges within the focus (Julien and Hollister, 1975; David and Grewal, 1976). Nevertheless, the drugs have distinct pharmacological actions which is not surprising in view of their structural dissimilarity.

Carbamazepine is well known to have an active metabolite carbamazepine-10,11-epoxide (Kerr and Levy, 1989; fig. 12) which has a similar spectrum of anticonvulsant activity as the parent (Albright and Bruni, 1984; Bourgeois and Wad, 1984). In man, typical therapeutic serum levels of carbamazepine and carbamazepine epoxide are 4–12 μg/ml (17–51 μM) and 1.5 μg/ml (6 μM), respectively (Altafulla et al., 1989). For carbamazepine, CSF levels may range from 17–31% of the plasma concentration; CSF to plasma ratios for carbamazepine epoxide are higher, typically 45–55% (Morselli et al., 1989).

1. Block of voltage-dependent Na^+ channels. Like phenytoin, carbamazepine inhibits voltage-dependent Na^+ channels. This action was initially suggested by its depressant effect on action potentials recorded in a peripheral nerve preparation (Honda and Allen, 1973) and is compatible with its phenytoin-like effect on PTP (Hershkowitz et al., 1978). Like phenytoin, carbamazepine limits sustained high-frequency repetitive firing of cultured mammalian central neurons at clinically relevant concentrations (>4 μM). This effect, which is shared by carbamazepine-epoxide but not by the inactive derivative carbamazepine-10,11-dihydroxide, has been attributed to an effect on Na^+ channels (McLean and Macdonald, 1986a). Voltage-clamp studies have in large measure supported this view, but higher concentrations were required. Thus, carbamazepine at very high concentrations (250–1000 μM) was reported to reduce Na^+ currents recorded under voltage-clamp in *Myxicola* giant axons (Schauf et al., 1974) and at lower concentrations (30 μM) in neuroblastoma cells (Willow et al., 1985) and in mammalian myelinated nerve fibers (Schwarz and Grigat, 1989). As is the case for phenytoin, the Na^+ channel block was voltage and frequency dependent so that the degree of inhibition was enhanced at depolarized potentials and by repetitive activation of the channels. Like phenytoin, carbamazepine shifts the h_∞ curve for Na^+ currents to more negative membrane potentials and slows recovery from inactivation (Schwarz and Grigat, 1989). Therefore, carbamazepine is also believed to bind preferentially to inactivated Na^+ channels and to prevent the inactivated channels from undergoing the transition to the closed state from which they can reopen (Courtney and Etter, 1983). These electrophysiological observations have to some extent been supported in biochemical experiments. Thus, Willow and Catterall (1982) demonstrated that carbamazepine blocks [^{3}H]batrachotoxin binding to synaptosomes as does phenytoin. Although at normal resting potentials the interaction was weak (IC_{50}, 394 μM), the IC_{50} was three-fold lower (131 μM) when the synaptosomes were incubated under depolarizing conditions. In addition, carbamazepine produced a substantial block of batrachotoxin-activated $^{22}Na^+$ influx in cultured neuroblastoma cells and rat brain synaptosomes at more reasonable concentrations (K_i, 20–40 μM) (Willow et al., 1984). At therapeutic brain concentrations of 10–50 μM, Willow and Catterall estimated that approximately 25–50% of the receptor sites associated with Na^+ channels are occupied. This degree of block would only occur under strongly depolarized conditions as is presumably the case during a seizure.

Worley and Baraban (1987) have provided additional electrophysiological evidence that carbamazepine can interact with the batrachotoxin site on Na^+ channels at therapeutically relevant concentrations. These investigators demonstrated that veratridine and aconitine, drugs that activate Na^+ channels via an action at the batrachotoxin site, inhibit population spike responses recorded in the CA_1 pyramidal cell layer of the hippocampal slice preparation. Low concentrations of carbamazepine (10–30 μM) and a series of carbamazepine analogs were found to reverse the veratridine-induced suppression of the population spike. Moreover, the rank order of potencies of the analogs in this electrophysiological test system matched their abilities to inhibit [^{3}H]batrachotoxin binding to synaptosomes. In these electrophysiological experiments, carbamazepine was highly effective at concentrations well within the therapeutic range. The enhanced potency of the drug in reversing veratridine-induced suppression of Na^+ channels compared with its activity in the [^{3}H]batrachotoxin-binding assay is not understood but may, at least in part, relate to the voltage- and frequency-dependent properties of the carbamazepine interaction with Na^+ channels. In summary, these observations strongly support the concept that carbamazepine interacts with voltage-dependent Na^+ channels at therapeutic concentrations. Nevertheless, it cannot be stated with certainty that the anticonvulsant activity of the drug is specifically related to this effect. In fact, Olpe et al. (1985) pointed out that imipramine, an iminostilbine that is structurally related

to carbamazepine, is a more potent local anesthetic (Na^+ channel blocker) than carbamazepine yet fails to specifically affect epileptiform discharges at concentrations at which carbamazepine is strongly active. Similarly, many unrelated drugs including the phenothiazine and butyrophenone neuroleptics, certain adrenoceptor-blocking drugs, and antihistamines, are far more potent than carbamazepine as antagonists of [^{3}H]batrachotoxin binding yet fail to share carbamazepine's unique anticonvulsant activity (McNeal et al., 1985). Presumably, these drugs block Na^+ channels in a mechanistically different way from carbamazepine, although this remains to be demonstrated.

2. Interaction with adenosine receptors. Interest in the possibility that the anticonvulsant action of carbamazepine may relate to an interaction with adenosine receptors developed as a result of the observation of Lewin and Bleck (1977) that carbamazepine but not phenytoin or phenobarbital could inhibit adenosine stimulation of cyclic AMP accumulation in rat cortical slices. Subsequent studies using radioligand-binding techniques confirmed that at therapeutic concentrations carbamazepine was unique among commonly used anticonvulsants in its ability to displace the adenosine agonist [^{3}H]phenylisopropyladenosine from binding to rat brain membranes (K_i, 44 μM; Skerritt et al., 1982). Adenosine receptors in the CNS have been classified into two subtypes termed A_1 and A_2 depending upon whether agonist binding inhibits or stimulates, respectively, the formation of cyclic AMP (Williams, 1989). Despite the early studies indicating that carbamazepine could inhibit adenosine enhancement of cyclic AMP turnover, more recent binding studies have demonstrated that carbamazepine acts primarily on A_1 adenosine receptors labeled with the A_1-selective agonist [^{3}H]N^6-cyclohexyladenosine ([^{3}H]CHA; K_i, 24.5 μM; Marangos et al., 1983; Weir et al., 1984) and less so on A_2 adenosine receptors labeled with the A_2-preferring agonist [^{3}H]N-ethylcarboxamidoadenosine (K_i, 112 μM; Skerritt et al., 1983; Fujiwara et al., 1986). In fact, the inhibitory effect of carbamazepine on adenosine-induced cyclic AMP accumulation in brain slices occurs only at high concentrations (0.2–1 mM; Lewin and Bleck, 1977; Skerritt et al., 1983). Nevertheless, these results clearly demonstrate that, at least as far as the A_2 site is concerned, carbamazepine acts as an *antagonist*. The situation with regard to the A_1 site is less straightforward. Marangos et al. (1985) showed that chronically administered carbamazepine (oral route) produces a selective increase in adenosine receptors labeled with [^{3}H]CHA or the adenosine antagonist [^{3}H]diethylphenylxanthine in virtually all brain areas, supporting the concept that the drug acts as an antagonist (see also Marangos et al., 1987; Daval et al., 1989). Additional evidence in favor of an antagonist interaction derives from studies of the effect of GTP on the binding of carbamazepine. Several studies have demonstrated that GTP reduces agonist binding to adenosine receptors, whereas antagonist binding is unaffected by the nucleotide (Goodman et al., 1982; Yeung and Green, 1983; Lohse et al., 1984). Skerritt et al. (1983) reported that the potency of carbamazepine as an inhibitor of [^{3}H]phenylisopropyladenosine binding was unaffected by guanosine triphosphate, supporting its characterization as an antagonist (see also Weir et al., 1990). Moreover, Marangos et al. (1987) recently demonstrated that the temperature dependence of binding for carbamazepine to A_1 adenosine receptors labeled with [^{3}H]CHA is similar to that of adenosine receptor antagonists and differs from that of receptor agonists. Finally, in support of these neurochemical studies, Phillis (1984) demonstrated that adenosine-induced depression of neocortical neuron firing is reduced (at least in duration) by iontophoretically applied carbamazepine. Thus, the presently available data support the concept that carbamazepine is an antagonist of both adenosine receptor subtypes. In accord with this conclusion is the observation of Weiss et al. (1985) that adenosine antagonists fail to block the anticonvulsant effect of carbamazepine as they should if the anticonvulsant activity of carbamazepine were due to its action as an adenosine agonist.

The recognition that carbamazepine is an antagonist at both the A_1 and A_2 subtypes of adenosine receptors raises serious questions for the hypothesis that its anticonvulsant effects are mediated via an interaction with purinergic systems. Adenosine antagonists, such as the methylxanthines caffeine and theophylline, are potent CNS stimulants (Snyder, 1985) with proconvulsant and, at high doses, convulsant activity (Zwillich et al., 1975; Albertson et al., 1983a,b). This behavioral activity is presumably related to their ability to block the powerful inhibitory action of adenosine on excitatory neurotransmitter release (Dunwiddie, 1985) as well as to their antagonism of the direct depressant effect of adenosine on postsynaptic neurons (Trussell and Jackson, 1985; 1987; Dunwiddie and Fredholm, 1989). As expected, adenosine and metabolically stable adenosine receptor agonists have anticonvulsant activity in animals (Maitre et al., 1974; Dunwiddie and Worth, 1982; Albertson et al., 1983b; Barraco et al., 1984) and inhibit epileptiform activity in the hippocampal slice preparation (Dunwiddie, 1980). [Dunwiddie and Worth (1982) pointed out, however, that it is unlikely that adenosine agonists would be clinically useful as anticonvulsants because they elicit profound sedation even at doses that have relatively weak anticonvulsant effects.] Thus, despite the relatively high affinity of carbamazepine for adenosine receptors (compared, for example, to its affinity for voltage-dependent Na^+ channels), it would appear that the adenosine receptor-binding activity of the drug does not account for its anticonvulsant activity. In support of this conclusion is the observation of Marangos et al. (1983) that the anticonvulsant potencies of a series of carbamazepine ana-

logs failed to correlate with their binding affinities for adenosine receptors.

3. Effects on catecholamine systems. Carbamazepine's structural similarity to the iminodibenzyl tricyclic antidepressant imipramine suggests that the drugs might have similar pharmacological actions. Like imipramine, carbamazepine inhibits the uptake of [^{3}H]norepinephrine into synaptosomes at high concentrations (100 μM; Purdy et al., 1977); however, this effect could not be confirmed in in vivo studies (Quattrone et al., 1981).

4. Interaction with peripheral type benzodiazepine receptors. In a survey of the ability of carbamazepine to displace various radioligands from binding to rat brain membranes, Marangos et al. (1983) noted that peripheral type benzodiazepine-binding sites labeled with [^{3}H]Ro 5–4864 (4′-chlorodiazepam) were susceptible to competitive displacement at concentrations comparable to clinically effective therapeutic serum levels (K_i, 45 μM). Subsequently, Weiss et al. (1985) made the surprising observation that Ro 5–4864 could block the anticonvulsant effect of carbamazepine on amygdaloid-kindled seizures in rats. Moreover, the effect of Ro 5–4864 was itself reversed by PK-11195, an antagonist of peripheral type benzodiazepine receptors (Verma and Snyder, 1989). These observations have provided a tantalizing indication that peripheral type benzodiazepine receptors might mediate the anticonvulsant activity of carbamazepine. Interestingly, Weizman et al. (1987) observed that chronic carbamazepine treatment in human epileptic patients results in an upregulation of [^{3}H]PK-11195-binding sites on blood platelets. However, Marangos et al. (1985) failed to observe a statistically significant increase in [^{3}H]Ro 5–4864 binding in rats treated chronically with carbamazepine despite a marked increase in adenosine receptor binding.

The recognition that benzodiazepine binding to peripheral organs occurs via an acceptor site that is pharmacologically distinct from the CNS receptor that mediates the anticonvulsant and other well-known pharmacological actions of these drugs was made not long after the conventional (central type) benzodiazepine receptor was characterized using radioligand-binding methods (Braestrup and Squires, 1978). However, it has only recently been appreciated that peripheral benzodiazepine receptors are functionally active, both in the brain and in peripheral organs, and that specific peripheral benzodiazepine receptor ligands can exert a unique spectrum of pharmacological actions via their interaction with these acceptors (Saano et al., 1989).

In contrast to the anticonvulsant action of conventional benzodiazepine agonists (see section III, A), the peripheral benzodiazepine receptor agonist Ro 5–4864 exerts a proconvulsant action at low doses and can induce seizures at higher doses (Weissman et al., 1983; Bénavidès et al., 1984). Some but not all (see Weissman et al., 1985a,b) investigators have observed that the proconvulsant (Bénavidès et al., 1984; Dubroeucq et al., 1984) and even the direct convulsant (File, 1984; Seale et al., 1987) action can be reversed by the peripheral benzodiazepine receptor antagonist PK-11195, supporting the concept that Ro 5–4864 exerts its convulsant action, at least in some circumstances (particularly potentiation of audiogenic seizures), via an interaction with peripheral type benzodiazepine receptors. PK-11195 fails to protect against seizures in other animal seizure models, including those produced by maximal electroshock, pentylenetetrazol (Bénavidès et al., 1984), and picrotoxin (File, 1984). Moreover, Ro 5–4864 has been demonstrated to have an excitatory action on neuronal activity in several in vitro electrophysiological preparations (Skerritt et al., 1984; Weissman et al., 1984; Simmonds, 1985; Basile et al., 1989), although these have not been demonstrated to be reversed by PK-11195 (Basile et al., 1989). The PK-11195-insensitive (nonperipheral type benzodiazepine receptor-mediated) actions of Ro 5–4864 may be related to effects of the drug on the $GABA_A$ receptor-channel complex, either via a direct interaction of the drug with the Cl^- ionophore (Ticku and Ramanjaneyulu, 1984; Weissman et al., 1985a) or as a result of binding to an allosteric site that modulates opening of the Cl^- channel which, incidentally, is *distinct* from the central type benzodiazepine-binding site (Gee, 1987; Gee et al., 1988; see section III, A, 1).

In view of the multiple actions of Ro 5–4864, it is very difficult to come to a conclusion regarding the relevance of the interaction between carbamazepine and peripheral benzodiazepine receptors. In the study of Weiss et al. (1985), the proconvulsant effect of Ro 5–4864 could have resulted in "functional" antagonism of the protective effect of carbamazepine without specific receptor antagonism. In summary, although carbamazepine does appear to interact with brain peripheral type benzodiazepine receptors at therapeutically relevant concentrations, it remains to be proven that the anticonvulsant effects of the drug are related to this interaction. Thus, there is no single cellular action of carbamazepine that at present can be said to unequivocally account for its anticonvulsant activity; the working hypothesis implicating the phenytoin-like effect of the drug on voltage-dependent Na^+ channels is perhaps the most plausible.

5. Clinical efficacy. Carbamazepine was first evaluated for the treatment of epilepsy in the early 1960s (Loiseau and Duche, 1989a). Its effectiveness was demonstrated in several European clinical trials and later in two trials carried out in the United States. Rodin et al. (1974) conducted a double-blind, add-on study of carbamazepine in 37 patients. Carbamazepine reduced the frequency of complex partial seizures by 83% and of generalized tonic-clonic seizures by 55%. Cereghino et al. (1974) evaluated carbamazepine in a complex study design in which three groups of patients received phenytoin, phenobarbital, or carbamazepine. Carbamazepine

was shown to be as effective as the other two drugs in preventing partial and generalized tonic-clonic seizures. The study by Mattson et al. (1985) documents the equal efficacy of carbamazepine and phenytoin and shows that these two drugs cause less impairment in the patient's quality of life than do barbiturates (see also Meador et al., 1990). Carbamazepine is well tolerated by most patients and does not cause phenytoin-like hirsutism or gingival hyperplasia. In one study, it produced less behaviorial toxicity than phenytoin (Smith et al., 1987). Disadvantages of carbamazepine use include the risk of blood dyscrasias (an overstated fear) and its short half-life, which often requires a dosing three times a day. A recent report suggests that the teratogenicity of carbamazepine is similar to that of other antiepileptic drugs (Jones et al., 1989). For practical purposes, neither phenytoin nor carbamazepine is sedative so that they are much better tolerated in clinical practice than barbiturates.

D. Barbiturates

The barbiturates (alkyl or aryl 5-substituted derivatives of barbituric acid) produce a reversible depression of the CNS that can range from mild sedation to general anesthesia, depending upon the dose. As a consequence, the barbiturates were for many years used clinically as sedatives and hypnotics, until they were supplanted by the safer benzodiazepines. In addition to their depressant action, most barbiturates also have anticonvulsant activity, although some analogs can induce seizures (Skerritt and Macdonald, 1984). However, it is the capacity of certain barbiturates, such as phenobarbital (fig. 3), to exert maximal anti-seizure activity at doses below those that are markedly sedative or hypnotic that makes them clinically useful for epilepsy therapy. Thus, phenobarbital is active in most animal seizure models and has a broader spectrum of action than phenytoin in that it is able to protect against both electroshock and pentylenetetrazol-induced seizures (e.g., see Swinyard et al., 1952; Craig and Shideman, 1971; Killam, 1976) and is able to suppress amygdaloid-kindled seizures (Callaghan and Schwark, 1980). Phenobarbital protects against pentylenetetrazol seizures at dose of 10 mg/kg, p.o., in mice, whereas about twice the dose is required to prevent maximal electroshock seizures (Gallagher, 1989). The dose for motor toxicity in the rotorod ataxia test (TD_{50}) is 70 mg/kg and the hypnotic dose (HD_{50}) is 100 mg/kg.

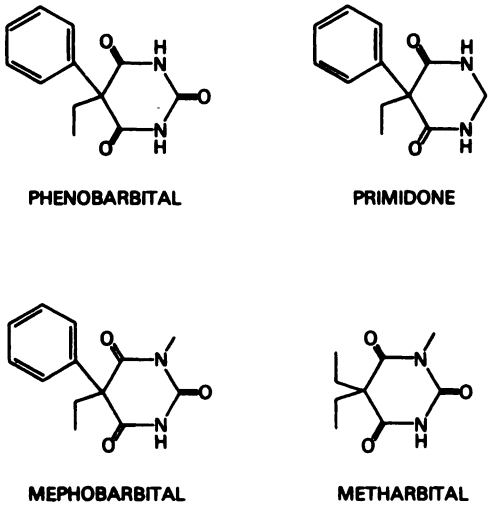


FIG. 3. Structures of representative barbiturates.

The deoxybarbiturate primidone (5-ethyldihydro-5-phenyl-4,6[1H,5H]-pyrimidine-dione; fig. 3) is a widely used antiepileptic drug that, in man, is metabolized primarily to phenylethylmalonamide and phenobarbital (Bourgeois, 1989). Phenylethylmalonamide has a similar spectrum of anticonvulsant activity to phenobarbital in that it is active against both maximal electroshock and pentylenetetrazol seizures but is 16–30 times less potent (Leal et al., 1979; Bourgeois et al., 1983). In contrast, primidone itself is nearly as potent as phenobarbital against maximal electroshock seizures but has little activity against pentylenetetrazol seizures, suggesting that it may act by a different mechanism (Bourgeois et al., 1983). The actual role of the parent and the two active metabolites in the clinical antiepileptic activity of primidone is difficult to determine (Bourgeois, 1989).

Like phenytoin, phenobarbital has a wide variety of pharmacological actions on neurons. Despite approximately 80 years of clinical use and a detailed understanding of the cellular mechanisms underlying the anesthetic properties of barbiturates, there is still no consensus as to why phenobarbital differs from other barbiturates in being more potent as an anticonvulsant than as a sedative. The depressant action of anesthetic barbiturates is believed to relate primarily to their ability to enhance GABA-mediated inhibitory responses by a specific interaction with the $GABA_A$ receptor-Cl^- channel complex (Olsen, 1988). Thus, barbiturates produce a powerful augmentation and prolongation of both presynaptic (Eccles et al., 1963; Miyahara et al., 1966; Nicoll, 1972) and postsynaptic (Nicoll et al., 1975; Nicoll and Wojtowicz, 1980; Curtis and Lodge, 1977; Wolf and Haas, 1977; Pickles and Simmonds, 1978; Scholfield, 1978; Tsuchiya and Fukushima, 1978) inhibition in a wide variety of systems. This action is specific for GABA responses mediated by $GABA_A$-type receptors (Newberry and Nicoll, 1985). In addition, barbiturates can enhance GABA-activated $^{36}Cl^-$ flux from brain slices (Wong et al., 1984; Yang and Olsen, 1987a) and cell-free systems (synaptoneurosomes: Schwartz et al., 1985; microsacs: Allan and Harris, 1986; Yu et al., 1988). Further discussion of the cellular mechanisms underlying the effect of barbiturates on $GABA_A$ receptor mechanisms is given in section II, D, 2.

1. Block of voltage-dependent Ca^{2+} channels. In addition to their effects on synaptic inhibition, barbiturates are also able to reduce depolarization-evoked neurotransmitter release in a wide variety of systems (Kalant and

Grose, 1967; Richter and Waller, 1977; Coleman-Riese and Cutler, 1978; Nicoll and Iwamoto, 1978; Potashner et al., 1980). This latter action is probably due to blockade of voltage-dependent Ca^{2+} channels in nerve terminals, and it has been shown that barbiturates can inhibit depolarization-stimulated Ca^{2+} influx into synaptosomes (Blaustein and Ector, 1975; Ondrusek et al., 1979; Leslie et al., 1980), inhibit the Ca^{2+}-dependent release of preloaded radiolabeled neurotransmitters from synaptosomes (Haycock et al., 1977), and reduce the maximal rate of rise and duration of Ca^{2+}-dependent action potentials (Heyer and Macdonald, 1982; Goldring and Blaustein, 1982). To more directly characterize the interaction with Ca^{2+} channels, barbiturate effects on Ca^{2+} currents recorded under voltage-clamp conditions have been studied in invertebrate (Nishi and Oyama, 1983a,b; Ikemoto et al., 1986) and vertebrate (Werz and Macdonald, 1985) neurons. It has been suggested that these studies of somatic Ca^{2+} channels may provide insight into events occurring at the nerve terminal. At high concentrations (typically 0.5–2 mM for phenobarbital), barbiturates produce a dose-dependent reduction in the peak Ca^{2+} current and accelerate its time-dependent decay (inactivation). The block of the current is greater with depolarization from more positive membrane potentials, indicating a higher affinity of the drug for the inactivated state of the channel in a manner comparable to phenytoin's block of Na^+ channels (section II, A, 1). The speeding of the decay could be due either to an allosteric enhancement of the inactivation mechanism of the channel or to an open channel block in which the drug diffuses into and binds to the ionophore of the channel when the ion gate is opened by depolarization. There are also effects on h_∞ of the channel (i.e., inactivation occurs at membrane potentials closer to resting potential; Ikemoto et al., 1986; Gross and Macdonald, 1988). These latter effects are presumably due to an allosteric mechanism.

Recently, a novel class of voltage-dependent Ca^{2+} channels, referred to as N-type, have been described in neurons (Nowycky et al., 1985). These N-type Ca^{2+} channels, which have different kinetic properties and voltage dependency from other Ca^{2+} channels in neurons, may be the predominant Ca^{2+} channel type responsible for Ca^{2+} influx and neurotransmitter release from nerve terminals (Miller, 1987). Gross and Macdonald (1988) reported that barbiturates selectively affect N-type (and L-type, but not T-type) Ca^{2+} currents in dorsal root ganglion cells, thus perhaps more precisely defining the way in which they suppress transmitter release. Recently, Gundersen et al. (1988) obtained similar results in studies of voltage-dependent Ca^{2+} channels expressed by injection of human brain (temporal lobe) mRNA into *Xenopus* oocytes. The Ca^{2+} currents recorded by these investigators were pharmacologically similar to N-type Ca^{2+} currents of dorsal root ganglion neurons (ω-conotoxin sensitive and dihydropyridine resistant). As in other systems that have been examined, barbiturates depressed the Ca^{2+} current amplitude, speeded its decay, and enhanced its steady-state inactivation. However, phenobarbital's inhibition of Ca^{2+} current occurs at concentrations higher than antiepileptic therapeutic brain levels and, in fact, the structural specificity of the effect in a series of barbiturates correlated poorly with the anesthetic potencies of the drugs (Olsen, 1988). Thus, whether effects on Ca^{2+} channels are important to either the anticonvulsant or CNS-depressant actions of barbiturates remains to be determined.

2. Potentiation of GABA-mediated inhibition. As discussed above, the anesthetic actions of barbiturates are believed to relate, in large measure, to the ability of these drugs to potentiate GABA-mediated inhibitory synaptic transmission. This concept is supported by the strong correlation between the anesthetic potency of barbiturates and their effects on GABA receptors as, for example, assayed by blockade of GABA-dependent $^{36}Cl^-$ uptake or by inhibition of [^{35}S]*t*-butylbicyclophosphorothionate binding to the ionophore portion of the GABA receptor-channel complex (Huidobro-Toro et al., 1987). (The interaction between barbiturates and [^{3}H]*t*-butylbicyclophosphorothionate binding is noncompetitive so that the fact that barbiturates affect binding does not imply that the barbiturate acceptor site is identical with the [^{3}H]*t*-butylbicyclophosphorothionate site.) These and a wide variety of other radioligand-binding data, particularly with detergent-solubilized GABA receptors (King et al., 1987), support the concept that barbiturates enhance GABA receptor activity by binding to a site that is physically located on the GABA receptor-channel complex (Olsen, 1988).

Electrophysiological studies have provided insight into the way in which barbiturates modulate GABA receptor function. Fluctuation (noise) analysis of GABA-activated Cl^- currents in cultured spinal cord neurons suggested that pentobarbital could increase the average duration of GABA-activated channel openings without affecting the single channel conductance (Barker and McBurney, 1979; Mathers and Barker, 1980). This conclusion was further refined with patch-clamp recordings of GABA-activated single channel currents (Mathers, 1985; Twyman et al., 1989; MacDonald et al., 1989). These studies demonstrated that GABA channels open in bursts interrupted by frequent brief flickers to a closed (nonconducting) state. (The flicker closings are probably not resolved with fluctuation analysis and therefore the mean open time estimates may correspond to the *burst* duration.) The barbiturates pentobarbital (Mathers, 1985; MacDonald et al., 1989) and phenobarbital (Twyman et al., 1989) increased the probability of channel opening and prolonged the duration of burst events, without affecting the single channel conductance (Mathers, 1987). The burst event may correspond to the period

in which the GABA receptor is occupied by agonist. In radioligand-binding studies it has been shown that barbiturates shift the GABA receptor to a state in which the affinity for GABA is increased and the rate at which GABA dissociates is decreased (Yang and Olsen, 1987b). It is plausible that, in the presence of barbiturates, the prolonged occupancy of the GABA receptor allows, on average, a greater number of channel openings to occur prior to dissociation of the agonist and termination of the burst.

Analysis of the interaction of barbiturates with $GABA_A$ receptors expressed from subunit-encoding cloned cDNAs is beginning to provide a picture of the molecular events that account for the barbiturate effect (Olsen and Tobin, 1990). To allow these elegant experiments to be carried out, the $GABA_A$ receptor was solubilized and partially sequenced, and synthetic oligonucleotide probes based upon peptide fragments of the native receptor protein were used to clone full-length cDNAs coding for subunits of the receptor. The $GABA_A$ receptor is an heterooligomeric complex consisting of at least two (α and β) and, in some cases, three (α, β, and γ) subunits (Pritchett et al., 1989b). cDNAs for each of the subunits have been cloned from a human fetal brain cDNA library. Functional GABA-activated Cl^- channels can be expressed when mRNA derived from the cloned subunit cDNAs are injected into *Xenopus* oocytes. Interestingly, pentobarbital potentiates responses to GABA when α- and β-subunits are coexpressed (Levitan et al., 1988a) or when either of these subunits is expressed singly (Blair et al., 1988), suggesting that a barbiturate-binding site is present on either subunit (or that the binding site can be formed by a multimer of identical subunits). [This is in contrast to the situation for benzodiazepines in which both the α and β subunits and a novel γ subunit are required to obtain benzodiazepine-binding activity (Pritchett et al., 1989b; see section III, A, 1).] Similar results have also been obtained when cloned $GABA_A$ receptor subunits were transiently expressed in human embryonic kidney cells (Pritchett et al., 1988). Potentiation appears to occur with binding of a single pentobarbital molecule. In the near future, it can be expected that the barbiturate-binding region of the subunits will be defined, and ultimately, it may be possible to specify the way in which barbiturates alter the protein's binding and gating properties.

3. Relevance of $GABA_A$ receptor interactions to anticonvulsant efficacy. Whereas the CNS-depressant effects of barbiturates almost certainly are due to their interaction with the $GABA_A$ receptor-Cl^- channel complex, the preferential ability of antiepileptic barbiturates to block seizures while producing relatively little sedation remains unexplained. In fact, in contrast to the anesthetic barbiturates, phenobarbital is relatively weak as a potentiator of GABA responses (Schwartz et al., 1985; however, see Schulz and Macdonald, 1981), and it has been suggested that the GABA actions are important to the depressant and not the anticonvulsant actions of the drugs (Allan and Harris, 1986). A somewhat different view has been proposed by Macdonald and Barker (1978b) based upon the observation of Barker and Ransom (1978b) (also reported by Nicoll and Wojtowicz, 1980) that barbiturates can directly activate Cl^- conductance in cultured neurons, even in the absence of GABA, by an action that does not involve the GABA recognition site (see also, Akaike et al., 1985; Akaike et al., 1987). Recently, it has been demonstrated that pentobarbital can directly activate $GABA_A$ receptor subunits expressed in *Xenopus* oocytes, conclusively showing that the barbiturate-induced Cl^- current specifically involves the GABA receptor-channel complex (Levitan et al., 1988a). Anesthetic barbiturates have been shown to be relatively (in comparison with GABA augmentation) more potent as direct agonists of Cl^- current than is phenobarbital. It has, therefore, been proposed that, whereas the anticonvulsant effects of barbiturates are related to GABA augmentation, it is GABA augmentation and the additional direct agonist activity of the anesthetic barbiturates that causes them to be such potent CNS depressants (Schultz and Macdonald, 1981). At present, however, the importance of the direct or modulatory effects on GABA receptor function in the clinical actions of antiepileptic barbiturates is uncertain.

4. Other effects on voltage-dependent ion channels. Barbiturates have been shown to interact with ion channel systems in excitable cells other than GABA-activated Cl^- channels and voltage-dependent Ca^{2+} channels. Of particular interest are the observations of Wilson and his colleagues that barbiturates at low doses and in a pharmacologically specific manner can enhance a voltage-dependent K^+ current in *Aplysia* neurons (Cote et al., 1978; Huguenard and Wilson, 1985). The result of this effect is to inhibit repetitive action potential firing by enhancing the normal process of spike frequency adaptation that depends upon the K^+ current (Zbicz and Wilson, 1981). Although a similar effect of barbiturates has as yet not been demonstrated in mammalian central neurons, certain structurally related antihypertensives can activate a comparable K^+ current in hippocampal neurons (Politi et al., 1989, and it has been proposed that K^+ channel activation could be a novel mechanism of antiepileptic drug action (Rogawski et al., 1990a; Zona et al., 1990).

At very high doses, barbiturates can block axonal conduction (Krupp et al., 1969; Staiman and Seeman, 1974; Vazquez et al., 1975; Nicoll and Iwamoto, 1978) and suppress somatic action potentials (Goldring and Blaustein, 1982) presumably by a local anesthetic type action on voltage-dependent Na^+ channels, but this effect is unlikely to be relevant to the clinical actions of the drugs.

5. Block of excitatory transmission. Ligand-gated cation

channels that mediate fast excitation of neurons may represent an important site of barbiturate action. Thus, at relatively low concentrations barbiturates can block both ganglionic (Nicoll, 1978; Nicoll and Iwamoto, 1978) and neuromuscular (Gage and McKinnon, 1985) nicotinic receptor channels and can inhibit responses mediated by excitatory amino acid receptors, with a preference for those of the non-NMDA type (Ransom and Barker, 1975; Nicoll, 1975; Nicoll and Wojtowicz, 1980; Teichberg et al., 1984; Miljkovic and MacDonald, 1986; Simmonds and Horne, 1988; Sivilotti and Nistri, 1989). The antiepileptic action of barbiturates obviously does not relate to the ganglionic or neuromuscular blocking actions of the drugs. However, the effects on central excitatory amino acid transmission cannot be dismissed as easily. Barbiturates have been reported to potentiate the anticonvulsant effects of the excitatory amino acid antagonist MK-801 (section V, E, 3), whereas diazepam, which also augments GABAergic neurotransmission, was inactive (Kulkarni and Ticku, 1989). These results are not inconsistent with the idea that the potentiating effect resulted from an action on excitatory amino acid-mediated responses. Moreover, in contrast to its relatively weaker effects on GABA receptor-mediated responses and voltage-sensitive Ca^{2+} channels, phenobarbital is equipotent to the anesthetic barbiturates pentobarbital and secobarbital in inhibiting excitatory amino acid responses (Gage et al., 1986). These data are compatible with the idea that the relatively greater anticonvulsant activity of phenobarbital in comparison with its depressant action resides, at least in part, in its ability to block excitatory transmission. Nevertheless, it should be recognized that, in contrast to the potent anticonvulsant effects of NMDA receptor antagonists (section V, E), drugs like the barbiturates that preferentially block non-NMDA receptors typically fail to show substantial anticonvulsant activity in animal seizure models. Clearly, further studies of the effects of phenobarbital on excitatory amino acid receptor systems and the relationship of these effects to anticonvulsant activity are required.

In conclusion, in the normal brain, the main actions of barbiturates at clinically relevant concentrations are on synaptic transmission: GABA-mediated inhibition is enhanced and glutamate-mediated excitation may be depressed. Effects on voltage-dependent K^+ and Ca^{2+} channels may also be of importance, but further research is needed to clarify the role of these effects. However, an answer to the central question regarding the differences between the mode of action of the anticonvulsant and sedative-anesthetic barbiturates will probably require a greater understanding of the physiology of epileptic brain. For example, conditions within epileptic brain could preferentially enhance the activity of the normally relatively weak anticonvulsant barbiturates. Prichard and Ransom (1989) pointed out that during an epileptic seizure conditions within the brain may be more acidic than normal. Because the ring nitrogens of phenobarbital are stronger acids (pK_a 7.3) than the nitrogens in other barbiturates (the electron-withdrawing character of the phenyl group tends to increase the electronegativity of the nitrogens), at more acidic pH, the proportion of phenobarbital molecules in the uncharged (protonated) state would be greater. Because the uncharged form is probably the active one, at low pH, the phenobarbital concentration is effectively increased; other barbiturates with higher pK_a values would not gain this advantage. Clues to potential differences between the anticonvulsant and sedative actions may also be found in the well-known clinical observation that tolerance to the sedative effects of barbiturates is greater than that to the antiepileptic effect.

6. Clinical efficacy. Phenobarbital was the first antiepileptic drug marketed in this century. After its introduction in 1912, phenobarbital largely replaced the toxic bromide salts which previously were the mainstays of epilepsy therapy. Clinical studies that prove the efficacy of barbiturates are limited because the drug was not scrutinized by the current regulatory process prior to marketing. This dilemma is well stated by Painter (1989) who noted that "the choice of phenobarbital for the treatment of neonatal seizures is not based on its proven superiority as an anticonvulsant agent but on tradition and many years of familiarity. . . ." The same could be said for the use of this drug in almost every other seizure type for which it may be indicated. Although the drug is used for generalized tonic-clonic and partial seizures in both children and adults, and for most neonatal seizures, its reputation has become tarnished in recent years because of its sedative and behavioral side effects. There is substantial evidence that the drug has deleterious effects on general intelligence, perceptual motor and memory function, and behavior. In a study by Vining et al. (1987), 21 children with epilepsy were given, in a double-blind crossover design, either phenobarbital or valproate. Therapeutic plasma levels of each drug were maintained for 6 months. Detrimental effects on Wechsler Intelligence Scale results and other performance test scores during phenobarbital administration documented that phenobarbital more strongly interfered with mental function than did nonsedative antiepileptic drugs. In another study, children treated with phenobarbital had a much higher prevalence of major depressive disorders than those treated with carbamazepine (Brent et al., 1987). However, Mitchell and Chavez (1987) reported no psychometric or behavioral differences between children receiving carbamazepine and phenobarbital, and, in a randomized double-blind crossover study in 15 adult patients with complex partial seizures, Meador et al. (1990) observed only subtle effects of phenobarbital on neuropsychological performance in comparison with carbamazepine and phenytoin. Recently, Farwell et al. (1990), in a long-term double-blind study of children

with febrile seizures, reported that phenobarbital caused a significant (8.4 point) depression in cognitive performance as measured in an intelligence test without providing any prophylaxis for the development of subsequent seizures. Metabolic studies using positron emission tomography have documented that, even at therapeutic doses and serum levels, phenobarbital depresses human cerebral glucose metabolism (Theodore et al., 1986a) much more than does phenytoin (Theodore et al., 1986b). The clinical importance of this depression is uncertain, although it is tempting to infer a relationship to the adverse neuropsychological effects of the drug. Theodore and Porter (1983) removed all sedative antiepileptic drugs from 78 patients with severe epilepsy. Seizure frequency actually improved in some patients, and only one patient was worse. Toxicity was decreased in 46 patients (59%), with improvements noted in diplopia, ataxia, daytime sleepiness, and behavior problems. This study shows that sedative antiepileptic drugs are not necessary for optimal seizure control, even in severely affected patients, and that the removal of such drugs from the regimen may decrease medication toxicity.

Barbiturates marketed for epilepsy other than phenobarbital include primidone (section II, D), mephobarbital (N-methylphenobarbital; fig. 3), and metharbital (N-methylbarbital; fig. 3) (Eadie, 1989). Primidone and mephobarbital have phenobarbital as a major metabolite (Porter, 1989), which complicates the interpretation of their clinical advantages. Metharbital, which is metabolized to barbital, is said to have greater sedative and less antiepileptic activity than phenobarbital (Rall and Schleifer, 1980). Its relative efficacy compared with other antiepileptic drugs is unknown.

III. Drugs with a Broad Spectrum of Clinical Antiepileptic Activity

A. Benzodiazepines

The benzodiazepines (fig. 4) are potent anticonvulsants in a wide variety of animal seizure models. The drugs are particularly effective against pentylenetetrazol-induced seizures but are also effective against other chemically induced seizures including those induced by picrotoxin and flurothyl, in various focal seizure models including those induced by alumina or strychnine, in reflex epilepsies such as those occurring in photosensitive baboons or audiogenic mice, in kindled seizures, and in absence-like seizures occurring in the tottering mutant mouse (Swinyard and Castellion, 1966; Reinhard and Reinhard, 1977; Heller et al., 1983; Swinyard et al., 1989). At higher doses, the drugs block maximal electroshock seizures and those induced by systemic strychnine. More than 50 chemically distinct benzodiazepines are marketed worldwide. Although pharmacokinetic differences exist among individual drugs and relative potencies may vary in the different anticonvulsant screens, they all show a similar anticonvulsant profile which is presumed to relate to their common mechanism of action: facilitation of GABA-mediated synaptic inhibition in the CNS. Thus, for the prototype benzodiazepine diazepam, the ED_{50} for protection against pentylenetetrazol seizures in mice is 0.3 mg/kg, p.o., whereas the corresponding value in the maximal electroshock test is 19 mg/kg. In the case of diazepam, motor incoordination is produced at higher doses than are required to protect against seizures in either of the two anticonvulsant screens (TD_{50}, 57 mg/kg), although the separation between the anticonvulsant and toxic doses is obviously far greater for the pentylenetetrazol test than for the maximal electroshock test. For clonazepam, however, the maximal electroshock ED_{50} (78 mg/kg) is greater than the TD_{50} (3.4 mg/kg) which is far greater than the pentylenetetrazol ED_{50} (0.06 mg/kg) (Swinyard et al., 1989). The reason why there are relative potency differences between benzodiazepines is not known.

1. Potentiation of GABA-mediated inhibition. The ability of benzodiazepines to potentiate GABAergic neurotransmission was discovered in the mid-1970s by Haefely (1975). Subsequently, the existence of high-affinity, saturable, binding sites for benzodiazepines (referred to as "benzodiazepine receptors") were identified in brain membranes by radioligand-binding techniques (Squires and Braestrup, 1977; Möhler and Okada, 1977). The role of these binding sites in the anticonvulsant actions of benzodiazepines was supported by the high correlation between the anticonvulsant potencies of benzodiazepine receptor agonists in animal seizure models and their affinities for the binding site in vitro (Möhler and Okada, 1977). Further supportive evidence was provided by in vivo experiments showing that occupancy of central benzodiazepine receptors by diazepam correlated very closely with protection against pentylenetetrazol-induced seizures (Paul et al., 1979). Interestingly, only a relatively small fraction (<30%) of benzodiazepine receptors need to be occupied to manifest maximal seizure protection. Perhaps the strongest evidence supporting the involvement of benzodiazepine receptors in the anticonvulsant activity of benzodiazepines is provided by studies with the benzodiazepine receptor antagonist flumazenil (Ro 15–1788) which has been shown to block the anticonvulsant effects of diazepam against pentylenetetrazol-induced seizures in rats (Nutt et al., 1982), to attenuate the anticonvulsant action of diazepam in epileptic chickens (Pedder et al., 1987) and in amygdaloid-kindled rats (Albertson et al., 1982), and to block the anticonvulsant effect of flurazepam in rats (Bourn et al., 1985). The action of flumazenil is specific in that it does not reduce the anticonvulsant effects of phenobarbial, valproate, or progabide (section V, B; Nutt et al., 1982). However, it should be noted that flumazenil may have some antiepileptic activity by itself at high doses due to weak partial agonist activity at benzodiazepine receptors (Nutt et al., 1982; Albertson et al., 1982; File and Pellow, 1986; Scollo-

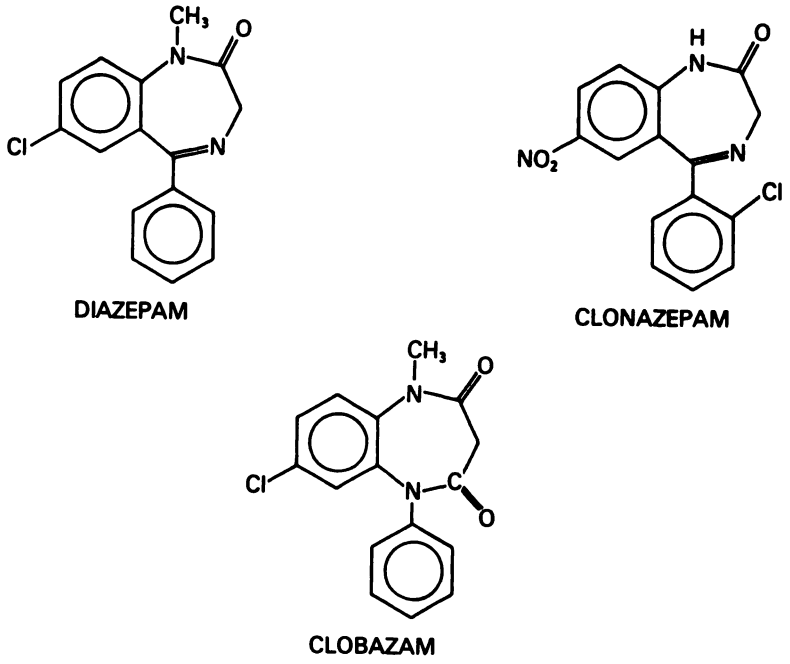


FIG. 4. Structures of representative benzodiazepines.

Lavizzari, 1984, 1988). This presumably accounts for its antiepileptic activity in human seizure disorders (section V, D, 2). It has been observed that benzodiazepine receptor number is transiently increased after either electroshock, pentylenetetrazol-induced or kindled seizures (Paul and Skolnick, 1978; McNamara et al., 1980), but the significance of this observation is unknown.

A wide variety of evidence supports the concept that the central type benzodiazepine receptor is a component of the $GABA_A$ receptor complex. In electrophysiological studies, benzodiazepines potently enhance synaptically mediated GABAergic inhibition as well as responses to exogenously applied GABA (Haefely, 1983). Moreover, the blockade by GABA antagonists (picrotoxin or bicuculline) of certain direct electrophysiological actions of benzodiazepines (e.g., depression of neuronal firing in the brainstem) further supports a link between benzodiazepines and GABA systems. Recordings from cultured neurons have allowed a detailed analysis of the pharmacological actions of benzodiazepines on GABA responses. Extracellular application of GABA stimulates an increase in Cl^- permeability that is mediated by the opening of Cl^--selective channels (Barker and Ransom, 1978a). Benzodiazepines reliably augment GABA responses without affecting responses to other inhibitory amino acids such as glycine, β-alanine, or taurine that are also mediated by Cl^--selective channels (Choi et al., 1977; Macdonald and Barker, 1978a). The augmentation is due to a shift to the left of the GABA dose-response curve; there is no alteration in the maximal GABA response, indicating that the sensitivity to GABA is increased without an increase in the total number of available Cl^- channels (Choi et al., 1981). Although the enhancement of GABA responses occurs with relatively low benzodiazepine concentrations (the drugs have a high potency), the maximal potentiation observed is modest (about two-fold) and substantially less than that produced by barbiturates. Studies with fluctuation analysis (Study and Barker, 1981) and single channel (patch-clamp) recording (Twyman et al., 1989) have demonstrated that benzodiazepines increase the frequency of channel opening, without affecting the single channel conductance or the burst duration. In contrast, the effect of barbiturates on GABA channels is to prolong burst duration without increasing burst frequency (section II, D, 2).

Molecular cloning and heterologous expression of the $GABA_A$ receptor subunits (section II, C, 1) have provided insight into the nature of the benzodiazepine receptor. The affinity-purified, detergent-solubilized $GABA_A$ receptor was initially characterized as consisting of two distinct subunits (α and β) (Casalotti et al., 1986). The smaller α-subunit (M_r, 48,000–53,000) was labeled by the benzodiazepine photoaffinity ligand [^{3}H]flunitrazepam and, therefore, was believed to bear the benzodiazepine-binding site (Möhler et al., 1980). DNA cloning has revealed the existence of three different α-subunit variants (Schofield et al., 1987; Levitan et al., 1988b). Surprisingly, the four individual subunits can by themselves each form functional $GABA_A$-sensitive ion channels with properties similar to the native receptor (Blair et al., 1988). However, not even the coexpression of α- and β-subunits together is sufficient to reconstitute receptors that express binding sites for benzodiazepines or that show substantial benzodiazepine-induced potentiation of GABA-activated Cl^- current (Pritchett et al., 1988; Lev-

itan et al., 1988a; Olsen and Tobin, 1990). In fact, a new $GABA_A$ receptor subunit, termed γ_2 ($M_r \sim 48{,}000$), which shares approximately 40% sequence identity with the α- and β-subunits, has recently been cloned, and coexpression of this subunit together with α- and β-subunits (in cultured human embryonic kidney cells) results in a completely functional receptor that possesses benzodiazepine-binding sites and shows the appropriate benzodiazepine responsiveness in voltage-clamp experiments (Pritchett et al., 1989b). These results suggest that all three subunits (α, β, and γ_2) are an integral part of the native GABA receptor-channel complex (at least for those GABA receptors that are benzodiazepine sensitive) and they call into question the localization of the benzodiazepine-binding site to the α-subunit. A further twist has been introduced by the discovery that GABA receptors consisting of different α-subunits (i.e., $\alpha_1\beta_1\gamma_2$, $\alpha_2\beta_1\gamma_2$, $\alpha_3\beta_1\gamma_2$) can have distinct pharmacological properties (Pritchett et al., 1989a). Thus, receptors of the composition $\alpha_1\beta_1\gamma_2$ had a higher binding affinity for the triazolopyridazine CL 218,872, an anticonvulsant nonbenzodiazepine, that binds to benzodiazepine receptors (type I) but which may cause less sedation than do benzodiazepines. Drugs targeted specifically to this receptor variant have the potential of being more clinically useful as anticonvulsants than the benzodiazepines. The cloning and expression of fully functional $GABA_A$ receptors now sets the stage for further definition with subunit-specific antibodies and site-directed mutagenesis of the molecular details underlying the modulatory effect of benzodiazepines.

2. Chronic effects. Although benzodiazepines are clinically valuable for the acute treatment of status epilepticus, the development of tolerance limits their practical usefulness in chronic epilepsy therapy. Benzodiazepines are also well known to cause physical dependence so that withdrawal symptoms may occur when they are discontinued. Further work will be needed to define the cellular events responsible for these phenomena. Some evidence, however, supports the idea that changes in the $GABA_A$ receptor complex produced by chronic exposure to benzodiazepines is responsible, at least in part, for the tolerance and dependence. Chronic benzodiazepine treatment produces a decrease in the functional activity of benzodiazepine receptors as determined by the ability of benzodiazepines to enhance GABA-mediated Cl^- flux in rat brain microsacs (Yu et al., 1988; Marley and Gallager, 1989). Some (Miller et al., 1988a) but not all (Gallager et al., 1984) studies have found an associated reduction in the number of benzodiazepine-binding sites. Thus, at present, it is uncertain whether the functional reduction reflects a receptor alteration or a change in the coupling between the benzodiazepine recognition site and GABA receptor-channel complex (Heninger and Gallager, 1988). In addition, several studies have demonstrated that chronic benzodiazepine administration can reduce the sensitivity of neurons to GABA (Gallager et al., 1984; Wilson and Gallager, 1988; Marley and Gallager, 1989), but it is not clear that this effect reflects a change in the GABA/benzodiazepine receptor per se (Yu et al., 1988).

Withdrawal of benzodiazepines results in a delayed increase in benzodiazepine receptor binding and in GABA agonist-stimulated Cl^- flux (Miller et al., 1988b), indicating that the withdrawal syndrome may also be related to changes occurring in the GABA receptor complex. Examination of the cloned GABA receptor should make it possible to better define the molecular changes that occur with chronic benzodiazepine treatment and this understanding may suggest strategies to interdict the development of tolerance and dependence. In fact, recent observations suggest that there are differences in the tolerance profiles of various benzodiazepines receptor agonists (Garratt et al., 1988) and certain drugs, particularly those that are partial agonists, may exhibit little in the way of tolerance. Thus, Haigh and Feely (1988) have reported that no anticonvulsant tolerance developed (in the mouse pentylenetetrazol model) to the imidazodiazepinone benzodiazepine receptor partial agonist Ro 16–6028. Similar results have also been obtained with the anticonvulsant benzodiazepine receptor ligand DN-2327, a non-benzodiazepine that has a 20-fold higher affinity for the benzodiazepine receptor than diazepam (Wada et al., 1989).

The most common side effects encountered with benzodiazepine treatment are drowsiness, dysequilibrium, and behavioral and personality changes (Sato, 1989). Although tolerance to these sedative and behavioral effects often develops with chronic treatment, some patients must discontinue treatment because they remain persistent problems. Recently, it has been observed that partial benzodiazepine receptor agonists are less sedative and produce fewer behavioral changes in rats than do full agonists yet have equivalent anticonvulsant activity (Coenen and van Luijtelaar, 1989). Although these animal studies suggest that partial benzodiazepine agonists may be superior to full agonists for chronic epilepsy therapy, this remains to be demonstrated in human subjects.

3. Non-benzodiazepine receptor-mediated actions. Benzodiazepines can produce a variety of effects on neurons that are unrelated to their interaction with the GABA receptor-Cl^- channel complex. These actions include inhibition of adenosine uptake and blockade of Na^+ and Ca^{2+} channels (see Haefely, 1989, for review). As discussed above, there is strong evidence linking the anticonvulsant activity of benzodiazepines to a specific interaction with benzodiazepine receptors of the type coupled to the GABA receptor. Perhaps the most serious challenge to this concept concerns the anticonvulsant activity of benzodiazepines in absence seizure models (Fariello and Ticku, 1983). Numerous animal studies have demonstrated that $GABA_A$ receptor agonists or

drugs that elevate brain GABA levels can worsen absence-like seizures or can even induce epileptiform activity de novo (Scotti de Carolis et al., 1969; Pedley et al., 1979; Myslobodsky et al., 1979; Fariello et al., 1981; Golden and Fariello, 1984; Fariello and Golden, 1987). For example, in rats with spontaneously occurring spike wave seizures, Marescaux et al. (1985) have shown that the GABA agonist THIP or the GABA-T inhibitors vigabatrin (section V, C, 1) or L-cycloserine markedly increase the total time the animals experience absence-like seizures. In contrast, diazepam abolishes spontaneous seizures in these animals and can also completely eliminate the aggravated seizures in animals treated with THIP or the GABA-T inhibitors. These results suggest that the antiabsence activity of diazepam, at least in the animal models, is not dependent upon the drug's ability to augment GABA-mediated inhibition. At present it is unclear which, if any, of the non-benzodiazepine receptor-mediated actions of the drug noted above might account for its antiabsence activity.

4. Clinical efficacy. The clinical use of benzodiazepines can be conveniently divided into two categories. First, the drugs are often given intravenously in the acute treatment of seizures, especially status epilepticus but also occasionally for febrile seizures. Second, the drugs are utilized in the long-term therapy of certain seizure types. For the acute management of seizures, the most widely used benzodiazepine is diazepam because high levels in the brain are rapidly obtained during intravenous administration; however, lorazepam, which has a speed of onset approximately equivalent to that of diazepam and a more prolonged duration of action, is gaining acceptance (Homan and Unwin, 1989). Other benzodiazepines such as clonazepam are also effective in the treatment of the various forms of status epilepticus (Sato, 1989). Diazepam in not useful for chronic therapy because it is difficult to obtain stable blood levels with intermittent dosing. For chronic therapy, nitrazepam is most commonly used, although it is not presently approved for sale in the United States; clonazepam is the second most popular drug.

Diazepam is usually quite safe and is very effective when administered intravenously for the treatment of convulsive status epilepticus, a life-threatening condition. The drug will abort seizures of almost every type and has been reported to stop initial seizure activity in 88% of patients with various types of status epilepticus (Schmidt, 1989b). The duration of its effectiveness is limited; for status epilepticus one cannot expect the drug to be effective for more than 1 hour, and more definitive measures must be taken in the interim (Porter, 1989). Lorazepam, which is preferred by some investigators and clinicians, is probably no more effective than diazepam, although some studies suggest that it causes less cardiorespiratory depression and has a longer duration of action (Homan and Walker, 1983). These differences do not appear to be pronounced (Crawford et al., 1987b). Benzodiazepines are also used, primarily in the pediatric population, for the acute treatment of clusters of seizures that are resistant to other antiepileptic drugs and in the prophylaxis of febrile seizures. Many epileptologists are finding that rectal diazepam is effective in such cases (Graves and Kriel, 1984).

Chronic epilepsy therapy with benzodiazepines is controversial because of the problems of tolerance and sedation (section III, A, 2). The drugs are most often used in the treatment of absence seizures, the Lennox-Gastaut syndrome, and the myoclonic epilepsies. They are less useful than other presently marketed antiepileptic drugs but are probably effective in the treatment of generalized tonic-clonic seizures, complex partial seizures, simple partial seizures, and other miscellaneous seizure types (Sato, 1989). However, the toxic effects of the benzodiazepines are similar to and at least as severe as those of phenobarbital. For example, in a study with clonazepam the most common side effects were drowsiness and ataxia, as well as behavioral and personality changes (Sato, 1989). Respiratory tract secretions may also increase. Of the 37 patients evaluated, 10 could not complete the study because of side effects of the drug. Nitrazepam is less potent and may be slightly less toxic, but the reported side effects are fundamentally the same as for clonazepam (Baruzzi et al., 1989). Clorazepate, which is converted rapidly and completely to the active metabolite N-desmethyldiazepam, appears to offer little advantage over other benzodiazepines (Wilensky and Friel, 1989; Porter, 1989). The 1,5-benzodiazepam clobazam is considered in section V, D, 1.

B. Valproate

Valproate (di-N-propylacetate), a branched fatty acid, is a colorless liquid whose anticonvulsant activity was fortuitously discovered when it was used as a solvent in a drug-screening program. Although initially identified on the basis of its ability to protect against pentylenetetrazol seizures, valproate was subsequently demonstrated to have a broad spectrum of anticonvulsant activity in a wide variety of animal seizure models (see Chapman et al., 1982; Löscher and Schmidt, 1988, for references). The drug is active against tonic and clonic seizures induced by a variety of chemoconvulsants in addition to pentylenetetrazol, including bicuculline, picrotoxin, 3-mercaptopropionic acid, isonicotinic acid, semicarbazide, strychnine, penicillin, and aminophylline (Bartoszyk et al., 1986b), and it is also active in the maximal electroshock test, against reflex seizures, and in the kindling model. However, valproate is only weakly protective against seizures induced by excitatory amino acids (Chapman et al., 1982; Ferrendelli, 1989). Although valproate is highly effective in preventing the spread of seizures from a cortical (cobalt or alumina) lesion or from a site of kindling, it has little or no activity against epileptiform discharges occurring within the focus itself

(Fariello and Smith, 1989). In this respect it resembles phenytoin, although valproate's much wider spectrum of anticonvulsant activity suggests a different mechanism of action.

An unusual characteristic of valproate is the high doses that are required to obtain anticonvulsant effects (e.g., 150–400 mg/kg, i.p., in mice; Chapman et al., 1982; Ferrendelli et al., 1989). This property does not appear to be due to its failure to penetrate the blood-brain barrier less well than other antiepileptic drugs because the fraction of serum levels detected in the CSF (equivalent to the free serum levels) is approximately the same as that for phenytoin (~10%; Levy and Shen, 1989). Another characteristic of valproate is that in animals the drug causes motor toxicity at doses that are close to those required to protect against seizures. Thus, for the maximal electroshock test (ED_{50}, 272 mg/kg, i.p., in mice), the protective index (TD_{50} for motor toxicity/ED_{50}) is only 1.6 compared to a value of 6.9 for phenytoin (Swinyard et al., 1989). Nevertheless, valproate is well tolerated in man and toxic side effects are rare in clinical practice. The generally accepted therapeutic range in plasma is 50–100 μg/ml (350–700 μM), although in animals higher (up to 200–500 μg/ml) plasma levels are often necessary for anticonvulsant activity (Chapman et al., 1982). Assuming 90% protein binding, concentrations in the extracellular space (equivalent to CSF levels) during valproate therapy in man are approximately 35–70 μM. At higher serum concentrations, valproate begins to saturate the available binding sites on serum albumin so that the proportion of free valproate increases and CSF levels may rise to 200 μM.

As a fatty acid, valproate enters several pathways of lipid metabolism resulting in the formation of a large number of metabolites (Baillie and Rettenmeier, 1989), some of which have anticonvulsant properties in their own right (Löscher et al., 1984; Löscher and Nau, 1985). In this regard, the mono-unsaturated metabolites are the most active, with the 2-en (*trans* isomer) and 4-en species having anticonvulsant activity comparable to valproate itself. Of all the metabolites, only 2-en-valproate is found in measurable quantities in brain (Nau and Löscher, 1982). This metabolite is cleared from brain tissue and plasma more slowly than valproate and may accumulate with prolonged treatment, thus accounting for the slow reversibility of the anticonvulsant effect produced by prolonged valproate treatment. This view has recently been questioned, however, with the finding that CSF (Löscher et al., 1988a) and brain (Levy and Shen, 1989) levels of 2-en-valproate in humans are too low to provide a substantial anticonvulsant effect.

Two general hypotheses have been proposed to explain the antiepileptic activity of valproate. The first of these proposes that valproate acts by enhancing GABA-mediated inhibition and relies primarily on data demonstrating that the drug increases brain GABA levels. The second hypothesis posits a phenytoin-like effect of valproate on voltage-dependent Na^+ channels. We consider the evidence for each of these hypotheses in turn.

1. Effects on GABA systems. Administration of valproate to mice (200 mg/kg, i.p.) causes an increase in whole brain and nerve terminal (synaptosomal) GABA (Godin et al., 1969; Löscher, 1981a,b; Poisson et al., 1984). In some (Kupferberg et al., 1975; Nau and Löscher, 1982) but not all (Anlezark et al., 1976; Kerwin and Taberner, 1981) studies the elevation in GABA levels was temporally correlated with the drug's anticonvulsant activity. There is an increase in plasma and CSF levels of GABA in patients being treated with the usual clinically effective doses of valproate (Löscher and Schmidt, 1980, 1981; Löscher and Siemes, 1984), which is compatible with the idea that effects on GABA metabolism may be relevant to the antiepileptic activity of the drug in human subjects. In this regard, it is interesting to note that there is an approximate correlation between the ability of valproate analogs to elevate GABA levels and their anticonvulsant potencies (Chapman et al., 1983), although one analog has been found that possesses anticonvulsant activity but does not affect GABA levels (Keane et al., 1983). The mechanism by which valproate increases GABA levels is not well understood. The drug inhibits several enzymes involved in GABA degradation, including GABA-T (Godin et al., 1969; Fowler et al., 1975; Löscher, 1980), succinic semialdehyde dehydrogenase (Van der Laan et al., 1979; Harvey et al., 1975), and aldehyde reductase (Whittle and Turner, 1978). The effect on GABA-T is weak compared with conventional inhibitors such as vigabatrin (section V, C, 1; Löscher, 1980; Larsson et al., 1986) and inhibition of enzyme activity does not appear to occur in vivo after administration of anticonvulsant doses of valproate (Emson, 1976; Löscher and Nau, 1982; Nau and Löscher, 1982) or in vitro in intact cells (Gram et al., 1988). In addition, valproate may also increase the activity of glutamic acid decarboxylase, the enzyme responsible for GABA synthesis (Chapman et al., 1982; Phillips and Fowler, 1982; however, see Emson, 1976). The increase in glutamic acid decarboxylase activity was found to parallel the elevation of brain GABA levels caused by a single dose of valproate (Nau and Löscher, 1982) and to remain elevated with chronic administration of the drug (Löscher and Nau, 1982). However, in in vivo experiments, Löscher (1989) found the GABA synthesis rate to be enhanced only in the substantia nigra and to a lesser extent in the striatum. Which, if any, of the actions on GABA metabolic enzymes is responsible for the effect on brain GABA levels remains to be clarified.

Several investigators using electrophysiological recording techniques have reported that valproate can enhance neuronal responses to exogenously applied GABA in vivo (Schmutz et al., 1979; Gent and Phillips, 1980) and in vitro (Macdonald and Bergey, 1979; Baldino

and Geller, 1981; Harrison and Simmonds, 1982; Preisendörfer et al., 1987). In addition, valproate inhibits (IC_{50}, 500 μM) the binding of [^{3}H]dihydropicrotoxinin to the ionophore of the GABA receptor-channel complex (Ticku and Davis, 1981). However, the millimolar concentrations required to potentiate GABA responses in the electrophysiological studies are far higher than the normal therapeutic levels of the drug, indicating that augmentation of GABA-mediated inhibition by a postsynaptic mechanism is unlikely to account for the anticonvulsant action of the drug under normal circumstances (McLean and Macdonald, 1986b). Thus, if the anticonvulsant activity of valproate is mediated by effects on GABAergic systems, this is likely to be due to a presynaptic (elevation in GABA levels) rather than a postsynaptic (effect on the GABA receptor-Cl^- channel complex) mechanism. In fact, at least one study has shown that high concentrations of valproate (300 μM) can enhance K^+-stimulated GABA release (from cultured cortical neurons), supporting the hypothesis of a presynaptic mechanism, although surprisingly in this study the drug failed to elevate the GABA content of the cells (Gram et al., 1988). In addition, in in vivo experiments valproate has been reported to enhance the binding of [^{3}H]flunitrazepam to mouse brain benzodiazepine receptors, an action shared by peripherally acting $GABA_A$ receptor agonists. This observation supports the conclusion that the effects of valproate on GABA metabolism result in functionally significant effects on postsynaptic GABA receptors (Koe, 1983).

Despite the attractiveness of the hypothesis that the antiepileptic activity of valproate is somehow linked to its effects on GABAergic brain systems, valproate has a distinctly different spectrum of anticonvulsant activity from drugs for which the evidence of a GABAergic mechanism is stronger (i.e., these drugs are typically much less effective against electroshock seizures than against pentylenetetrazol seizures). Thus, it is likely that one or more alternative mechanisms will need to be invoked to account for the antiepileptic activity of valproate in all of the situations in which it is effective.

2. Block of voltage-dependent Na^+ channels. Like phenytoin and carbamazepine, valproate limits the ability of cultured CNS (cortical and spinal cord) neurons to fire Na^+-dependent action potentials at high frequency (McLean and Macdonald, 1986b). This effect of valproate is one of the few that occurs at concentrations equivalent to those present in the CSF of patients treated with clinically effective doses of the drug (6–200 μM). Although the precise biophysical mechanism underlying the ability of the drug to reduce sustained repetitive firing has not been elucidated, the effect probably relates to a phenytoin-like use- and voltage-dependent blockade of voltage-dependent Na^+ channels. In the studies carried out to date, effects on Na^+ channels were inferred indirectly from changes in the maximal rate of increase of Na^+-dependent action potentials. In the presence of valproate, there was a progressive slowing in the rate of increase of action potentials during a train, whereas such use-dependent slowing did not occur under control conditions. In addition, the limitation in repetitive firing occurring in the presence of valproate could be diminished by depolarizing from *hyperpolarized* (more negative than −65 mV) membrane potentials. Like phenytoin and carbamazepine, the use- and voltage-dependent effects of valproate on Na^+ conductance are compatible with the requirements of an anticonvulsant to block repetitive discharges during a seizure while having a minimal effect on normal neuronal firing. In fact, Griffith and Taylor (1988b) recently reported a phenytoin-like block of PTP by valproate in hippocampal CA_1 neurons at concentrations (30–200 μM) that did not affect single evoked synaptic potentials. This effect on synaptic potentiation is likely to be a consequence of the use-dependent block of Na^+ channels by valproate. However, unlike the situation with phenytoin, biochemical studies have failed to demonstrate an interaction between valproate and Na^+ channels at relevant concentrations, either in a batrachotoxin-stimulated $^{22}Na^+$ flux assay (Willow et al., 1984) or in a [^{3}H]batrachotoxin-binding assay (Willow and Catterall, 1982; fig. 2). In the voltage-clamp studies carried out to date, effects of valproate on Na^+ currents were observed only at high millimolar concentrations (VanDongen et al., 1986) or not at all with external application of the drug (Fohlmeister et al., 1984). Since these studies were conducted in peripheral axons, delineation of the precise way in which valproate limits sustained, high-frequency firing and PTP will require more detailed electrophysiological studies in mammalian neurons. Moreover, 2-en-valproate, a metabolite of valproate that is as potent an anticonvulsant as valproate in several animal seizure models including the maximal electroshock test (see above), had no effect on sustained high-frequency repetitive firing (McLean and Macdonald, 1986b), raising questions about the Na^+ channel hypothesis.

3. Toward an understanding of the mechanism of action of valproate. Because valproate has such a wide spectrum of anticonvulsant activity, it is attractive to accept the view that the drug's clinical activity may relate to a combination of mechanisms. Thus, the phenytoin-like effect on Na^+ channels is compatible with its activity against electroshock seizures, its general ability to prevent seizure spread, and its utility against generalized tonic-clonic and partial seizures in man, whereas its interaction with GABAergic systems could explain the broader spectrum of activity than phenytoin or carbamazepine. Insufficient data are available at present to definitively establish either of these mechanisms, and, as we have noted, there are inconsistencies that call into question both the Na^+ channel and the GABA hypotheses. Thus, it is likely that alternative hypotheses

will be provided in the future. For example, acute doses of valproate (200–400 mg/kg, i.p., in rodents) have been consistently found to decrease brain levels of the excitatory amino acid aspartate (Schechter et al., 1978). The time course for this effect corresponds with the period of seizure protection, and there is a stronger correlation between the anticonvulsant potencies of a series of valproate analogs and their ability to reduce cerebral aspartate levels than with their effects on GABA levels (Chapman et al., 1983; 1984). The mechanism whereby valproate influences aspartate levels is unknown, and as yet there is no evidence that the effect is physiologically important. Nevertheless, these observation highlight the fact that the full spectrum of pharmacological actions of valproate are not yet well understood.

4. Clinical efficacy. Valproate's broad spectrum of anticonvulsant activity in animal seizure models is reflected in its diverse clinical utility. Although its original indication was for the treatment of absence seizures, valproate also appears to be effective against certain myoclonic seizures, generalized tonic-clonic seizures, and perhaps partial seizures. Valproate is highly effective against both the behavioral and EEG manifestations of absence seizures (Simon and Penry, 1975; Penry et al., 1976). With the use of 12-hour telemetered EEGs to measure the frequency of generalized spike and wave discharges, valproate was found to be as effective as ethosuximide (section IV, A) in a double-blind, response-conditional crossover study of absence seizures in 45 patients (Sato et al., 1982). Some enthusiasm about the usefulness of valproate as an effective agent for partial seizures is emerging (Turnbull et al., 1985; Dean and Penry, 1988); more definitive data will be forthcoming from the ongoing U. S. Department of Veterans Affairs' controlled clinical trial. Valproate is clearly effective against primary generalized tonic-clonic seizures, whether these seizures occur in isolation or in combination with other generalized seizure types such as absence or myoclonia (Collaborative Study Group, 1987; Chadwick, 1988). The efficacy of valproate against secondarily generalized partial seizures has not yet been determined, but it remains the opinion of many epileptologists that valproate is less effective than carbamazepine or phenytoin for such attacks (Porter, 1989).

IV. Drugs Used Primarily in the Treatment of Absence Seizures

A. Ethosuximide

The succinimide ethosuximide (fig. 5) is distinguished from other clinically important antiepileptic drugs, including structurally similar compounds like phenytoin, in that it is highly efficacious in the treatment of absence seizures and is inactive against other seizure types. This narrow range of clinical activity is reflected in ethosuximide's unique anticonvulsant profile in animal seizure models. Exthosuximide specifically blocks pentylenetetrazol- and bicuculline-induced clonic seizures in mice (ED_{50}, 130 mg/kg, i.p.; Swinyard et al., 1989) yet fails to have any activity against tonic seizures in the maximal electroshock test except at anesthetic doses (Reinhard and Reinhard, 1977). The drug is also effective in a variety of other animal models of generalized absence seizures and inhibits the absence-like seizures that occur spontaneously in mutant tottering mice (Heller et al., 1983), in Wistar rats (Marescaux et al., 1984), and in a strain of genetically epilepsy-prone Kyoto-Wistar rats (Sasa et al., 1988) as well as those produced by systemic administration of γ-hydroxybutyrate (Godschalk et al., 1976; Snead, 1978; 1988). The unique profile of activity exhibited by ethosuximide implies that it has a novel and distinct mechanism of action, at least in comparison to drugs like phenytoin and carbamazepine that are inactive against absence seizures or may worsen them (Marescaux et al., 1984). Until recently, however, it was unclear what this mechanism might be. Ethosuximide fails to limit sustained high-frequency repetitive firing of neurons at clinically relevant concentrations (McLean and Macdonald, 1986b) and thus it presumably does not exert a phenytoin-like action on voltage-dependent Na^+ channels, a conclusion that is compatible with its poor activity in the maximal electroshock test. Moreover, ethosuximide does not potentiate postsynaptic GABA responses (Barnes and Dichter, 1984), as do other drugs that are effective in the treatment of absence seizures. (It may, however, interact with the picrotoxin site on the $GABA_A$ receptor-channel complex; Coulter et al., 1989a.) Recently, it has been demonstrated that ethosuximide, unlike other prototype antiepileptic drugs, is a selective antagonist of T-type voltage-dependent Ca^{2+} channels in thalamic neurons, and this observation has allowed the formulation of a rational hypothesis regarding its antiepileptic activity.

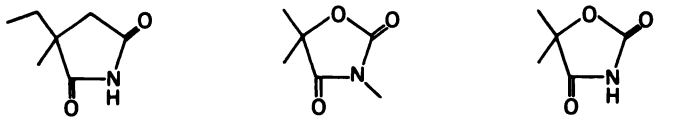


FIG. 5. Structures of representative succinimides.

1. Thalamocortical mechanisms in absence epilepsy. To appreciate how blockade of T-type Ca^{2+} channels can result in antiabsence activity, it is necessary to review the basic neuronal mechanisms that are believed to underlie generalized absence seizures. Current understanding of these mechanisms is based historically upon the "centrencephalic" hypothesis of Penfield and Jasper (1954) which proposes that neurons in the diencephalon and brainstem play a determining role in the generalized seizure discharge. This idea has been substantially modified and extended in recent years largely by Gloor (1984) and his collaborators using the feline penicillin model of generalized epilepsy. Cats treated with high doses of

penicillin (a weak GABA receptor antagonist; see, e.g., Weiss and Hablitz, 1984) exhibit ethosuximide-sensitive seizures (Guberman et al., 1975) that have similar behavioral correlates and EEG manifestations to human absence seizures. In this model, the expression of cortical spike-wave seizure discharges is dependent upon the existence of an intact thalamus. Moreover, during the seizure discharge, cortical and thalamic neurons tend to fire together. These observations have led to the concept that the stereotyped 3-Hz spike-wave EEG signature of absence epilepsy results from oscillations within a closed circuit encompassing the powerful reciprocal connections between thalamus and cortex. The importance of thalamocortical interactions in the genesis of the spike-wave discharge has recently received support from experiments using an inbred rat strain with spontaneous absence seizures (Vergnes et al., 1987).

The spike-wave discharges that occur during the generalized seizure do not represent an abnormal phenomenon induced de novo by the convulsant drug but appear to be an accentuation of the normal physiological processes that generate spindling in the EEG. Thalamic neurons can exist in two firing modes, depending upon the resting potential (Steriade and Llinás, 1988). Under normal waking conditions, the cells fire in a tonic (nonburst) mode. However, upon hyperpolarization as, for example, occurs during sleep, there is an abrupt change to the phasic (burst) firing mode. Using an in vitro slice preparation from the thalamus, Jahnsen and Llinás (1984a,b) demonstrated that the shift to phasic firing occurs as a result of the deinactivation of a Ca^{2+}-dependent regenerative potential, referred to as the "low-threshold spike" (fig. 6). Subsequently, it was shown that the low-threshold spike is mediated by T-type voltage-dependent Ca^{2+} channels (Suzuki and Rogawski, 1989). T-type Ca^{2+} channels are inactivated at the normal resting potential but become deinactivated upon membrane hyperpolarization. Depolarization from this hyperpolarized level results in the generation of a low-threshold spike with a burst of Na^+-dependent action potentials riding on its crest. Burst firing of thalamic neurons is believed to be critical to the expression of sleep spindles in the cortical EEG, and it has been argued that the interaction between thalamus and cortex that occurs during the spike-wave discharge is similar to that occurring during spindling, except that it is stronger and more synchronous (Gloor, 1984). If such is the case, then the seizure discharge too would seem to be contingent upon burst firing in thalamic neurons. At present, the specific events leading to the initiation and maintenance of the seizure discharge are unclear. Nevertheless, it is apparent that the thalamocortical oscillations that mediate the seizure discharge are directly dependent upon the integrity of T-type Ca^{2+} channels which allow thalamic neurons to fire in a burst mode.

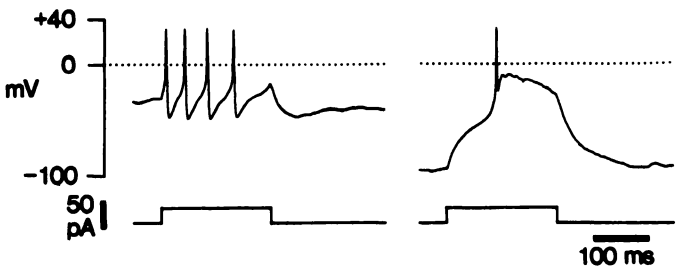


FIG. 6. Intracellular recording using the whole cell patch-clamp technique from an isolated guinea pig thalamic (lateral geniculate) neuron showing deinactivation of the low-threshold spike and the consequent change from "tonic" (left) to "phasic" (right) firing upon membrane hyperpolarization. (S. Suzuki and M. A. Rogawski, unpublished.)

2. Block of T-type voltage-dependent Ca^{2+} channels. Voltage-clamp recordings from neurons acutely isolated by enzymatic dissociation of rat and guinea pig thalamic slices show the existence of two distinct Ca^{2+} current components, termed T and L (Suzuki and Rogawski, 1989; Coulter et al., 1989b; Hernández-Cruz and Pape, 1989). The T-type Ca^{2+} current is characterized by its low threshold for activation and rapid time-dependent inactivation with maintained depolarization (see Tsien et al., 1987, for review). In contrast, the L-type Ca^{2+} current has a high threshold for activation and inactivates minimally with maintained depolarization. Among mammalian central neurons that have been examined to date, thalamic neurons are unusual in having a relatively large T-type current, and this, at least in part, accounts for the unique and characteristic firing properties these cells exhibit in situ.

Recently, Coulter et al. (1989c) reported that ethosuximide produces up to a 40% reduction in the amplitude of the T-type Ca^{2+} current in thalamic neurons (fig. 7). The EC_{50} of this effect is 200 μM. Because effective ethosuximide plasma levels typically range from 40–100 μg/ml (285–710 μM) (Sherwin, 1989), the effect on the T-type Ca^{2+} current occurs at clinically relevant concentrations. (Ethosuximide is only minimally bound to plasma proteins; Chang, 1989.) Ethosuximide block of the T-type Ca^{2+} current was voltage dependent and was markedly reduced at depolarized potentials. The drug did not alter the time course of activation or inactivation of the current, its voltage-dependency for activation or steady-state inactivation, or its recovery from inactivation. Thus, unlike phenytoin's action on voltage-dependent Na^+ channels, ethosuximide fails to alter gating of the T-type Ca^{2+} channel. The effect of ethosuximide on T-type Ca^{2+} channels was pharmacologically specific in that the structurally related but pharmacologically inactive compound succinimide failed to block the T-type current (Coulter et al., 1989d). However, dimethadione, the active metabolite of the antiabsence drug trimethadione (section IV, B), at therapeutically relevant concentrations also reduced the T-type Ca^{2+} current (Coulter et al., 1984c) as did desmethsuximide, the active metabolite of another antiabsence drug methsuximide (section

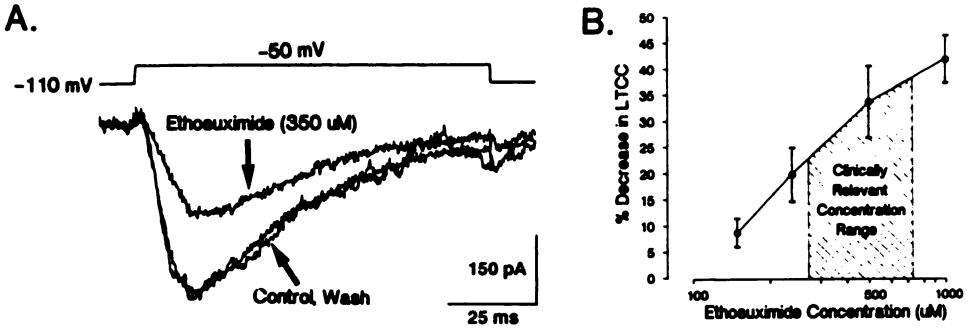


FIG. 7. Blockade of the T-type voltage-dependent Ca^{2+} current by ethosuximide. A, The current was activated by a voltage-clamp step from a holding potential of −110 mV to −50 mV. B, Concentration-effect curve for decrease in T-type Ca^{2+} current. (From Coulter et al., 1989c; used with permission.)

V, C; fig. 8) (Coulter et al., 1990). Interestingly, valproate, despite its effectiveness against absence seizures, was inactive, indicating that it is possible to prevent absence seizures by mechanisms other than T-channel blockade (see, e.g., Depaulis et al., 1988). Finally, as noted previously, although phenytoin did block the T-type Ca^{2+} channel, this effect was small (<10% reduction) at clinically relevant concentrations. Thus, drugs that block T-type Ca^{2+} channels at clinically relevant concentrations appear to be effective antiabsence agents, whereas those that fail to block the channel are clinically inactive. These observations are all consistent with the idea that the specific antiabsence activity of ethosuximide and dimethadione result from their ability to block T-type Ca^{2+} channels at concentrations that do not affect other ion channel systems. The reduction in the T-type current results in a suppresion of the low threshold spike in thalamic neurons and a consequent dampening of the thalamocortical oscillations that are critical to the generation of absence seizures.

3. Clinical efficacy. Ethosuximide has been the drug of choice for the treatment of absence seizures since its introduction in 1960. The drug is relatively nontoxic and nonsedative. Valproate (section III, B, 4) is preferred if the patient has generalized tonic-clonic seizures in addition to absence attacks. The effectiveness of ethosuximide has been documented in a single-blind study using multiple criteria for determination of efficacy (Browne et al., 1975). In 37 patients receiving the drug, 9% achieved at least 90% control of their attacks and 95% achieved at least 50% control. Sherwin et al. (1973) undertook a similar study that showed not only that approximately 75% of patients with absence seizure could gain seizure control but also that monitoring of plasma drug levels improved the results. Because of its very narrow spectrum of activity, ethosuximide is rarely used except for the treatment of absence seizures.

B. Trimethadione

The oxazolidinedione trimethadione (fig. 5) was the first marketed antiepileptic drug effective against absence attacks (Lennox, 1945). Along with its analog, paramethadione, it was the only medication available for absence seizures until the appearance of succinimides almost a decade later. Trimethadione is more effective than the weakest succinimide, phensuximide, and it was not until the availability of ethosuximide that the diones were no longer necessary as primary therapy. Trimethadione is rapidly demethylated by hepatic microsomal enzymes to its active metabolite dimethadione (Butler et al., 1965). Typical plasma dimethadione levels are 470–1200 μg/ml (3.3–8.4 mM); neither trimethadione nor dimethadione are bound to plasma proteins. Since the advent of valproate, the use of the diones has become uncommon, because of the high incidence of sedation and visual disturbances (hemeralopia) they cause and the potential for serious toxic reactions (Booker, 1989).

Like ethosuximide, trimethadione is highly effective against pentylenetetrazol-induced seizures (ED_{50}, 250–300 mg/kg, i.p., in mice; Everett and Richards, 1944; Swinyard et al., 1989) and is less active against maximal electroshock seizures (Goodman et al., 1953). At higher doses (500 mg/kg), trimethadione can block strychnine- and picrotoxin-induced seizures in mice (Everett and Richards, 1944). Early studies implicated the thalamus as a potential site of action of trimethadione (Morell et al., 1959; Schallek and Kuehn, 1963) and indicated that the drug acted by a distinct mechanism from phenytoin in that it was poorly active in blocking seizure spread within the cortex (as expected from its weak activity in the electroshock test). Also unlike phenytoin, the drug is unable to block PTP (Esplin and Carto, 1957). As noted before, Coulter et al. (1989c) recently showed that trimethadione's active metabolite dimethadione can block the T-type Ca^{2+} current in thalamic neurons (40–52% reduction at concentrations of 4–8 mM), providing a cellular basis for its antiabsence activity. Like ethosuximide, dimethadione failed to alter the kinetic properties of the T-type Ca^{2+} current or its h_∞ curve. However, it was less selective than ethosuximide in that it significantly reduced the L-type Ca^{2+} current, and this poor selectivity may account for its greater tendency to cause dose-dependent side effects at clinically effective concentrations.

C. Phensuximide and Methsuximide

Two other succinimides that are potentially useful for absence seizures are phensuximide and methsuximide (fig. 8). Phensuximide was marketed in the United States in 1953 and was the first alternative to the more toxic diones. The drug was initially greeted with enthusiasm but within a few years was noted to be less potent than trimethadione and has never been completely accepted as an effective agent. Phensuximide is apparently active against both maximal electroshock seizures in mice (ED_{50}, 183 mg/kg, p.o.) and pentylenetetrazol seizures in rats (~125 mg/kg, p.o.) (Chen et al., 1963). The fundamental pharmacological reason for the poor activity of phensuximide in the treatment of epilepsy may be that neither the parent nor its demethylated metabolite, desmethylphensuximide (fig. 8), accumulate to any significant extent in the body (Porter et al., 1979). The rapid removal of the metabolite is most probably due to the action of a liver enzyme, dihydropyrimidinase, which opens the succinimide ring and quickly inactivates desmethylphensuximide. This enzyme cannot open the ring in desmethylmethsuximide because of the protection provided by the additional methyl group (fig. 8). Because the ring-opened compound is inactive, no effective antiepileptic drug accumulates.

Methsuximide, the 2-methylated analog of phensuximide (fig. 8), is occasionally an effective alternative to ethosuximide in the treatment of absence seizures, although it is more toxic than ethosuximide. Unlike ethosuximide, methsuximide is able to block maximal electroshock seizures (ED_{50}, 84 mg/kg, p.o., in mice; Chen et al., 1963) as well as pentylenetetrazol seizures. As predicted by its activity in the animal tests, methsuximide may have a broader spectrum of clinical antiepileptic activity than ethosuximide (Browne et al., 1989). Methsuximide is metabolized by N-demethylation to form the active metabolite N-desmethylmethsuximide (Chen et al., 1951; fig. 8) which is slowly metabolized and therefore accumulates in the plasma. Methsuximide was recently found to be effective in a wide variety of seizure types in a majority of 34 pediatric patients who were treated with the drug (Andrews et al., 1989).

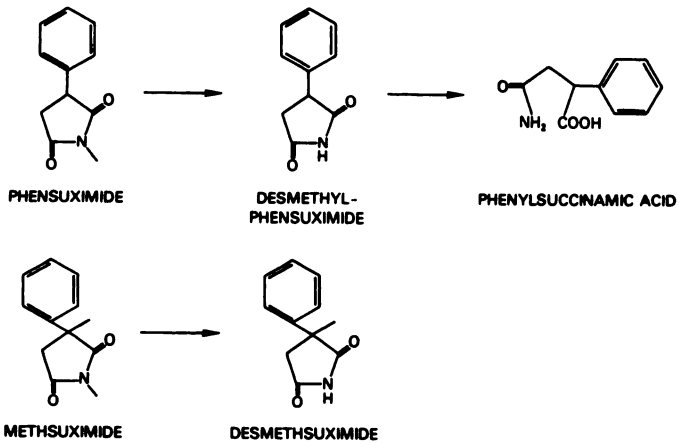


FIG. 8. Metabolism of phensuximide and methsuximide. (Adapted from Porter and Kupferberg, 1982; used with permission.)

D. Acetazolamide

The sulfonamide acetazolamide has a wide spectrum of anticonvulsant activity in animal seizure models. It is a potent inhibitor of maximal electroshock seizures (Anderson et al., 1986) and at higher doses protects against pentylenetetrazol- and picrotoxin-induced seizures (Woodbury and Kemp, 1989). Acetazolamide has also been shown to protect against reflex (audiogenic) seizures in mice (Engstrom et al., 1986). The major pharmacological action of acetazolamide is noncompetitive inhibition of carbonic anhydrase. This enzyme catalyzes the hydration of CO_2 to form carbonic acid which immediately dissociates to H^+ and bicarbonate anion (fig. 9). Carbonic anhydrase is found in many sites throughout the body, but the anticonvulsant effect of acetazolamide is specifically related to inhibition of the enzyme in the CNS, where it is localized in glial cells. At clinically effective doses, acetazolamide produces a >99% inhibition of brain carbonic anhydrase. In the absence of carbonic anhydrase activity, CO_2 released by metabolically active neurons builds up in the extracellular space and in neurons. Exactly how the increase in tissue pCO_2 decreases neuronal excitability is not well understood. Experiments described by Anderson et al. (1986) have suggested that the ability of acetazolamide to block the spread of maximal electroshock seizures is related to the inhibition of carbonic anhydrase within the cytoplasm of glial cells; in contrast, the drug may decrease seizure susceptibility by inhibiting carbonic anhydrase in myelin.

Despite its high initial efficacy, acetazolamide has only limited usefulness in the chronic treatment of seizure disorders because patients rapidly develop tolerance. A similar tolerance also occurs in experimental animals. The development of tolerance is believed to be due to an increase in carbonic anhydrase activity occurring as a result of activation of existing enzyme molecules and de novo synthesis of the enzyme. In addition, chronic acetazolamide may cause a proliferation of glial cells containing carbonic anhydrase.

Acetazolamide is briefly effective against most types of seizures, including generalized tonic-clonic and complex partial seizures and especially absence seizures (Woodbury and Kemp, 1989), although it is rarely used because of the development of tolerance. The drug is occasionally used on an intermittent basis to prevent catamenial seizures.

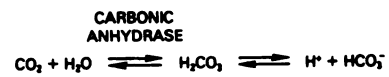


FIG. 9. Reaction catalyzed by carbonic anydrase.

V. Developmental Stage Drugs

We next review presently available information regarding mechanism and efficacy for drugs currently undergoing preclinical and clinical evaluation. The drugs are organized according to presumed mechanism of action. In all cases the mechanistic information is fragmentary and our tentative conclusions are often based on analogy with the more thoroughly studied prototype drugs. Our limited knowledge reflects the fact that until a drug receives widespread clinical acceptance, research into basic mechanisms is often limited or even nonexistent. Nevertheless, this preliminary classification is useful because those drugs whose mechanism of action mimics that of presently marketed drugs may offer only incremental advantages in epilepsy therapy (for example, by having a more favorable side effect profile), whereas other compounds whose mechanism of action and spectrum of anticonvulsant activity is truly different offer the possibility of breakthrough advances in epilepsy therapy. Of course, as new information is gathered, the classifications are likely to change.

A. Drugs Whose Anticonvulsant Profile Is Similar to Phenytoin

1. Zonisamide. Zonisamide (1,2-benziosoxazole-3-methanesulfonamide; fig. 10) is a member of a novel class of benzisoxazole anticonvulsants that includes CGS 18416A (section V, A, 4). These structurally related compounds have a spectrum of anticonvulsant activity that is similar to, although perhaps not identical with, phenytoin in animal seizure models. Like phenytoin (and also carbamazepine), zonisamide protects against maximal electroshock seizures (ED_{50}, 19.6 mg/kg, p.o., in mice) but fails to affect clonic seizures induced by pentylenetetrazol (Bartoszyk and Hamer, 1987). The protective index in the maximal electroshock test (rotorod TD_{50}/ED_{50}) is 11.6 compared to values of 9.1 and 10.6 for phenytoin and carbamazepine, respectively (Masuda et al., 1980). The drug also has activity against reflex seizures in Mongolian gerbils (Bartoszyk and Hammer, 1987), has effects on kindled seizures in rats (Kamei et al., 1981), and can block certain chemically induced cortical seizure discharges, as do phenytoin and carbamazepine (Ito et al., 1980; 1986). In line with a phenytoin-like mechanism of action, zonisamide blocked sustained repetitive firing of cultured mouse central neurons (IC_{50}, 3.7 μM) but had no effect on responses to GABA or glutamate in these cells (Rock et al., 1989). Therapeutic total plasma levels of zonisamide are 15–20 μg/ml and the drug is 50% bound to plasma proteins. If the CSF concentration approximates free serum levels, the concentrations of zonisamide in the CSF under therapeutic conditions would be more than sufficient to block repetitive firing. Schauf (1987) reported voltage-clamp studies of the effect of zonisamide on Na^+ currents in an invertebrate axon. The drug caused a shift in the steady-state inactivation of Na^+ currents that was similar to that produced by phenytoin, suggesting that, like phenytoin, zonisamide stabilizes Na^+ channels in their inactivated state.

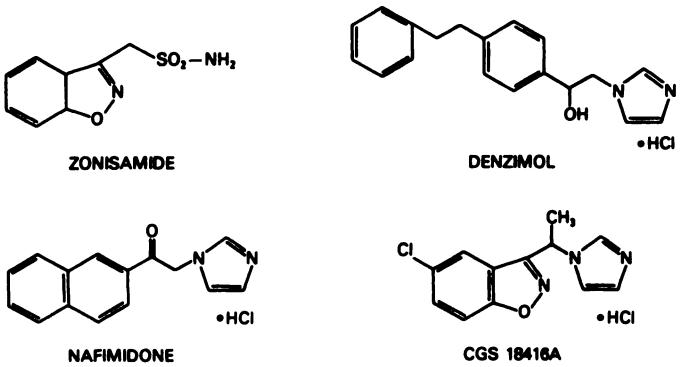


FIG. 10. Structures of benzisoxazole and imidazole anticonvulsants.

Despite the strong evidence supporting a phenytoin-like effect on Na^+ channels in the mechanism of action of zonisamide, even at high doses (100 mg/kg) the drug was unable to mimic phenytoin's effect on PTP of ventral root potentials in spinalized rats (Ito et al., 1986). Moreover, the drug is able to suppress cortical seizure foci in cats (Ito et al., 1980), an effect not seen with phenytoin. Recently, some evidence has been presented supporting the concept that, at concentrations within the therapeutic range, zonisamide is able to interact with the $GABA_A$/benzodiazepine receptor. Thus, the drug is able to inhibit [^{3}H]flunitrazepam (a benzodiazepine receptor agonist) and [^{3}H]muscimol (a $GABA_A$ receptor agonist) binding to rat brain membranes. In addition, [^{3}H]zonisamide binds in a saturable manner to rat brain membranes and the ligand can be partially displaced by the benzodiazepine clonazepam (Mimaki et al., 1988). Therefore, there are specific binding sites in the brain for zonisamide that may have some relationship to benzodiazepine receptors. Because zonisamide did not alter responses to GABA in cultured spinal cord neurons (Rock et al., 1989), the physiological relevance of these binding sites is unclear. However, in studies of zonisamide on excitatory and inhibitory mechanisms in the cat spinal trigeminal nucleus, a valproate-like profile of activity was found (Fromm et al., 1987), which could support a GABAergic mechanism of action. These observations have encouraged the continued evaluation of zonisamide for the treatment of valproate-sensitive seizure types, such as myoclonus.

A large number of clinical studies of zonisamide have been performed in the United States and Japan. In a well-controlled multicenter trial, Ramsay et al. (1984) studied zonisamide in 65 patients; some patients achieved a reduction in seizure frequency. Wilensky et al. (1985) compared zonisamide monotherapy to carbamazepine monotherapy in an open study of eight patients with uncontrolled partial seizures; the drug

showed some activity in five of the patients. A pilot study reported by Sachellares et al. (1985) showed encouraging results in 10 patients with refractory partial seizures. Henry et al. (1988) observed striking effectiveness of zonisamide in myoclonus epilepsy.

More recent clinical studies have been performed in Japan. Open studies in children include those of Sakamoto et al. (1988), Takahashi et al. (1987), Oguni et al. (1989), Iinuma et al. (1988), and Shuto et al. (1989) who found the drug effective in children with a variety of seizure types. In adults, varying degrees of success have been found in a series of open studies by Takeda et al. (1987) and Shimizu et al. (1987). Studies in the United States were terminated because of an increased incidence of renal calculi observed in long-term trials. The curious difference of opinion about the severity and incidence of this side effect between American and Japanese investigators remains unresolved.

2. Imidazoles: Denzimol. The imidazole denzimol (N-{β-[4-(β-phenylethyl)phenyl]-β-hydroxyethyl}-imidazole; fig. 10) has a similar profile of anticonvulsant activity to phenytoin in that it is protective against maximal electroshock seizures (ED_{50}, 5.3 mg/kg, i.v., in mice at 1 hour) but is ineffective against clonic seizures induced by pentylenetetrazol (Nardi et al., 1981; Graziani et al., 1983). Its protective index in the maximal electroshock test (TD_{50} in rotorod ataxia test/ED_{50}) 1 hour after oral administration in mice calculated from the data of Graziani et al. (1983) is 5.2 which is somewhat lower than that of phenytoin (8.4) but greater than that of phenobarbital (2.6) or valproic acid (1.3). The drug is also effective against sound-induced seizures in DBA/2 mice, and its protective action in this model can be diminished by pretreatment with purine (aminophylline) and benzodiazepine (Ro 15–1788) receptor antagonists (De Sarro et al., 1987). Like phenytoin (Gallager et al., 1980), denzimol produces an increase in the number of benzodiazepine receptor sites and is able to potentiate the ataxia-inducing and anticonvulsant (pentylenetetrazol test) activity of benzodiazepines (Mennini et al., 1984), but the role of benzodiazepine receptors in the anticonvulsant activity of denzimol remains to be determined.

Controlled clinical trials with denzimol are lacking. The preliminary clinical data are summarized by Testa and Bertin (1986). The pilot studies reviewed by these authors suggested that the drug has efficacy against complex partial seizures. One additional study recently reported by Benassi et al. (1988b) evaluated denzimol in 10 patients with poorly controlled partial seizures. The drug was added to current therapy in an open trial lasting 12 weeks. A sustained decrease in seizure frequency occurred in five patients. No serious side effects were noted, but nausea and vomiting caused two patients to stop taking the drug; the other eight patients completed the trial. The optimal doses appeared to be between 300 and 600 mg/day. However, as of mid-1988, evaluation of the drug had apparently been suspended (R. Testa, personal communication).

3. Imidazoles: Nafimidone. Like the structurally related imidazole denzimol, nafimidone [1-(2-naphthoylmethyl)imidazole HCl; fig. 10] protects against maximal electroshock seizures in mice and rats (ED_{50}, 15 mg/kg, i.p., in mice) but is inactive against pentylenetetrazol-induced clonic seizures. Its protective index (TD_{50} in a traction test/ED_{50}) 30 min after oral administration in mice was 6.3 (Walker et al., 1981; Buhles et al., 1986). However, animals receiving nafimidone exhibited adverse behavioral signs including abnormal postures and altered locomotor activity at doses as low as 30 mg/kg, i.p. In amygdaloid-kindled rats, nafimdone (25–50 mg/kg, i.p.) had only moderate protective activity against seizures, but these animals showed toxicity (sedation and ataxia) (Albertson and Walby, 1988). At very high doses (100–120 mg/kg), a proconvulsant effect of the drug was also observed consisting of spontaneous EEG spike and wave complexes, seizures, and death. However, promising results were obtained in one add-on clinical trial in adult males with intractable partial seizures (Treiman et al., 1985).

4. CGS 18416A. CGS 18416A (fig. 10) is structurally similar to zonisamide in having a benzisoxazole moiety and also to denzimol and nafimidone because of its imidazole group. CGS 18416A is effective in the maximal electroshock test (ED_{50}, 17.3 mg/kg, p.o., in mice) but is inactive in the subcutaneous pentylenetetrazol test and in protecting against picrotoxin- or bicuculline-induced seizures in mice; no impairment of motor function was noted in mice or rats at doses up to 200 mg/kg, p.o. (Bernard et al., 1989). Biochemical studies have suggested that the drug may have a phenytoin-like action on voltage-dependent Na^+ channels. The drug is currently undergoing clinical trials.

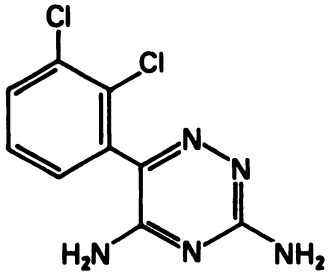
5. Imidazoles: Other arylalkylimidazole anticonvulsants. Robertson et al. (1986) demonstrated that a number of other arylalkyl groups when coupled to imidazole result in highly potent anticonvulsant molecules. In particular, fluorenyl-, benzo[*b*]thienyl-, and benzofuranyl-substituted arylalkylimidazoles were particularly active. Like denzimol and nafimidone, all of these compounds were protective in the maximal electroshock test but had little or no activity against pentylenetetrazol-induced clonic seizures, clearly demonstrating that the alkylimidazole portion of the molecule is the active pharmacophore; it is suggested that the lipophilic aryl portion allows the compounds to cross the blood-brain barrier. The drugs were also able to promote the binding of [^{3}H]flunitrazepam to benzodiazepine receptors, both in vivo and in vitro. All arylalkylimidazoles including denzimol and nafimidone interact strongly with cytochrome P-450 so that they impair the metabolism and increase levels of other anticonvulsant drugs, a potential disadvantage to

their clinical use (Kapetanovic and Kupferberg, 1984; 1985; Treiman et al., 1985).

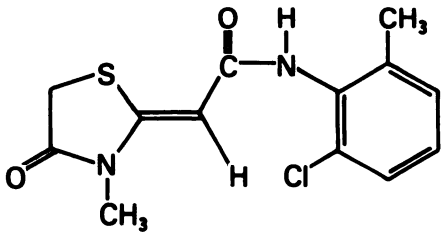
6. Lamotrigine. With the recognition that chronic treatment with antiepileptic drugs could lead to an impairment in folate metabolism and the further demonstration that folates could produce seizures in animals (Hommes and Obbens, 1972; Obbens and Hommes, 1973; Baxter et al., 1973), a series of antifolates were evaluated for anticonvulsant activity. The phenyltriazine lamotrigine [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine; fig. 11] emerged from this screening program. Although it is structurally related to antifolate drugs, lamotrigine itself has only very weak antifolate activity and structure-activity studies have failed to show a correlation between antifolate activity and anticonvulsant potency. Nevertheless, lamotrigine has high potency in the maximal electroshock test (1.9 mg/kg, p.o., in the mouse) and relatively low motor toxicity compared with phenytoin. Lamotrigine can also block the development and the expression of kindled seizures in rats (Miller et al., 1986b) and can potently inhibit afterdischarges (electrographic seizure-like activity) induced by electrical stimulation in anesthetized rats, dogs, and marmosets (Wheatley and Miller, 1989). Like phenytoin, lamotrigine was inactive in the pentylenetetrazol seizure test (against clonic seizures), suggesting that the two drugs may have similar mechanisms of action. In fact, with a similar potency to phenytoin, lamotrigine (ED_{50}, 20–100 μM) blocks veratrine-evoked transmitter release from rat neocortical slices (Leach et al., 1986). The observation that the drug fails to affect release stimulated by high K^+ suggests that it may be interacting specifically with voltage-dependent Na^+ channels, perhaps in a similar way to phenytoin.

As of 1986 there were only preliminary data to suggest clinical efficacy of lamotrigine (Miller et al., 1986a). Since that time, however, a number of controlled clinical trials have documented the efficacy of the drug. The study by Jawad et al. (1989) showed a significant improvement in the 21 patients with partial seizures who completed the trial. The controlled study by Binnie et al. (1989) showed promise, especially in terms of a reduction in the number of EEG spikes. Loiseau et al. (1989) studied lamotrigine in 23 patients with refractory partial seizures using a double-blind, crossover design; a moderate reduction in seizures was observed. Richens and Yuen (1989) performed a meta-analysis of the four controlled studies of lamotrigine and concluded that approximately 30% of refractory patients will have a 50% reduction in seizure frequency.

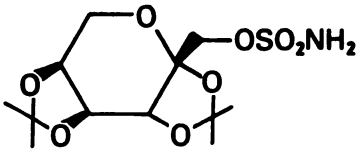
In open studies, Matsuo et al. (1989) evaluated 10 male patients with partial epilepsy. The drug was well tolerated by seven of the patients at a dose of 400 mg/day. Reduction of existing concomitant antiepileptic drugs was possible in four, and monotherapy with lamotrigine was achieved in two. Mikati (1989) observed that lamo-



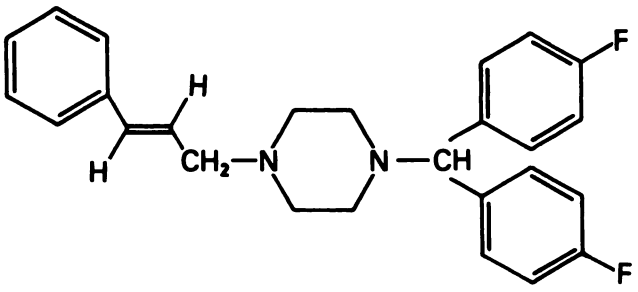
LAMOTRIGINE



RALITOLINE



TOPIRAMATE



FLUNARIZINE

FIG. 11. Structures of diverse phenytoin-like anticonvulsants.

trigine was effective during long-term (<2 years) administration in four patients with drug-resistant seizures. Sander et al. (1989) evaluated lamotrigine as an add-on to existing therapy in 85 patients and found the drug most useful in generalized tonic-clonic and atypical absence seizures. Wallace (1989) studied lamotrigine in nine children and suggested that the drug may be useful in myoclonic absences, tonic seizures, and myoclonic jerks. Betts et al. (1989) studied lamotrigine in 70 patients; 50% were improved in this open study. Controlled studies are underway in a number of countries, including the United States, and optimism is high for marketing within the next year or two in some countries.

7. Ralitoline. The thiazolidinone ralitoline [(Z)-N-(2-chloro-6-methylphenyl)-(3-methyl-4-oxo-thiazolidine-2-ylidene)acetamide; fig. 11], like phenytoin, has high activity against maximal electroshock seizures (ED_{50}, 2 mg/kg, p.o., in mice) but fails to be protective in the pentylenetetrazol test. The drug also has a similar anticonvulsant profile to phenytoin against reflex epilepsy in Mongolian gerbils (Bartoszyk and Hamer, 1987) and is said to be protective against reflex seizures in DBA/2 mice and photosensitive baboons; at higher doses the drug has been shown to be protective against hippocampal kindled seizures in rats (Bartoszyk et al., 1986a). In addition, ralitoline is said to have activity against audiogenic seizures, seizures in photosensitive baboons, and against kindled seizures. Ralitoline is more potent than phenytoin in slowing the rate of increase of action potentials in cardiac muscle, suggesting that it may have a similar action on voltage-dependent Na^+ channels as does phenytoin (Wagner et al., 1987).

Ralitoline has not been subjected to more than a few clinical studies, all of which are pilot in nature. The drug has a very short half-life (<4–6 hours), which may require a special delayed-release formulation prior to definitive study. Thus, no statements regarding efficacy are possible at this time.

8. Topiramate. Topiramate, a sulfamate-substituted monosaccharide [2,3:4,5-bis-O-(1-methylethylidine)-β-D-fructopyranose; fig. 11], is structurally distinct from other anticonvulsant drugs. The compound has reasonably high potency in the maximal electroshock test (ED_{50}, 38 mg/kg, i.p., in mice; 17.5 mg/kg, p.o., in rats) but is essentially inactive in the pentylenetetrazol test (Maryanoff et al., 1987). Thus, its profile is similar to that of phenytoin; however, with a protective index in the maximal electroshock test (TD_{50} for motor toxicity/ED_{50}) of approximately 12, it is relatively less toxic. Moreover, topiramate has an unusually long duration of action (>8 hours when given orally in mice). In a clinical study of the interaction of topiramate with carbamazepine, no major interaction was found at various doses of topiramate (Wilensky et al., 1989). Likewise, in patients given topiramate, up to 1200 mg/day, no interactions were found between topiramate and either phenytoin or valproate (Floren et al., 1989). In an add-on open study, topiramate was shown to be efficacious in patients with refractory partial seizures. The drug had no significant toxicity when taken for up to 1 year; side effects consisted mainly of mild cognitive impairment. Multicenter double-blind controlled studies are in progress (Vaught et al., 1989).

9. Flunarizine. The difluorinated piperazine derivative flunarizine {(E)-1[bis(4-fluorophenyl)methyl]-4-(3-phenyl-2-propenyl) piperazine; fig. 11} is a potent organic Ca^{2+} channel antagonist that is able to block T-type as well as L-type Ca^{2+} channels in some tissues (Tytgat et al., 1988). The drug preferentially relaxes vascular smooth muscle with little effect on the heart (Godfraind, 1987) and has a number of clinical indications based upon this distinct spectrum of activity (Todd and Benfield, 1989). In 1975, Desmedt et al. reported that flunarizine and the related smooth muscle-selective Ca^{2+} channel antagonist cinnarizine were highly effective in protecting mice and rats against maximal electroshock seizures. (The ED_{50}s for the two drugs are 21 and 49 mg/kg, p.o., respectively, in mice.) Like phenytoin and carbamazepine, flunarizine and cinnarizine are inactive against clonic seizures produced by pentylenetetrazol, although all of these drugs prevent the tonic phase. Flunarizine also has activity against tonic seizures induced by D,L-allylglycine (Ashton and Wauquier, 1979a), bicuculline (Wauquier et al., 1986), and sound stimulation in DBA/2 mice (Wauquier et al., 1986; De Sarro et al., 1986); it blocks kindled seizures in rats and dogs (Ashton and Wauquier, 1986b; Vezzani et al., 1988b; Wauquier et al., 1979); and provides partial protection against myoclonus in photosensitive baboons (De Sarro et al., 1986). In general, the anticonvulsant profile of flunarizine in these various models is similar to that of phenytoin and, like phenytoin, the drug causes little neurological toxicity at anticonvulsant doses.

In line with its Ca^{2+} channel-blocking activity, flunarizine is able to bind with high affinity to calcium channel antagonist ([^{3}H]nitrendipine) acceptor sites in brain membranes (Leysen and Gommeren, 1984; Gould et al., 1984). Nevertheless, there is no evidence that the anticonvulsant activity of the drug is mediated through an action on neuronal Ca^{2+} channels. In fact, although other Ca^{2+} channel antagonists, particularly those of the dihydropyridine type, can block seizures in a variety of animal models (De Sarro et al., 1988; Meyer et al., 1990), their spectrum of anticonvulsant activity is entirely different from that of flunarizine in that they fail to block maximal electroshock seizures at doses that protect against pentylenetetrazol-induced clonic seizures (Hoffmeister et al., 1982; Popoli et al, 1988; Wong and Rahwan, 1989; S. Yamaguchi and M.A. Rogawski, unpublished observations), whereas, as noted before, flunarizine blocks maximal electroshock tonic seizures but not pentylenetetrazol-induced clonic seizures. Moreover,

even when administered intracerebroventricularly, flunarizine fails to affect pentylenetetrazol-induced seizure activity, although these seizures are blocked in a dose-dependent fashion by intracerebroventricular injection of dihydropyridine Ca^{2+} channel antagonists (Morón et al., 1989; 1990). Finally, flunarizine like phenytoin and carbamazepine has been shown to prevent epileptiform bursting in the in vitro hippocampal slice, whereas nimodipine and the phenylalkylamine Ca^{2+} channel-antagonist verapamil were inactive (Ashton et al., 1986). Because no other organic Ca^{2+} channel blocker (except for the structurally similar piperazine cinnarizine) is able to block tonic seizures like flunarizine, it seems unlikely that Ca^{2+} channel antagonist activity of the drug accounts for this action.

What then is the mechanism of anticonvulsant action of flunarizine? The strong similarity in the anticonvulsant profile of flunarizine and phenytoin suggests that they may have common mechanisms of action. Moreover, there is suggestive evidence that flunarizine may interact with voltage-dependent Na^+ channels in a fashion similar to phenytoin. First, like phenytoin, flunarizine (0.1–1 μM) limits sustained high-frequency repetitive firing of cultured mammalian central neurons (McLean, 1987), an action that has been attributed to use-dependent block of Na^+ channels. Second, flunarizine displaces [^{3}H] batrachotoxin from binding to Na^+ channels in rat brain synaptosomes (Grima et al., 1986).

Flunarizine is marketed (primarily for the treatment of migraine and vertigo) in 38 European, Latin American, Asian, and African countries and more than 7 million patient-years of exposure have been documented (F. de Beukelaar, personal communication). The drug is safe and side effects are generally mild and dose related. Early clinical studies of flunarizine concentrated on determining the appropriate dose that was likely to be effective. Because of the drug's very long half-life (the drug may be detectable in plasma 4 months after its discontinuation!; Frosher et al., 1988), crossover trials are generally considered to be impractical, and, in fact, no effect of the drug was observed in one crossover study (Alving et al., 1989). However, other controlled clinical trials have been encouraging. One of these (Frosher et al., 1988) demonstrated modest efficacy in patients with drug-resistent complex partial seizures; another (Overweg et al., 1984) showed a significant improvement in a similar patient population. In a randomized double-blind study, Battaglia et al. (1989) obtained positive results in 17 children (ages 6–21 years) with a variety of drug-resistant epilepsies. Finally, Binnie (1989), in an extensive review of several additional clinical studies, concluded that approximately one-third of therapy-resistent patients respond to the drug. Two double-blind trials are underway; the first of these is a parallel design, multicenter trial sponsored by the Epilepsy Branch of the National Institute of Neurological Disorders and Stroke, Bethesda, MD. The second is a 40-patient study under the direction of Dr. A. Shakir of Kuwait University. These studies will be critical in the ultimate determination of the efficacy of the compound.

10. Oxcarbazepine. Oxcarbazepine (10,11-dihydro-10-oxo-carbamazepine; fig. 12) is an analog of carbamazepine in which a keto group has been added to the 10-position of the azepine ring. This change results in an important difference in metabolism between the two drugs. Although both carbamazepine and oxcarbazepine are ultimately converted to the inactive *trans*-diol, the effect of 10-oxidation is to prevent the formation of the epoxide intermediate. In man, oxcarbazepine is instead rapidly converted to the active metabolite 10-hydroxycarbazepine (Schtz et al., 1986) which appears to be responsible for most of the anticonvulsant effect. Thus, oxcarbazepine is a prodrug for 10-hydroxycarbazepine. The differences in metabolism give oxcarbazepine three potential advantages over carbamazepine. First, oxcarbazepine is a weaker inducer of hepatic microsomal enzymes (Wagner and Schmidt, 1987) so that there may be less difficulty in adjusting dosage when it is used in conjunction with other antiepileptic drugs and there should be less effect on the levels of other drugs or hormones that are metabolized in the liver. Second, bypassing the production of carbamazepine epoxide may eliminate some of the side effects believed to be caused by this metabolite, such as nausea, headache, diplopia, dizziness, and drowsiness (Patsalos et al., 1985). Third, allergic skin reactions are less frequent during treatment with oxcarbazepine than with carbamazepine (Dam et al., 1989), and only a small fraction (27%) of patients who are allergic to carbamazepine cross-react with oxcarbazepine (Gram and Philbert, 1986). The drug does, however, appear to cause hyponatremia like carbamazepine (Johannessen and Nielson, 1987; Nielsen et al., 1988).

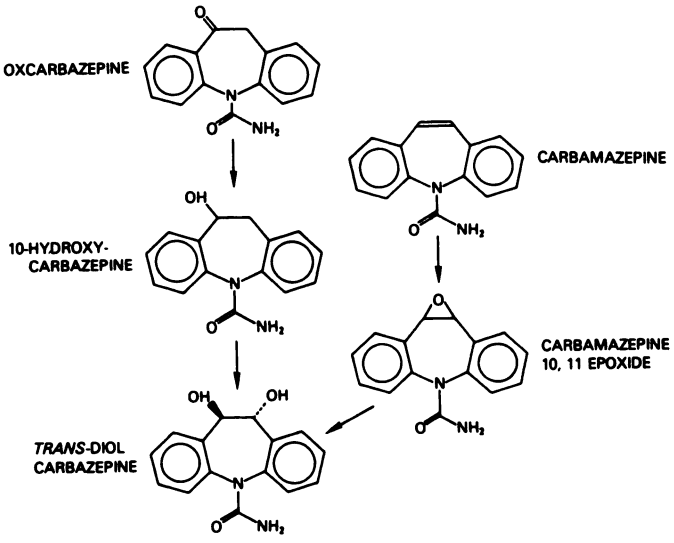


FIG. 12. Comparison of the metabolism of oxcarbazepine and carbamazepine.

Like carbamazepine, oxcarbazepine and 10-hydroxycarbazepine are effective against tonic seizures in the maximal electroshock test [although the dose required is approximately 50% higher (ED_{50}, 10–20 mg/kg, p.o., in rats and mice)] but are less active against pentylenetetrazol-, picrotoxin-, or strychnine-induced seizures (Dam and Jensen, 1989). The drugs also prevent partial seizures in rhesus monkeys induced by application of alumina gel to the motor cortex.

More than 700 patients with epilepsy have been studied in clinical trials with oxcarbazepine (Dam and Jensen, 1989). Most clinical studies have compared the drug with its prototype carbamazepine. Early controlled studies concluded that the efficacy of the two drugs was not distinguishable but that oxcarbazepine had fewer adverse effects (Houtkooper et al., 1987; Reinikainen et al., 1987). In a large multicenter study of patients with newly diagnosed epilepsy, Dam et al. (1989) showed similar results: there was no significant difference in seizure frequency between carbamazepine and oxcarbazepine and, again, the latter compound appeared to be better tolerated by some patients. Recently, in a single-blind study, Aikia et al. (1989) found phenytoin and oxcarbazepine to be similarly effective after 1 year of therapy with each.

11. Remacemide. The structurally novel anticonvulsant remacemide [(±)-2-amino-N-(1-methyl-1,2-diphenylethyl)acetamide; PR 934–423 or FPL 12924AA] emerged from a drug discovery program aimed at creating a molecule whose three-dimensional structure matched that of phenytoin. In fact, this approach resulted in a compound whose anticonvulsant profile is surprisingly similar to that of phenytoin. Thus, remacemide is protective in the maximal electroshock test in mice (ED_{50}, 78 mg/kg, p.o.) and rats (29 mg/kg) and is essentially inactive against pentylenetetrazol-induced seizures. The drug is also active against audiogenic seizures in DBA/2 mice (ED_{50}, 86 mg/kg) (Palmer et al., 1990) but fails to block seizures induced by picrotoxin, bicuculline, and strychnine. It is inactive against kindled seizures in rats and does not retard the development of kindling (G. C. Palmer, personnel communication). The protective index in the maximal electroshock test (rotorod TD_{50}/ED_{50}) is 5.6 (however, this can vary markedly depending upon the species of mouse used). Although both enantiomers of remacemide are active in the electroshock test, the (−)isomer is more potent than the racemate which, in turn, is more potent than the (+)isomer. Interestingly, the drug is quite effective in protecting mice against seizures (ED_{50}, 57 mg/kg, i.p.) and lethality induced by intravenous NMDA suggesting that it might interact with NMDA receptors. However, in electrophysiological experiments, the drug failed to affect NMDA-induced depolarization of neurons in the in vitro hippocampal slice preparation (G. C. Palmer, personnel communication). Moreover, although remacemide does interact with the MK-801 and glycine acceptor sites on the NMDA receptor-channel complex, its affinities at these sites are probably too weak to explain the in vivo anticonvulsant activity (IC_{50} values, 64 and 168 μM, respectively). [Rats protected in the electroshock test had CSF levels of 153 ng/ml (0.5 μM); Wilson et al., 1988.] Like other drugs that are primarily effective against maximal electroshock seizures, remacemide blocks sustained repetitive firing in cultured neurons at relatively low concentrations (6.4 μM). Thus, at present, a phenytoin-like interaction with voltage-dependent Na^+ channels is the most plausible mechanism to explain remacemide's anticonvulsant action. Remacemide has successfully survived animal toxicological testing and phase I clinical testing in humans; it is currently undergoing clinical evaluation in patients with seizure disorders.

B. Progabide, an Agonist of the GABA Receptor-Cl^- Channel Complex

As reviewed above, there is strong evidence that many of the antiepileptic drugs in common clinical use (e.g., benzodiazepines, barbiturates, and valproate) exert their anticonvulsant actions, at least in part, by enhancing GABA-mediated inhibition in the CNS. This recognition has led to the rational development of several potentially useful new drugs that also enhance central inhibition through an interaction with the GABA system but do so by novel mechanisms. One such compound is progabide (4-{[(4-chlorophenyl,5-fluro-2-hydroxyphenyl)methylene]amino}-butanamide; fig. 13), a lipid-soluble derivative of the amidated form of GABA (GABAmide), which, unlike GABA, is readily able to cross the blood-brain barrier. Within the brain, progabide undergoes a series of metabolic transformations resulting in active and inactive metabolites. Of particular importance is its deamidation to the much less lipid-soluble acid SL 75102 (fig. 13) which is then slowly converted to GABA. Alternatively, the imine bond of progabide can undergo hydrolysis leading to the formation of GABAmide (Worms et al., 1982). Progabide, SL 75102, GABAmide, and of course GABA, are all direct agonists of brain GABA receptors, and these four compounds account for 70% of the brain radioactivity after administration of radiolabeled progabide (Morselli et al., 1986). Thus, progabide, GABAmide, and SL 75102 have been shown to have moderate affinity for high-affinity GABA receptors with

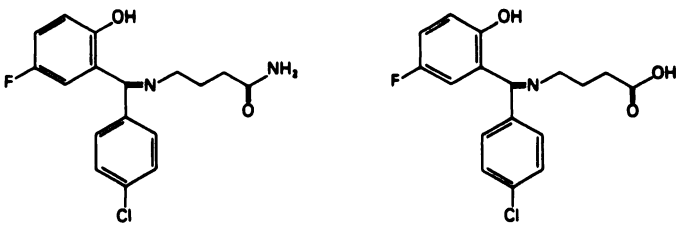


FIG. 13. Structures of progabide and its active metabolite SL 75102.

IC_{50} values in displacement assays using [^{3}H]GABA of 35, 17, and 1.5 μM, respectively (Lloyd et al., 1982). However, even SL 75102 is a substantially weaker ligand than the selective $GABA_A$ receptor agonist muscimol (IC_{50}, 9 nM) or GABA itself (IC_{50}, 60 nM). Like GABA and muscimol, progabide and SL 75012 can increase (in a bicuculline-sensitive fashion) the in vitro and in vivo binding of [^{3}H]diazepam or [^{3}H]flunitrazepam to brain benzodiazepine receptors (Lloyd et al., 1982; Koe, 1983). Because progabide and SL 75012 do not antagonize the modulatory effect of GABA in this assay, as do the partial agonists THIP and isoguavacine, they appear to be full *agonists* at the GABA recognition site. Also like GABA, but in contrast to muscimol, the novel compounds bind to $GABA_B$ receptors with approximately similar affinities as they bind to $GABA_A$ receptors (Bowery et al., 1982). Progabide and SL 75012 are highly specific for the GABA receptor system per se and do not significantly influence GABA synthesis, metabolism, or reuptake (Lloyd et al., 1982). Electrophysiological studies in peripheral ganglia have confirmed that SL 75102 can act as a full agonist at both $GABA_A$ and $GABA_B$ receptors (Desarmenien et al., 1981; Bowery et al., 1982). Thus, SL 75102 depolarizes superior cervical ganglion neurons by activating Cl^- channels with equal efficacy to GABA but one-tenth the potency, and this effect is competitively antagonized by bicuculline.

Local intracerebral injections of the $GABA_A$ agonist muscimol into, for example, the substantia nigra are well known to protect against seizures (Sperber et al., 1989; Depaulis et al., 1988). However, muscimol penetrates into the brain poorly and is unsuitable for clinical use as an antiepileptic because of its toxicity (Baraldi et al., 1979; Pedley et al., 1979). Similarly, the peripherally acting GABA receptor agonist THIP has some anticonvulsant activity but is also too toxic to be used clinically (Meldrum and Horton, 1980; Löscher, 1985; Depaulis et al., 1988). Surprisingly, however, progabide has a very wide spectrum of anticonvulsant activity in animal seizure models *and* low toxicity. Thus, the drug is effective against tonic seizures in the mouse maximal electroshock test (ED_{50}, 75 mg/kg, i.p.) and against clonic seizures in the mouse pentylenetetrazol test (ED_{50}, 30 mg/kg) (Worms et al., 1982; Morselli et al., 1986) but exhibits motor toxicity only at high doses (rotarod ED_{50}, 250 mg/kg, i.p.; Morselli et al., 1986). In addition, progabide can prevent seizures caused by a variety of other chemoconvulsants including bicuculline, picrotoxinin, allylglycine, penicillin, and strychnine (Golden and Fariello, 1984); it is active against reflex seizures in DBA/2 mice, photosensitive baboons (Cepeda et al., 1982) and Mongolian gerbils (Löscher, 1985); and it is weakly active against amygdaloid-kindled seizures in rats (Joy et al., 1984; Löscher and Schwark, 1985). This anticonvulsant activity presumably reflects direct stimulation of $GABA_A$ receptors by progabide and its metabolites because the selective $GABA_B$ receptor agonist baclofen fails to prevent seizures in most models (Mehta and Ticku, 1988). However, because progabide has a broader spectrum of anticonvulsant activity than the selective $GABA_A$ agonist muscimol, activation of $GABA_B$ receptors may to some degree play a role in its clinical activity.

An enormous amount of clinical data has accumulated concerning progabide (Morselli et al., 1986; 1989). Open studies have repeatedly suggested that progabide is an effective agent; one of these was published as late as 1988 by Benassi et al. (1988a). The drug is said to have a broad spectrum of antiepileptic activity, being effective in the treatment of simple and complex partial seizures, generalized tonic-clonic seizures, and myoclonic seizures, but not absence seizures (Morselli, 1989). Unfortunately, two factors have slowed progabide's acceptance. The first is the accumulation of controlled clinical trials that failed to document the efficacy of the drug (Dam et al., 1983; Schmidt and Utech, 1986; Leppik et al., 1987). Although these studies are partially offset by other controlled studies that suggest that efficacy is indeed present (Van der Linden et al., 1981; Loiseau et al., 1983; Weber et al., 1985; Martinez-Lage et al., 1984), enthusiasm for the drug has been somewhat diminished by these negative trials.

The second factor is the drug's tendency to cause hepatotoxicity (comparable in incidence and severity to that of isoniazid), which, by itself, would not have slowed the development of the drug. Progabide has been marketed in France since 1985. Its fate in other countries is uncertain, but it is no longer under investigation in many, including the United States.

C. Drugs That Potentiate Inhibition by an Action That Does Not Involve an Interaction with the GABA Receptor-Channel Complex

1. Vigabatrin. The GABA analog vigabatrin (γ-vinyl-GABA; fig. 14) is a specific, enzyme-activated inhibitor of the GABA catabolic enzyme GABA-T. The drug becomes covalently linked to GABA-T at its active site and thereby causes an irreversible inhibition of the enzyme (Lippert et al., 1977). Although GABA itself is unable to penetrate the blood-brain barrier, vigabatrin does pass into the CNS and measurable levels can be detected in the lumbar CSF after a single oral dose (representing about 10% of blood levels in human subjects; Ben Menachem et al., 1988). The peak levels achieved in the CSF (~3–12 μM; Pitkänen et al., 1988; Riekkinen et al., 1989; Ben Menachem et al., 1988) after single or multiple 50 mg/kg, p.o., dose(s) are close to those necessary to inhibit GABA-T in vitro (IC_{50}, 24 μM; Larsson et al., 1986). In animals, brain GABA-T activity is rapidly reduced by 80% after a single injection of vigabatrin (Jung et al., 1977) and the fraction of the enzyme inhibited can be enhanced with repeated doses (Perry et al., 1979). Recovery of GABA-T activity requires synthesis of new enzyme which takes several days (Lippert et al., 1977;

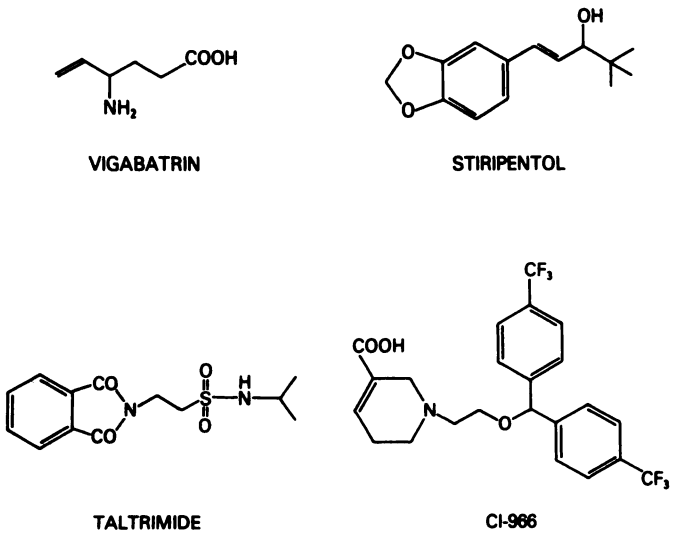


FIG. 14. Structures of several drugs that enhance central inhibition.

Larsson et al., 1986). Because transamination by GABA-T represents the only important pathway for catabolism of brain GABA, the irreversible inhibition of GABA-T by vigabatrin results in a prolonged elevation in brain GABA levels (Jung et al., 1977). This elevation appears to occur throughout the brain, both in neurons (Abdul-Ghani et al., 1981) and in glia (Neal et al., 1989). However, glial GABA-T is less sensitive to vigabatrin (Larsson et al., 1986), apparently because glial cells fail to possess a high-affinity uptake system for the drug (Schousboe et al., 1986). There is evidence that the excess neuronal GABA is in a releasable pool so that larger amounts of GABA are discharged with stimulation (Gram et al., 1988). Moreover, it has been suggested that the glial GABA can also be released with depolarizing stimuli, such as might occur as K^+ accumulates extracellularly during a seizure (Neal et al., 1989). Several studies have demonstrated that vigabatrin causes a several-fold increase in the CSF levels of GABA in epileptic patients receiving the drug (Schechter et al., 1984; Ben Menachem et al., 1988; Pitkänen et al., 1988; Riekkinen et al., 1989).

The elevation in brain GABA produced by vigabatrin is associated with a potent anticonvulsant effect in several animal seizure models (Palfreyman et al., 1981), including amygdala-kindled seizures (Myslobodsky et al., 1979; Kalichman et al., 1982; Shin et al., 1986), audiogenic seizures in genetically susceptible mice (Schechter et al., 1977), photogenic epilepsy in baboons (Meldrum and Horton, 1978), and certain chemically induced seizures (Bernasconi et al., 1988) including those produced by pentylenetetrazol (however, see Mysolobodsky et al., 1979), the GABA antagonist picrotoxin (however, see Kendall et al., 1981), and the glycine antagonist strychnine. Vigabatrin also appears to be capable of slowing the development of epilepsy in the kindling model (Shin et al., 1986). The effect of the drug in the maximal electroshock seizure model is controversial (Bernasconi et al., 1988; Iadarola and Gale, 1981). As expected, only the pharmacologically active S (+) optical isomer has anticonvulsant activity (Meldrum and Murugaiah, 1983). Several authors have observed a paradoxical proconvulsant effect of vigabatrin that may relate to a withdrawal phenomenon (Löscher et al., 1989), suggesting that investigators should be alert to possible increases in seizure frequency upon discontinuation of the drug. In summary, the antiepileptic action of vigabatrin almost certainly reflects its inactivation of GABA-T, and it therefore represents one of the few anticonvulsant drugs whose cellular target has been definitively identified. Nevertheless, the precise way in which inhibition of GABA-T results in prevention of seizures remains to be clarified (Bernasconi et al., 1988).

Controlled clinical trials have amply demonstrated that vigabatrin has antiepileptic activity as add-on therapy in previously drug-resistant patients. However, the drug presents an interesting toxicological dilemma. In mice, rats, dogs, and perhaps monkeys, vigabatrin produces a dose-related microvacuolization of the outer lamellar sheaths of myelinated axons, an effect referred to as "intramyelinic edema" (Butler et al., 1987; Butler, 1989; Graham, 1989). The lesions are somewhat similar to those produced by isoniazid, hexachlorophene, and triethyltin but are reversible and localized. The significance of these lesions has been repeatedly questioned, particularly because they have not been observed in humans (Anonymous, 1989; Porter, 1990). Although studies of the drug have been restricted in the United States, more than 2500 patients have been exposed to vigabatrin in European clinical trials. None of the patients under study have shown any evidence of toxicity that might be related to intramyelinic edema. In addition, a few pathological series have been negative. Trottier et al. (1989) and Paljärvi et al. (1990) failed to detect histopathological changes either with light or electron microscopy in brain specimens taken during epilepsy surgery from patients who had received long-term vigabatrin therapy. In three human postmortem cases, the abnormal changes seen in animals were not present (Olafsson et al., 1989). Efforts to detect early pathological changes in patients receiving vigabatrin using evoked potential measurements have been consistently negative (Kälviainen et al., 1989a; Liegeois-Chavel et al., 1989; Cosi et al., 1989), although it is not clear that such an approach will detect minimal lesions (Porter, 1990).

In spite of the uncertainty regarding the potential toxicity of vigabatrin, a surprising amount of high-quality clinical information is available, including complete reports from seven double-blind studies (Gram et al., 1983; Loiseau et al., 1986; Remy et al., 1986; Reynolds et al., 1988; Rimmer and Richens, 1984; Tartara et al., 1986; Tassinari et al., 1987). These studies clearly demonstrate that the drug is efficacious at doses of 1.5–3 g/day. The number of patients who completed each study was very

high, varying from 82–96%, indicating that the drug is well tolerated. In all seven studies the drug was effective, although in some (e.g., Remy et al.) the improvement only reached statistical significance for patients with complex partial seizures. Because this seizure type is the most important uncontrolled seizure type in adults, the drug appears to be a significant advance.

A large number of other recent studies have been reported in preliminary form; these have also been favorable. Reynolds (1990), in a double-blind study of 20 patients, documented the effectiveness of vigabatrin in patients with complex partial seizures. Other studies include those of Dam (1989), Trevisol-Bittencourt et al. (1989), Faedda et al. (1989), Tartara et al. (1989), Michelucci and Tassinari (1989), Chauvel et al. (1989), Gorz et al. (1989), Besser and Kramer (1989), Haan (1989), and Sivenius (1990). The antiepileptic activity of vigabatrin was confirmed in an unusual way by acute withdrawal of a single dose in a controlled investigation reported by Ried and Schmidt (1989).

There have been fewer trials of vigabatrin in children, although those that have been reported have shown comparable efficacy as in adults. Luna et al. (1989) studied 61 children with refractory epilepsy in a 16-week, single-blind, add-on, placebo-controlled trial. Thirty-eight percent showed a reduction of >50% in seizure frequency, and this beneficial effect was maintained for up to 11 months in some patients. Livingston et al. (1989) studied 135 patients with refractory seizures, including partial and generalized seizures, Lennox-Gastaut syndrome, and West syndrome. Thirty-seven percent of the children had a >50% reduction in seizures. Herranz et al. (1989) were unable to document the efficacy of vigabatrin in a single-blind study of children with partial epilepsy, although a few individual patients appeared to be improved. In an open trial of vigabatrin in infantile spasms, some patients appeared to respond (Chiron et al., 1989).

Conspicuous by their absence are controlled studies from North America. The closest approximation is a multicenter study described by Browne et al. (1989) in which 89 patients with refractory complex partial seizures were treated with doses averaging 3.2 g/day (range 1–4 g/day). Fifty-one percent of the patients had ≥50% reduction in seizure frequency; the major adverse reactions were drowsiness, ataxia, headache, irritability, dizziness, and unsteadiness. Sixty-six patients having a favorable response continued to receive the drug for up to 73 months (median 44 months). No toxicity other than reversible, dose-dependent side effects were detected and only 11 patients experienced clinically significant "breakthrough" seizures during the follow-up period.

Except for a handful of patients, studies of vigabatrin in the United States were halted in 1983. Although vigabatrin has been approved for marketing in England, Ireland, and France, its future in North America is uncertain. The drug has been released for study by the U.S. Food and Drug Administration, but several years of clinical investigations will be required prior to approval for marketing.

2. Stiripentol. Stiripentol {4,4-dimethyl-1-[3,4-(methylendioxy)-phenyl]-1-penten-3-ol; fig. 14} has a broad spectrum of anticonvulsant activity against electrically and chemically (pentylenetetrazol and bicuculline) induced seizures (Poisson et al., 1984). The ED_{50} against electroshock seizures in rats is approximately 240 mg/kg, i.p., and against pentylenetetrazol seizures in mice about 200 mg/kg, i.p. (Vincent, 1986). The drug has also been shown to delay the onset of seizures precipitated by 4-deoxypyridoxine HCl in alumina gel-treated rhesus monkeys (Lockard et al., 1985). The action of the drug to delay but not to prevent seizures in this model was similar to valproate and was different from that of other anticonvulsants (phenytoin, carbamazepine, phenobarbital, and diazepam). Like valproate, stiripentol increases the whole brain GABA level (22% at 300 mg/kg in mice) (Poisson et al., 1984). Two possible mechanisms could account for this effect: inhibition of GABA uptake (Poisson et al., 1984) and blockade of GABA-T (Wegmann et al., 1978).

Stiripentol has been widely evaluated in both Europe and the United States. As of mid-1988, >200 patients had been studied in Spain, France, and the United States. Pilot studies in patients with refractory partial seizures include that of Martinez-Lage et al. (1987) in which 16 of 26 patients were helped, Loiseau et al. (1988) in which 6 of 9 patients improved, and Rascol et al. (1989) in which at least 5 of 7 patients responded. Levy et al. (1989) demonstrated that stiripentol reduces the clearance of carbamazepine and that the daily dose of carbamazepine should be reduced immediately after the introduction of stiripentol regardless of age. Farwell et al. (1989) evaluated stiripentol in an open study of atypical absence seizures and found the drug to be promising. Preliminary results from another trial of refractory absence seizures were also encouraging (Loiseau and Duche, 1989b). Controlled clinical trials are underway, but no data are available from such studies at this time.

3. Milacemide. Milacemide (2-N-pentylaminoacetamide; fig. 15) is a potent antagonist of pentylenetetrazol- and bicuculline-induced seizures whose anticonvulsant activity is believed to result from its conversion in brain to the inhibitory amino acid glycine (van Dorsser et al., 1983) and possibly also from its ability to increase regional GABA levels (Janssens de Varebeke et al., 1983). The anticonvulsant profile of milacemide is unusual in that the drug blocks both the tonic and clonic components of bicuculline-induced seizures at low doses (ED_{50}, 5.7 mg/kg, p.o.; van Dorsser et al., 1983), whereas much higher doses are required in other seizure models (e.g., the ED_{50} against pentylenetetrazol seizures is 741 mg/

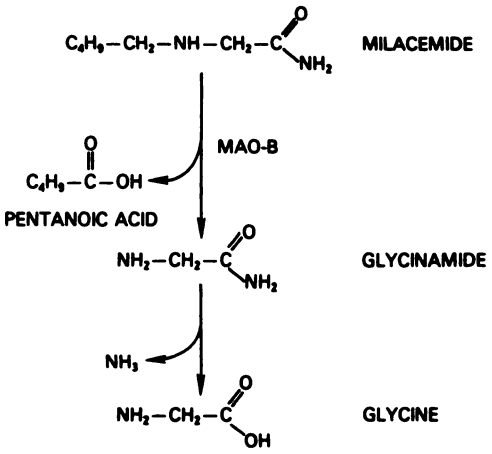


FIG. 15. Metabolism of milacemide to glycine.

kg). High doses of milacemide can also reduce the duration of the afterdischarge in kindled rats (Albertson et al., 1984b) and have been reported to suppress spike firing induced by cortical application of cobalt powder (Roba et al., 1986). The drug is inactive against reflex seizures in DBA/2 mice (Chapman and Hart, 1988) or Mongolian gerbils (Löscher, 1985). Milacemide has a low propensity to cause neurological toxicity and fails to cause ataxia in rats or to prolong pentobarbital-induced sleeping time in mice in doses as high as 1000 mg/kg, p.o.

Unlike glycine, milacemide readily crosses the blood-brain barrier and is actively metabolized to glycinamide, primarily by monoamine oxidase-B (Janssens de Varebeke et al., 1988; 1989) and possibly also to a lesser extent by monoamine oxidase-A (Truong et al., 1989). The drug has a high affinity for monoamine oxidase-B (K_m, 30–80 μM; Janssens de Varebeke et al., 1988), and inhibits the enzyme in a partially reversible manner (Janssens de Varebeke et al., 1989) so that patients taking the drug would be advised to follow the same dietary restrictions as for other monoamine oxidase inhibitors. Glycinamide is further converted to glycine, leading to significant increases in glycine concentrations in many brain areas (Chapman and Hart, 1988). In rats, 2 hours after an oral dose of milacemide (100 mg/kg), glycine levels were elevated by 12% in the brainstem and 30% in the forebrain. These increased levels of glycine presumably cause neuronal inhibition and a resultant anticonvulsant effect via an action on strychnine-sensitive glycine receptors (Alger, 1985). In fact, glycine itself has been reported to have anticonvulsant activity in some seizure models when injected intracerebroventricularly (Lapin, 1981) or even systemically in some cases (Toth et al., 1983). Glycine can also enhance excitation via its interaction with the strychnine-insensitive glycine site on the NMDA receptor-channel complex (Johnson and Ascher, 1987). Whether the elevation of brain glycine levels produced by milacemide causes a physiologically relevant effect on excitatory neurotransmission is unknown. However, it is of interest to note that milacemide produces regionally specific increases in brain metabolic rate as measured by the uptake of [^{3}H]2-deoxyglucose (Roba et al., 1986).

Although milacemide does not alter whole brain GABA levels, it can produce substantial regional increases in the GABA content of certain brain areas. For example, the GABA content of the substantia nigra increases by 40% in rats treated with a single 100-mg/kg, p.o., dose. This effect appears to occur as a result of an in vivo increase in the activity of the GABA-synthesizing enzyme glutamic acid decarboxylase (Jannsens de Varebeke et al., 1983). The relative importance of the effects on GABA and glycine to the anticonvulsant activity of milacemide are unknown, and the ability of milacemide to block bicuculline-induced seizures at doses less than those that have been reported to increase inhibitory amino acid levels suggests that additional mechanisms may need to be invoked.

More than 500 epileptic patients have been exposed to milacemide at various dosage levels, some for as many as 5 years. However, in spite of the substantial clinical experience with the drug, only a few definitive studies are available. One study, that of Houtkooper et al. (1986), evaluated 60 patients in a double-blind placebo-controlled parallel design; it was found that 9 of 29 patients responded to milacemide, whereas only 2 of 29 responded to placebo. This effect, however, was not statistically significant. In a two-center double-blind placebo-controlled randomized parallel group study of 40 patients, Norton et al. (1986) found that, of the 21 patients receiving milacemide, 4 had a response of more than a 50% decrease in seizures; 4 others had a partial response. Because of these marginal effects, development of the drug is no longer being pursued in the United States.

4. Taltrimide. The sulfur-containing amino acid taurine, which is present in brain at concentrations comparable to GABA and glycine, has long been known to inhibit central neurons via activation of Cl^- channels in a strychnine-sensitive fashion (Huxtable, 1989; Mathers et al., 1989). Cross-desensitization experiments have suggested that taurine can activate glycine receptors (Krishtal et al., 1988; however, see Okamoto and Sakai, 1980). Taurine is a polar compound that poorly crosses the blood-brain barrier. Consequently, like GABA or glycine, it has little in the way of anticonvulsant activity, except when applied directly to the surface of the brain. However, the recognition that taurine has a potent inhibitory action on neurons was the impetus to synthesize a series of lipophilic derivatives and to test their efficacy as anticonvulsants. Of the compounds screened, taltrimide (2-phthalimidoethanesulphon-N-isopropylamide; fig. 14) was considered the most promising because of its efficacy and low toxicity. Taltrimide has been shown to be protective against maximal electroshock seizures in mice, to suppress reflex seizures in genetically epilepsy prone rats, and to prevent seizures induced by various convulsant

drugs including pentylenetetrazol, bicuculline, picrotoxin, isoniazid, thiosemicarbazide, and strychnine (Kontro and Oja, 1987a; Nakagawa and Huxtable, 1985).

Taltrimide and its dealkylated metabolite 2-phthalimidoethanesulphonamide (MY-103) are potent inhibitors of [^{3}H]taurine binding to brain membranes; taltrimide has about the same affinity as taurine in this assay (Kontro and Oja, 1987a,b). Although the precise nature of taurine-binding sites is yet to be clarified, these studies are consistent with the idea that taltrimide is a taurine agonist, although electrophysiological studies will be necessary to confirm this point. Taltrimide does not appear to bind to the $GABA_A$ receptor or to benzodiazepine receptors (Malminen and Kontro, 1989). Low concentrations of taltrimide and MY-103 have also been reported to enhance K^+ depolarization-induced release of GABA from cerebral cortical slices, and it has been suggested that this may also contribute to the anticonvulsant activity of the drug (Kontro and Oja, 1987a).

Information regarding the potential clinical efficacy of taltrimide is limited. An add-on study in nine drug-resistant patients, five with progressive myoclonus epilepsy and four with complex partial seizures, failed to show any activity (Airaksinen et al., 1987), and at higher doses the drug appeared to increase the seizure frequency (Koivisto et al., 1986). More recently, however, Iivanainen et al. (1989), in a randomized placebo-controlled crossover study of 17 patients, concluded that the drug was as effective in primary generalized epilepsy as valproate but that it was not effective in partial seizures.

5. CI-966. An alternative strategy for enhancing central GABA-mediated inhibition is blockade of GABA reuptake into nerve terminals which occurs via a high-affinity, sodium-dependent transport system. However, conventional GABA reuptake blockers such as L-2,4-diaminobutyrate, guvacine, and nipecotic acid fail to penetrate the blood-brain barrier and are, therefore, not useful clinically. CI-966 is a nipecotic acid derivative that has emerged from a program to develop blood-brain barrier-permeable GABA reuptake blockers by coupling nipecotic acid (or a structurally related analog) to a lipophilic anchor. CI-966 has a substantially higher potency as a GABA reuptake blocker than nipecotic acid or guvacine (IC_{50}, 0.30 versus 5.2 and 6.8 μM, respectively) and is behaviorally active even when administered orally, indicating that it crosses the blood-brain barrier. As expected from its specific action on GABA systems, CI-966 is a potent blocker of pentylenetetrazol-induced clonic seizures (ED_{50}, 0.5–1.0 mg/kg, p.o., in mice) but prevents maximal electroshock seizures only at higher doses (2.6 mg/kg; Taylor et al., 1990). In mice, these doses were substantially lower than those that caused ataxia (64 mg/kg). Unfortunately, in dogs and monkeys, the drug causes ataxia and other neurological side effects including tremors and myoclonus at low doses (dogs: 5 mg/kg, p.o.; monkeys: 3 mg/kg, i.m.). In single-dose trials in two healthy human volunteers, CI-966 (50 mg, p.o.) caused severe psychiatric and neurological side effects, including psychotic symptoms, mania, myoclonus, and parkinsonism (Sedman et al, 1990). These observations have resulted in CI-966 being withdrawn from further clinical evaluation (C. P. Taylor, personal communication).

6. Tiagabine. A second and perhaps better tolerated centrally active nipecotic acid derivative is tiagabine {R(−)-N-[4,4-di(3-methyl-thien-2-yl)-but-3-enyl]nipecotic acid HCl; NO-05–0328}. Although structurally similar to CI-966, tiagabine is a more potent selective inhibitor of neuronal and glial GABA uptake, having an IC_{50} of 67 nM (Braestrup et al., 1990). The drug only very weakly interacts with the $GABA_A$ or benzodiazepine recognition sites and does not bind to other neurotransmitter receptors. Despite its higher in vitro affinity for the GABA uptake site than CI-966, tiagabine is somewhat less potent as a blocker of pentylenetetrazol-induced clonic seizures in mice (ED_{50}, 1.3 mg/kg, i.p.; M. W. Pierce, personal communication), suggesting that it may less effectively penetrate the blood-brain barrier. In addition to its activity against pentylenetetrazol seizures, tiagabine blocks audiogenic seizures in DBA/2 mice (0.4 mg/kg) and amygdaloid-kindled seizures in rats (3 mg/kg). The drug is also active against reflex seizures in photosensitive baboons at doses that do not cause neurological impairment. However, tigabine only weakly protects against maximal electroshock seizures (40 mg/kg, i.p., in rats). In rats and mice, the drug causes sedation, impairment of motor function, and neurological side effects incuding tremor and posturing only at doses considerably greater than those that protect against seizures (>12.5 mg/kg, i.p.). Similarly, in human trials, oral doses up to 10 mg daily caused only mild and transient symptoms, whereas a single 24-mg, p.o., dose caused unacceptable side effects in all subjects. Whether nontoxic doses of tiagabine will provide useful antiepileptic activity in human patients remains to be determined.

D. Drugs That Bind to Benzodiazepine Receptors

1. Clobazam. Clobazam (fig. 4) is a 1,5-benzodiazepine which differs from 1,4-benzodiazepines such as diazepam in having a nitrogen in the 5-position instead of at the 4-position of the heterocyclic ring. Initial studies of the anticonvulsant activity of clobazam indicated that the drug had a similar profile to other benzodiazepines in that it is able to protect against clonic seizures induced by pentylenetetrazol, bicuculline, picrotoxin, and strychnine and also against tonic seizures in the maximal electroshock test (Barzaghi et al., 1973; Trimble and Robertson, 1986). Subsequently, clobazam (Chapman et al., 1978) and its active metabolite N-desmethylclobazam (Meldrum and Croucher, 1982) were shown to protect against reflex seizures in DBA/2 mice and photosensitive baboons. Clobazam is also effective against amygdaloid-kindled seizures in rats (Ichimaru et al., 1987; Rosenberg

et al., 1989; Tietz et al., 1989). However, of particular interest was the observation first noted in humans (Hindmarch, 1979) and then confirmed in animal studies (Shenoy et al., 1982; Stéru et al., 1986; Trimble and Robertson, 1986) that clobazam produces less sedation and motor toxicity at anticonvulsant doses than other benzodiazepines such as diazepam or nitrazepam. Thus, clobazam is approximately equipotent with diazepam in preventing electroshock seizures, one-fifth as potent in protecting against pentylenetetrazol-induced clonic seizures, and one-ninth as potent in inducing motor toxicity in the rotorod ataxia test. The basis for the selective anticonvulsant activity of clobazam is unknown and does not appear to hold in all seizure models (Tietz et al., 1989). Nevertheless, clobazam's high relative potency against electroshock seizures indicates that the drug should be examined for phenytoin-like actions. As with 1,4-benzodiazepines, chronic administration of clobazam results in the development of tolerance to the sedative *and* anticonvulsant actions of the drug in both animals and human subjects (Gent et al., 1984; Young et al., 1988).

There are a large number of well-controlled clinical studies that demonstrate clobazam's short-term activity against partial and generalized seizures in patients of all ages and the drug is said to be relatively effective in the Lennox-Gastaut syndrome (Hindmarch and Stonier, 1981; Hentschel, 1987; Shorvon, 1989). Presumably because it is a benzodiazepine, and because benzodiazepines have a excellent safety record, the drug has been rapidly approved in at least 50 countries throughout the world, with the notable exception of the United States. Nevertheless, no definitive study has as yet documented that, when corrections for potency are made, the drug is less sedating than other benzodiazepine in human studies. As with all benzodiazepines, the development of tolerance limits the usefulness of the drug in most patients; there may, however, be a few patients for whom the drug is effective on a long-term basis (Heller et al., 1988). Some investigators have suggested that the active metabolite N-desmethylclobazam may be clinically superior to the parent compound (Haigh et al., 1987).

2. *Flumazenil.* As discussed in section III, A, 1, the benzodiazepine receptor antagonist flumazenil may actually have weak partial agonist activity at benzodiazepine receptors. As a consequence, the drug has anticonvulsant activity in animal seizure models. Recently, Scollo-Lavizzari (1984; 1988) reported that oral flumazenil when used alone or in combination with other antiepileptic drugs can reduce the frequency of electrographic spike and wave discharges and also decrease the number of behavioral seizures for periods of up to 42 months. The drug is being studied in Europe where controlled clinical trials are currently ongoing. Data from some of these studies may be available by late 1990.

E. Drugs That Block Excitatory Amino Acid Receptors

Recent advances in the physiology and pharmacology of excitatory amino acid transmitter systems have highlighted the potential of excitatory amino acid receptors as a target for anticonvulsant drugs. The amino acids glutamate and aspartate have long been known to excite neurons and cause convulsive activity when applied to the cerebral cortex (Hayashi, 1954; see Nistri, 1985, for additional references). However, clarification of the cellular mechanisms underlying these actions has only been provided in the past decade as a result of the development of selective agonists and antagonists largely by Watkins and his collaborators (Oliverman and Watkins, 1989; Monaghan et al., 1989; Collingridge and Lester, 1989). It has been possible to classify excitatory amino acid receptors, using these pharmacological tools, into three subtypes, identified by the agonists that selectively activate them: quisqualate [now more properly referred to by the more specific agonist AMPA (α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid)], kainate, and NMDA (Watkins, 1989). Each of these receptors is coupled to a cation channel that opens in response to agonist binding and acts to depolarize the target cell. The NMDA receptor-channel complex is endowed with a number of special features that distinguishes it from the quisqualate or kainate receptor channels. These features include a sensitivity to blockade by physiological concentrations of Mg^{2+}, a high permeability to Ca^{2+}, and a requirement for coactivation by glycine. Moreover, it is now apparent that the NMDA receptor plays a critical role in many types of seizures, and there is a growing body of data that implicates NMDA receptors in the development of some forms of epilepsy (Vezzani et al., 1988a; McNamara et al., 1988). The evidence linking NMDA receptors to acute seizures is two-fold. First, activation of NMDA receptors on neurons in, for example, the in vitro hippocampal slice leads to burst firing reminiscent of epileptiform discharges recorded in various seizure models (Peet et al., 1986a,b; 1987). In contrast, activation of quisqualate or kainate receptors produces steady depolarization but does not lead to bursting. Second, selective NMDA receptor antagonists and drugs that otherwise depress responses mediated by NMDA receptors are anticonvulsant in many seizure models. For the competitive antagonists, there is a strong correlation between their affinity for NMDA receptors and anticonvulsant potency (Pedder et al., 1989). Although none of the presently marketed antiepileptic drugs are believed to operate by blockade of NMDA receptors, several excitatory amino acid antagonists are currently undergoing clinical evaluation. In animal models, NMDA antagonists produce a number of neurological side effects, including effects on motor performance and memory function at doses close to those that protect against seizures. At present, it is unknown whether these and other potential neurological toxicities will prevent the use of

NMDA receptor-targeted drugs for the chronic treatment of seizure disorders in man.

1. Competitive antagonists of the NMDA recognition site. The first potent and selective competitive antagonists of the NMDA recognition site to be described by Watkins' group were straight chain analogs of glutamate with the ω-carboxyl group replaced by a phosphonic acid moiety. Examples of such compounds include APH (or AP5) and APV or (AP7) (fig. 16). These compounds were initially found to block reflex seizures in DBA/2 mice (Croucher et al., 1982) and also in baboons (Patel et al., 1988) and epileptic fowl (Pedder et al., 1989) and later were shown to have a wide spectrum of anticonvulsant activity. Thus, they are able to block seizures induced by various chemoconvulsants including NMDA itself and picrotoxin (Czuczwar and Meldrum, 1982) and are active against maximal electroshock seizures (De Sarro et al., 1984). In addition, the drugs are able to prevent focal seizures induced by application of cobalt to the cortex (Coutinho-Netto et al., 1981). NMDA antagonists are usually weaker against pentylenetetrazol- or strychnine-induced clonic seizures than they are in the electroshock test (however, see Ferkany et al., 1989) and the drugs only partially block fully kindled seizures (Peterson et al., 1983; Löscher et al., 1988b). [However, NMDA antagonists are extremely potent in preventing the development of kindled seizures in vivo (Callaghan and Schwark, 1980; McNamara et al., 1988) and in vitro (Anderson et al., 1987; Stasheff et al., 1989).] The drugs are also active against epileptiform activity in various in vitro models (Herron et al., 1985; Dingledine et al., 1986; Peet et al., 1986a,b; Horne et al., 1986; Gean et al., 1988; Stone, 1988; Hwa and Avoli, 1989; Aram et al., 1989). When injected intracerebroventricularly (Patel et al., 1988) or studied in in vitro preparations (Aram et al., 1989), APH and APV are among the most potent anticonvulsants known. However, the compounds are less active than phenytoin or phenobarbital following systemic administration, due to their limited blood-brain barrier permeability, and are inactive orally. In view of this problem, attempts were made to enhance the potency and brain penetration of the antagonists. This led to the synthesis of the next generation of antagonists which are cyclic (conformationally restricted) analogs of APV and APH: CPP and CGS 19755, respectively (fig. 16). Recently, an additional structurally distinct cyclic derivative of APH has been described: NPC 12626 (Ferkany et al., 1989; fig. 16). These compounds are an order of magnitude more potent than their parents as NMDA recognition site antagonists and are correspondingly more active as anticonvulsants (Davies et al., 1986; Chapman et al., 1987; Lehmann et al., 1987). For example, the ED_{50} values of CPP, CGS 19755, and NPC 12626 in the mouse maximal electroshock test are 2, 6, and 20 mg/kg, i.p., respectively, compared with 156 mg/kg for APH (Ferkany et al., 1989; Lehmann et al., 1988). The compounds have comparable potencies against reflex seizures in DBA/2 mice (Bennett et al., 1989) and against picrotoxin-induced convulsions (Lehmann et al., 1988).

Despite their high anticonvulsant potencies, all of the competitive NMDA receptor antagonists have the unfortunate problem of causing behavioral side effects that are related specifically to their effects on central excitatory amino acid transmission, including disruption of motor performance and impairment of memory (Morris et al., 1986; 1989; Löscher et al., 1988b; Tricklebank et al., 1989). At present, it is unknown whether these or other side effects will limit the usefulness of NMDA receptor antagonists in the chronic treatment of seizure disorders. Although some investigators have observed a moderate separation (up to two- to four-fold) in the doses required to block seizures and those that cause toxicity,

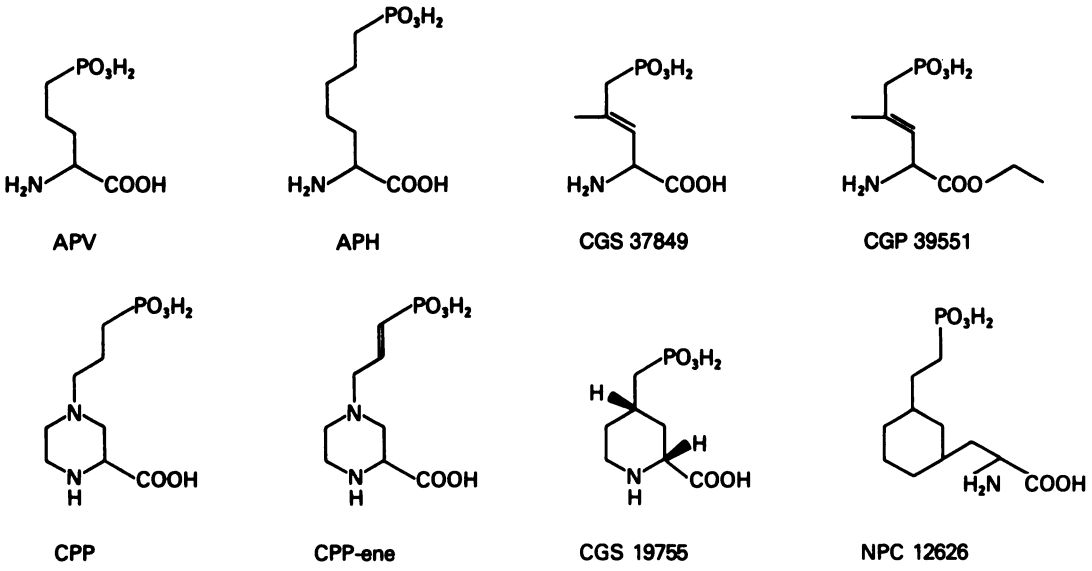


FIG. 16. Structures of competitive NMDA recognition site antagonists.

this may not be sufficient to allow the compounds to be used clinically. Of particular concern is the possibility that these compounds may cause PCP-like side effects as discussed in the next section. Although only human studies can definitively address this concern, there is some evidence from animal behavioral studies that the subjective effects of the competitive antagonists may not mimic those of PCP and related drugs. Thus, in rhesus monkeys CGS 19755 at doses up to 10 mg/kg did not show discriminative stimulus effects in animals trained to discriminate ketamine or MK-801, two PCP-like drugs (France et al., 1989; however, see Compton et al., 1987; Tricklebank et al., 1987; 1989; Willetts and Balster, 1988; Tang and Ho, 1988; Koek and Colpaert, 1990). Clinical studies with the competitive NMDA antagonists that are currently ongoing will address the issue of behavioral toxicity in man. In addition, it should be noted that there is some evidence that the drugs can produce adverse morphological changes in certain brain areas as has recently been demonstrated for noncompetitive antagonists (Olney et al., 1990; see further discussion below).

Recently, a new series of orally active competitive NMDA receptor antagonists has been described that will facilitate the evaluation of this class of compounds in man. These include the 3-unsaturated derivative of APV, CGP 37849, and its carboxyethylester, CGP 39551 (Fagg et al., 1990), and the dextrorotatory enantiomer of the 1-unsaturated derivative of CPP, D-CPP-ene (Herrling et al., 1989) (fig. 16). These compounds are highly active orally in the maximal electroshock test (e.g., ED_{50} for CGP 39551 is 4 mg/kg) and they also protect against reflex seizures in DBA/2 mice and against photically induced myoclonus in baboons (Meldrum et al., 1989; Chapman et al., 1990). CGP 37849 and D-CPP-ene are high-affinity ligands for the NMDA recognition site and are able to displace [^{3}H]CPP from binding to brain membranes with K_i values near 40 nM. In contrast, CGP 39551 is weakly active in in vitro binding studies, but it shows greater oral activity than CGP 37849, presumably because it is more readily absorbed and can be deesterified in vivo. CGP 39551 and D-CPP-ene are of particular interest because of their long duration of action. After a single dose they can protect against electroshock seizures in rats (Fagg et al., 1990; Herrling et al., 1989) and photically induced myoclonus in baboons (Meldrum et al., 1989) for up to 24 hours.

2. Noncompetitive antagonists of the NMDA receptor-channel complex. The dissociative anesthetics PCP and ketamine (fig. 17) have long been known to be potent anticonvulsants in a wide variety of animal seizure models (Johnson and Jones, 1990). For example, PCP is highly effective against maximal electroshock seizures (ED_{50}, 3 mg/kg, i.p. in mice; Chen and Bohner, 1961; Leccese et al., 1986; Rogawski et al., 1989), audiogenic seizures in DBA/2 mice (Chen and Bohner, 1961; Chapman and Meldrum, 1989), and seizures induced by various chemoconvulsants including NMDA (Leander et al., 1988c; Tricklebank et al., 1989) and flurothyl (Geller et al., 1981). Ketamine has also been shown to block maximal electroshock seizures (15 mg/kg, i.p.; Leccese et al., 1986; Leander et al., 1988c), to protect against seizures in genetically epilepsy-prone rats (Bourn et al., 1983) and in DBA/2 mice (Chapman and Meldrum, 1989), and to prevent chemically induced seizures induced by picrotoxin (Myslobodsky et al., 1981), mercaptopropionic acid (Taberner, 1976), and NMDA (Leander et al., 1988c; Tricklebank et al., 1989; Bennett et al., 1988). Both PCP and ketamine have potent prophylactic effects on the development of amygdaloid-kindled seizures in rats but are less effective in reducing seizure severity after kindling has been established (Callaghan and Schwark, 1980; Freeman et al., 1982; Gilbert, 1988). PCP and ketamine are only weakly active against clonic seizures induced by pentylenetetrazol, although both drugs effectively block the tonic phase (Chen and Bohner, 1961; Chen et al., 1966; Reder et al., 1980; Hayes and Balster, 1985).

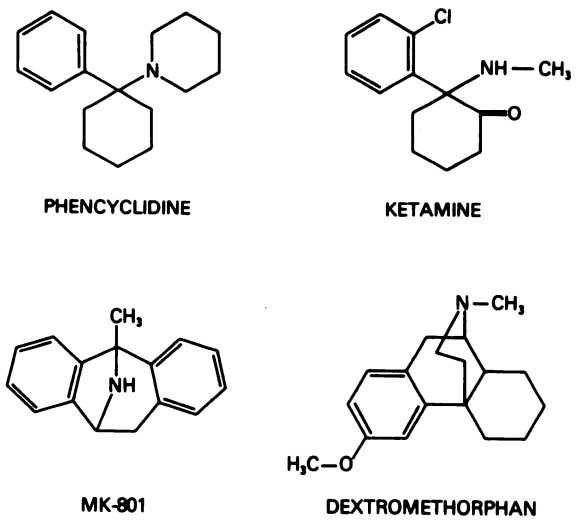


FIG. 17. Structures of noncompetitive NMDA receptor antagonists.

It is apparent that the anticonvulsant profile of PCP and ketamine is similar to that of the competitive NMDA receptor antagonists. However, the basis for the anticonvulsant activity of these drugs was unexplained until 1983 when Lodge and his collaborators reported that the drugs specifically blocked excitation of central neurons via NMDA receptors without affecting other excitatory or inhibitory amino acid transmitter receptor-mediated responses (Anis et al., 1983; Lodge et al., 1989). This breakthrough set the stage for more detailed electrophysiological studies that clearly demonstrated that the dissociative anesthetics do not interact with the NMDA recognition site (i.e., they block NMDA responses in a noncompetitive fashion; Harrison and Simmonds, 1985; Martin and Lodge, 1985) but rather bind to a pharmacologically specific site within the lumen of the NMDA

receptor-associated ionophore and thereby prevent ionic current flow through the channel (Honey et al., 1985; MacDonald et al., 1987). Thus, the blockade of the NMDA receptor channel by PCP and ketamine are voltage and use dependent, and trapping of the drugs within the closed channel can occur (however, see Davies et al., 1988; MacDonald and Nowak, 1990). Biochemical studies confirmed the noncompetitive nature of the interaction (Murphy et al., 1987; Snell and Johnson, 1986; Jones et al., 1987) and provided support for a blocking model in which the drugs bind to the NMDA receptor channel only when it is in the open (ligand-activated) conformation (Kloog et al., 1988a). That the noncompetitive block of NMDA receptor-mediated responses is critical to the anticonvulsant activity of dissociative anesthetics was shown by the good correlation between the anticonvulsant potencies of a series of PCP-related compounds in the maximal electroshock test and their abilities to block NMDA-induced lethality in mice [which is specifically related to their potencies as NMDA antagonists (Leander et al., 1988a,c].

Use dependency should theoretically enhance the efficacy to toxicity ratio of the noncompetitive NMDA antagonists compared with that of the competitive antagonists, because block would be potentiated during the strong stimulation of NMDA receptors that presumably occurs during a seizure. Another theoretical advantage of the noncompetitive blockers is the fact that their inhibitory effects could not be overcome by high synaptic levels of endogenous transmitter. It is unclear at present whether these theoretical points will translate into practical advantages that will allow competitive NMDA antagonists to assume a role as clinically useful anticonvulsants. Certainly, PCP, ketamine, and pharmacologically similar compounds are of no value in the chronic treatment of seizures because they cause gross motor and behavioral toxicity at anticonvulsant doses (Byrd et al., 1987; Tricklebank et al., 1989). However, anecdotal reports indicate that ketamine may be highly effective in the acute treatment of drug-resistant seizures (Davis and Tolstoshev, 1976). At high doses, PCP can induce seizures, an effect that may relate to its ability to block voltage-dependent K^+ channels (EC_{50}, 22 μM in hippocampal neurons; ffrench-Mullen and Rogawski, 1989). Ketamine, however, only blocks voltage-dependent K^+ channels at very high concentrations (EC_{50}, 2.1 mM; M. Bieda and M. A. Rogawski, unpublished observations) and in animal studies it fails to induce seizures even at lethal doses (Reder et al., 1980; Leccese et al., 1986). [Ketamine can, however, produce epileptiform alterations in the EEG, which has confused the issue of whether or not it is convulsant (Manohar et al., 1972; Ferrer-Allado et al., 1973; Celesia et al., 1974; DeVore et al., 1976; Myslobodsky et al., 1981).]

In addition to motor toxicity and the potential for exacerbating seizures at high doses, with any noncompetitive NMDA antagonist there will be the concern that the drug could cause PCP-like behavioral side effects, including the toxic psychosis seen in PCP abusers (Luby et al., 1959; Pradhan, 1984). As noted before, recent behavioral studies have indicated that the competitive antagonists might be less prone to this problem, although this remains to be proven definitively. Unlike the competitive antagonists, PCP and other noncompetitive NMDA antagonists have a wide variety of pharmacological actions unrelated to their effects on NMDA receptors. There is good reason to believe that many of the toxic side effects of PCP that are not shared by competitive NMDA antagonists are probably unrelated to NMDA receptor blockade and, therefore, it may be possible to design more specific noncompetitive drugs (Rogawski et al., 1989; 1990a). In fact, ketamine appears to cause relatively fewer adverse behavioral effects than does PCP (Garfield et al., 1972), suggesting that further investigation of its use in the acute treatment of drug-resistant seizures would be warranted. Similarly, certain compounds that are structurally related to PCP, such as PCA, its conformationally restricted analog 1,1-pentamethylenetetrahydroisoquinoline (Rogawski et al., 1989), and the ring-contracted congener PCA (Thurkauf et al., 1990), have high anticonvulsant potency in the mouse maximal electroshock seizure test but, unlike PCP or ketamine, fail to cause motor toxicity at anticonvulsant doses (although they do impair motor performance at 2.3- to 3.5-fold higher doses). PCA and its analogs have a lower affinity for PCP acceptor sites than does PCP. Nevertheless, in voltage-clamp recordings from cultured brain neurons, PCA does block NMDA responses, although the onset and recovery from block occur far more rapidly than is the case for PCP (S. M. Jones and M. A. Rogawski, unpublished observations). This observation suggests that the improved protective indices of PCA and its analogs may, at least in part, relate to their ability to rapidly block NMDA receptors during the excessive stimulation that occurs at the onset of the seizure discharge. (Of course, other properties of the molecules could also contribute to their anticonvulsant activity.) Similarly, competitive NMDA receptor antagonists also produce their block rapidly (in a non-use-dependent fashion) (Benveniste and Mayer, 1990) and this could contribute to their somewhat improved protective indices (section V, E, 1) compared with "slow" channel blockers such as PCP. In short, although use dependency may be a desirable property in an antiepileptic, the onset of block should occur rapidly enough to allow seizures to be aborted. Because PCA and its analogs are orally active, readily penetrate the blood-brain barrier, *and* are use dependent with a rapid onset of action, they could offer advantages over the competitive antagonists, although this remains to be demonstrated.

3. MK-801. In 1982, Clineschmidt et al. (1982a) reported that the dibenzocycloalkenimine MK-801 (dizo-

cilpine; fig. 17) was an exceedingly potent anticonvulsant in several animal seizure models, and, in fact, it is among the most potent anticonvulsant substances known. The drug was found to antagonize bicuculline-induced tonic seizures in mice at an astonishingly low dose of 0.023 mg/kg, p.o., and to protect in the maximal electroshock test with an ED_{50} of 0.35 mg/kg, p.o. (0.12–0.15 mg/kg, i.v. or s.c.; Leander et al., 1988c; McNamara et al., 1988; Tricklebank et al., 1989). In contrast, MK-801 was 31 times weaker against pentylenetetrazol-induced clonic seizures (ED_{50}, 11 mg/kg) than in the electroshock test, although it blocks tonic seizures induced by the drug with high potency. MK-801 has also been shown to be highly effective as an antagonist of NMDA-induced seizures in mice (Ferkany et al., 1988) and to protect against sound-induced seizures in DBA/2 mice (Chapman and Meldrum, 1989; Tricklebank et al., 1989) and pilocarpine-induced seizures in lithium-pretreated rats (a model of status epilepticus; Ormandy et al., 1989). The drug only partially protected against seizures in fully kindled rats, although it profoundly suppressed the development of kindling (McNamara et al., 1988; Gilbert, 1988; Sato et al., 1988; Young et al., 1989). MK-801 is inactive against strychnine-induced seizures (Clineschmidt et al., 1982a). When injected intracerebroventricularly, the high-affinity competitive antagonists CPP and CGS 19755 are about an order of magnitude more potent as anticonvulsants than is MK-801. On the other hand, following systemic administration, MK-801 is approximately 20-fold more potent than CPP and CGS 19755 as anticonvulsants, presumably because it so much more effectively crosses the blood-brain barrier. In fact, Chapman and Meldrum (1989) have determined that the dissociative anesthetics and MK-801 have a 100- to 400-fold more favorable brain uptake than do the competitive NMDA receptor antagonists.

The mechanism underlying MK-801's anticonvulsant activity was unknown until 1986 when Wong et al. revealed that MK-801 is a potent noncompetitive NMDA antagonist and suggested that, like PCP and ketamine, it might block the NMDA receptor-channel complex in its open conformation (see also, Foster and Wong, 1987; Halliwell et al., 1989). This conclusion was supported by studies with [^{3}H]MK-801 whose high-affinity binding to brain membranes could be competitively displaced by noncompetitive NMDA blockers such as PCP and ketamine, indicating that the MK-801 acceptor is near the dissociative anesthetic -binding site (Wong et al., 1988b; Kloog et al., 1988b). The open channel-blocking mechanism was confirmed in voltage-clamp recordings from cultured rat cortical neurons in which it was shown that binding and unbinding of MK-801 only occurred when the channel was in the agonist-activated (open) state. In single channel recordings from outside-out patches, MK-801 reduced the number of channel openings that were apparent and decreased the mean channel open time but did not significantly alter the unitary conductance of the channels, which is consistent with the open channel-blocking model (Huettner and Bean, 1988). Recently, however, it has been proposed that MK-801 can also gain access to its binding site within the ionophore of the NMDA receptor even when the channel is in the closed state (by a so-called "hydrophobic" pathway), but this appears to occur very slowly (τ ~3 hours; Javitt and Zukin, 1989).

The anticonvulsant profile for MK-801 as reviewed above is similar to that of other NMDA antagonists, supporting the conclusion that the ability of the drug to block seizures is dependent upon its interaction with NMDA receptors. Despite its impressive anticonvulsant potency, MK-801 is no different from other NMDA blockers in producing marked motor toxicity at anticonvulsant doses (Leander et al., 1988c). This problem alone makes it unlikely that the drug will ever be useful in the chronic treatment of seizure disorders, and, in fact, its clinical evaluation for this indication has been halted. Moreover, in various animal species, MK-801 has been shown to cause behaviors and discriminative stimulus effects that are nearly indistinguishable from those produced by PCP and ketamine (Tricklebank et al., 1987; 1989; Koek et al., 1988; Sanger and Jackson, 1989). Low doses of MK-801 have also been shown to impair learning in rats and mice (Danysz et al., 1988; Benvenga and Spaulding, 1988; Robinson et al., 1989; Butelman, 1989) and there are some animal data to suggest that the drug could have abuse potential (Herberg and Rose, 1989; Corbett, 1989). An interesting, but unexplained, property of the drug is its ability, like other dissociative anesthetics, to profoundly elevate cerebral glucose metabolism, an effect not shared by competitive NMDA antagonists (Nehls et al., 1988; Piercey et al., 1988; Kurumaji et al., 1989). A particularly troubling action of MK-801 is its tendency at relatively low doses (ED_{50}, 0.18 mg/kg, s.c) to cause vacuolization of multipolar and pyramidal shaped neurons in layers III and IV of the rat posterior cingulate and retrosplenial cortices (Olney et al., 1989), areas in which there are particularly profound elevations in glucose metabolism (Allen and Iversen, 1990). These changes are reversible at low doses, but at high doses (5 mg/kg) some necrosis of neurons is observed (Allen and Iversen, 1990). Interestingly, acute vacuolization is also produced by other noncompetitive NMDA antagonists such as PCP and ketamine with a rank order of potencies that corresponds with their potencies as NMDA blockers. In addition, the acute vacuolization response can be reproduced by the competitive NMDA antagonist APV (Olney et al., 1990), demonstrating that the neurotoxic effects occur specifically as a result of NMDA receptor blockade.

MK-801 produces a variety of side effects, some of which may not be dependent upon the NMDA-blocking activity of the drug. For example, like ketamine (Domino

et al., 1965), MK-801 has a marked sympathomimetic effect, causing increases in blood pressure in human subjects at very low doses (7.5–10 μg/kg, i.v.; Merck Sharp & Dohme Research Laboratories, unpublished data). The drug also stimulates respiration (Foutz et al., 1988), and it has an amphetamine-like locomotor stimulatory effect similar to that seen with PCP and ketamine but not with competitive NMDA antagonists (Clineschmidt et al., 1982b; Koek et al., 1988; Tang and Ho, 1988; Carlsson and Carlsson, 1989). MK-801 has a variety of effects on central catecholamine systems that could, at least in part, contribute to these diverse effects. MK-801 can block norepinephrine reuptake [but is very weak as a dopamine uptake blocker (Snell et al., 1988)] and some of its behavioral effects can be antagonized by α_1-adrenoceptor antagonists (Martin and Papp, 1984), suggesting that it may either directly or indirectly enhance the availability of norepinephrine. The drug also appears to potentiate dopamine availability. Thus, dopamine receptor antagonists are able to block certain of the behavioral effects of MK-801 (Clineschmidt et al., 1982b; Schmidt and Bubser, 1989). Moreover, upon intravenous administration in rats, the drug causes a marked increase in the firing of midbrain dopamine neurons (Steinfels et al., 1989) as does PCP (Raja and Guyenet, 1980; Freeman and Bunney, 1984). Because MK-801 and PCP are equipotent (0.12 mg/kg, i.v.) and inasmuch as iontophoretically applied competitive NMDA antagonists do not activate dopamine neurons (J. R. Walters and T. H. Lanthorn, personal communication), the effect is unlikely to be related to NMDA receptor blockade. Recently, Halliwell et al. (1989) showed that MK-801 can also block nicotinic acetylcholine responses at low doses. These non-NMDA receptor-mediated actions are an important aspect of the pharmacological profile of MK-801 and related dissociative anesthetic-like drugs that will need to be considered if drugs of this type are to be used clinically. Because the non-NMDA receptor-mediated effects are due to interactions of the drug at pharmacologically distinct sites, it may be possible to obtain analogs that maximize NMDA receptor-blocking activity and anticonvulsant efficacy and minimize the other potentially undesirable pharmacological actions.

Several clinical trials of MK-801 in normal volunteers and in patients with anxiety, depression, attention deficit disorder, narcolepsy, and seizure disorders have been completed. At low doses the drug is well tolerated, but with increasing dose (>5 μg/kg, i.v., or ~0.5 mg/day, p.o.) there is often an elevation in blood pressure (as noted before); frequent complaints of lightheadedness, numbness, headache, and dizziness in normal volunteers; and a high incidence of adverse behavioral effects in psychiatric patients. The drug has been studied in the treatment of various types of seizure disorders. An initial open label, add-on study in 22 patients with partial seizures was not very promising (Troupin et al., 1986). Although eight of the 13 patients who completed the initial phase of the study had a >50% improvement in seizure frequency, this improvement was not sustained, and only one patient showed improvement at the conclusion of the study (mean maximum dose 34 μg/kg/day). In a later double-blind, placebo-controlled, crossover trial of MK-801 (0.6–6 mg/day) as an add-on antiepileptic in 125 patients with poorly controlled partial seizures there was no significant reduction in seizure frequency (Merck Sharp & Dohme Research Laboratories, unpublished data). In a multicenter study in 16 patients with Lennox-Gastaut syndrome (0.6–12 mg/day) a high incidence of adverse experiences were reported including somnolence, ataxia, and mood changes. As a result of these disappointing results, clinical trials of MK-801 in epilepsy have been discontinued by the manufacturer (S. A. Reines, personal communication).

4. ADCI. The tricyclic structure of MK-801 (fig. 17) is similar to that of carbamazepine (fig. 12); therefore, the hybrid molecule ADCI (fig. 18) was synthesized with the aim of obtaining an anticonvulsant NMDA receptor antagonist with some of the favorable properties of carbamazepine (Rogawski et al., 1990a). ADCI has the basic dibenzocycloheptene-5,10-imine ring structure of MK-801 with a carbamyl group (as in carbamazepine) substituted at the 5-position. Like its precursors, ADCI was found to be an effective anticonvulsant in the mouse maximal electroshock test, having a potency almost identical with that of carbamazepine (ED_{50}, 8.9 mg/kg, i.p., in mice). However, in contrast to MK-801 which caused motor toxicity at three- to four-fold *lower* doses than those that protected against maximal electroshock seizures (TD_{50} for motor toxicity, 0.38 mg/kg), ADCI had a protective index of 5.5 (TD_{50}, 49 mg/kg), which is more akin to that of carbamazepine. Unlike carbamazepine, ADCI can also block pentylenetetrazol-induced clonic seizures (ED_{50}, 37 mg/kg) (S. Yamaguchi and M. A. Rogawski, unpublished observations). Of particular interest was the observation that ADCI protects against NMDA-induced seizures (ED_{50}, 15 mg/kg), suggesting that it has NMDA antagonist activity. [Carbamazepine, which is not an NMDA antagonist, only prevents NMDA-induced seizures at very high doses that also nonspecifically block seizures induced by agonists acting

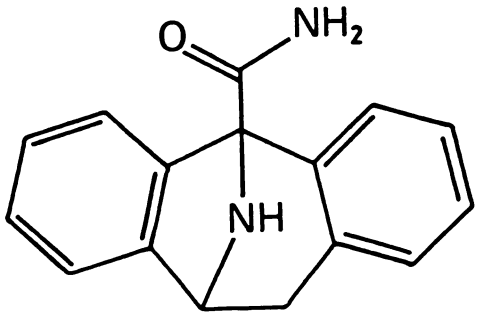


FIG. 18. Structure of ADCI.

at other excitatory amino acid receptor subtypes (Koek and Colpaert, 1990)]. Based upon these observations, the ability of ADCI to antagonize NMDA receptor-mediated responses was determined in voltage-clamp recordings from cultured rat hippocampal neurons. ADCI at near therapeutic brain concentrations for carbamazepine (30 μM; section II, C, 1) produced a 37% inhibition of NMDA-evoked responses, whereas carbamazepine at this concentration was inactive (S. M. Jones and M. A. Rogawski, unpublished observations). Presumably because of its NMDA receptor-blocking activity, ADCI has a broader spectrum of anticonvulsant activity in animal seizure models than does carbamazepine. Whether ADCI will offer advantages over carbamazepine for the treatment of resistant seizure disorders remains to be determined.

5. Dextromethorphan and dextrorphan. Dextromethorphan [(+)-3-methoxy-N-methylmorphinan; fig. 17], the unnatural enantiomer of a codeine-like opiate, has been in use for many years as a cough suppressant. Unlike codeine, dextromethorphan has no analgesic activity and no addiction liability. In 1983, Craviso and Musacchio (1983a,b) reported the existence of specific high-affinity-binding sites in brain for dextromethorphan that were distinct from opiate receptors. These binding sites did not appear to correspond with those for any known neurotransmitter, although structurally dissimilar antitussives such as carbetapentane and caramiphen were active at the site. Of particular interest was the observation that phenytoin could enhance dextromethorpan-binding affinity. Subsequently it was shown that the benzhydryl piperazine ropizine, an anticonvulsant with a similar spectrum to phenytoin (Novack et al., 1979; Edmonds et al., 1979), was also able to enhance dextromethophan binding (Musacchio et al., 1988). The binding interaction between dextromethorphan and anticonvulsants prompted Tortella and Mussachio (1986) to test dextromethorphan for anticonvulsant activity, and the drug was found to be active in the maximal electroshock seizure test, as were carbetapentane and caramiphen (Tortella et al., 1988b). Later, the drug was shown to prevent the development of amygdaloid-kindled seizures in rats (Feeser et al., 1988) and cats (Kuko and Wada, 1989), to decrease seizure intensity in fully kindled animals, and to block sound-induced seizures in DBA/2 mice (Chapman and Meldrum, 1989). In addition, dextromethophan has been shown to suppress epileptiform discharges in an in vitro hippocampal slice preparation (Wong et al., 1988a).

Although it seems reasonable that the anticonvulsant effects of the antitussives are mediated via their interaction with dextromethorphan-binding sites in brain, at present the nature of the binding site and consequently the anticonvulsant mechanism of the antitussives is unclear. Recently, it has been observed that σ-receptor ligands bind to dextromethorphan sites with high affinity (Klein et al., 1989; see also Musacchio et al., 1989). Moreover, localization of dextromethorphan-binding sites by receptor autoradiaography have revealed a striking similarity in the regional distribution of dextromethorphan and σ-sites labeled with conventional σ-ligands such as (+)-3-(3-hydroxyphenyl)-N-(1-propyl)piperidine and 1,3-di-*o*-tolylguanidine (Canoll et al., 1989). Although certain σ-site ligands have anticonvulsant activity (Chapman and Meldrum, 1989), this may be due to their interaction with the PCP acceptor associated with NMDA receptors and not due to their interaction with σ-sites. Thus, σ-ligands that do not bind to PCP sites such as (+)-3-(3-hydroxyphenyl)-N-(1-propyl) piperidine, 1,3-di-*o*-tolylguanidine, or haloperidol fail to block maximal electroshock seizures even at high doses (S. Yamaguchi and M. A. Rogawski, unpublished observations) and were inactive in an in vitro model of epileptogenesis (Aram et al., 1989). In fact, these σ-ligands may be proconvulsant in some situations (Tortella et al., 1989). In addition to interacting with dextromethorphan/σ-acceptor sites, dextromethorphan is also able to weakly block NMDA receptor-mediated responses (Church et al., 1985; Wong et al., 1988a; Aram et al., 1989). In vivo, dextromethorphan is efficiently demethylated to form dextrorphan (the dextrorotatory form of levorphanol) which is several-fold more potent as an NMDA antagonist and anticonvulsant (Tortella et al., 1988a; Chapman and Meldrum, 1989; Cole et al., 1989). Thus, it is possible that the anticonvulsant activity of dextromethorphan resides in its own weak NMDA receptor-blocking activity and, more important, in that of its metabolite dextrorphan. Moreover, several groups have observed that dextromethorphan is able to block NMDA-induced lethality in mice, supporting the idea that it or its metabolite is a functional NMDA antagonist (Ferkany et al., 1988; Leander, 1989). Interestingly, however, carbetapentane, an effective anticonvulsant in the maximal electroshock test (Tortella and Mussachio, 1986), was not able to protect against NMDA-induced lethality, nor is it able to block NMDA response in vitro (Aram et al., 1989). Leander (1989) has therefore argued that the antitussives have an anticonvulsant action separate from their PCP-like blockade of NMDA receptors.

Fisher et al. (1990) recently completed a double-blind crossover add-on study of dextromethorphan (120 mg/day) in nine patients with complex partial seizures who were receiving monotherapy with either phenytoin or carbamazepine. The drug was not effective; in fact, a nonsignificant *increase* in seizure frequency occurred. No adverse effects were noted. The dose used was much lower than that expected to be effective but was limited by the need for additional toxicological investigations in animals.

6. Alternative strategies for NMDA receptor blockade. In recent years, a number of modulatory sites have

been identified on the NMDA receptor-cation channel complex that are distinct from either the agonist recognition site (at which the competitive antagonists act) or the dissociative anesthetic-binding site. These include a strychnine-insensitive glycine site (Johnson and Ascher, 1987) and a site for polyamines (Ransom and Stec, 1988; Williams et al., 1989a). Agonist activation of both of these modulatory sites markedly enhances channel opening, and in the case of the glycine site, agonist occupancy is probably obligatory for channel gating (Kleckner and Dingledine, 1988). A number of more or less selective glycine site antagonists have been described including 7-chlorokynurenic acid (Kemp et al., 1988), cycloleucine (Snell and Johnson, 1988; Hershkowitz and Rogawski, 1989), quinoxaline analogs (Birch et al., 1988; Ogita et al., 1989; Kleckner and Dingledine, 1989; Harris and Miller, 1989; Kessler et al., 1989), 5-substituted indole-2-carboxylic acids (Huettner, 1989), and 1-aminocyclobutane-1-carboxylic acid (Hood et al., 1989). In addition, 1-hydroxy-3-amino-2-pyrrolidone (HA-966), a well-known selective NMDA antagonist that fails to bind to the NMDA recognition site (Lodge et al., 1989), has recently been identified as a partial agonist at the glycine site (Drejer et al., 1989; Fletcher and Lodge, 1988; Danysz et al., 1989; Foster and Kemp, 1989; Mangano et al., 1990; Singh et al., 1990). Antagonists of the polyamine site that have been described include the antiischemic drug ifenprodil and its analog SL 82.0715 (Carter et al., 1989; Reynolds and Miller, 1989), the polyamines putrescine, cadaverine and 1,3-diaminopropane (Williams et al., 1989b; Sacaan and Johnson, 1990), and arcaine (Reynolds, 1990). Recently, 7-chlorokynurenic acid has been shown to attenuate epileptiform bursting in an in vitro hippocampal slice preparation (Kleckner and Dingledine, 1989). Ifenprodil can apparently also block epileptiform discharges in an in vitro preparation (Robichaud et al., 1989) and both ifenprodil and SL 82.0715 appear to have a spectrum of anticonvulsant activity similar to PCP and MK-801 in animal seizure models, although they do not stimulate locomotor activity in rats (Zivkovic et al., 1989; Koek and Colpaert, 1990), are not recognized as PCP-like in drug discrimination trials (Sanger and Zivkovic, 1989), and fail to cause PCP- and MK-801-like effects on schedule-controlled behavior of rats (Sanger and Jackson, 1989), suggesting that they might have a more favorable side effect profile than either the competitive or noncompetitive antagonists. Nevertheless, it is unclear whether drug acting at the newly described modulatory sites will be useful clinically and, in fact, it has been difficult to show that the glycine antagonists have anticonvulsant activity in traditional animal seizure models (S. Yamaguchi and M. A. Rogawski, unpublished observations).

A number of different classes of drugs, other than dissociative anesthetics and MK-801, act as steric blockers of the ionophore portion of the NMDA receptor-channel complex, including certain spider toxins (Priestley et al., 1989), tricyclic antidepressants (Sernagor et al., 1989) and the anticholinesterase tetrahydroaminoacridine (Hershkowitz and Rogawski, 1990). Although on theoretical grounds compounds of this type might be expected to have anticonvulsant activity, none as yet has been found to be useful.

F. Drugs with a Novel Spectrum of Anticonvulsant Activity

1. Felbamate. Felbamate (2-phenyl-1,3-propanediol dicarbamate; fig. 19) is a dicarbamate that is structurally similar to the antianxiety agent meprobamate. In screening studies, the drug was found to have protective activity in several animal seizure models including the mouse maximal electroshock test (ED_{50}, 50.1 mg/kg, i.p.) and the mouse subcutaneous pentylenetetrazol test (ED_{50}, 148 mg/kg, i.p.) (Swinyard et al., 1986). At higher doses, the drug is active against picrotoxin and bicuculline seizures but not against strychnine seizures (Perhach et al., 1986). Although its absolute potency in these tests is low in comparison with currently marketed drugs, felbamate's minimal motor toxicity (TD_{50} in mouse rotorod, 816 mg/kg, i.p.) gives it a very favorable protective index. The drug has also been found to be effective in the prevention of seizures induced by cortical application of aluminum hydroxide gel in rhesus monkeys (Wallace Laboratories, unpub-

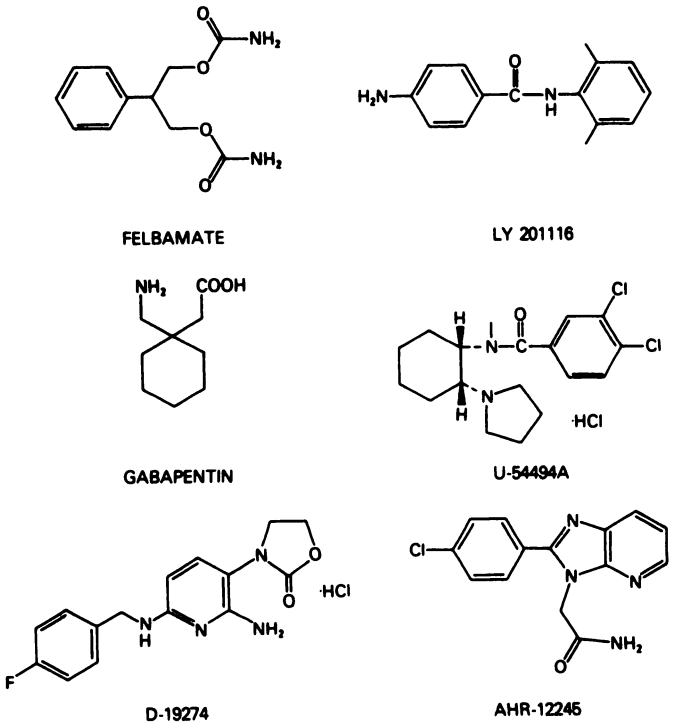


FIG. 19. Structures of felbamate, LY201116, gabapentin, U-54494A, D-19274, and AHR-12245.

lished data cited by Leppik and Graves, 1989). Felbamate's activity in both the mouse maximal electroshock and mouse subcutaneous pentylenetetrazol seizure tests is similar to that of phenobarbital and valproate, although unlike these two drugs, it is ineffective against strychnine-induced seizures. Thus, it has a unique profile of anticonvulsant activity. Felbamate had minimal systemic toxicity in animal testing even at very high doses (up to 3000 mg/kg, p.o.) and in the clinical studies that have been carried out to date.

Felbamate is a particularly interesting potential antiepileptic drug because of its remarkably low toxicity and unique spectrum of anticonvulsant activity. Although the drug is related to meprobamate, it does not cause prominent dose-related drowsiness but usually presents with gastrointestinal discomfort at high doses. Early clinical studies with the drug were carried out using doses up to 1600 mg/day (Wilensky et al., 1986), whereas later studies have used 3600 mg/day on a regular basis. Two well-controlled studies of felbamate in partial seizures have been completed. The first was a two-center, 22-week crossover study with concomitant use of phenytoin and carbamazepine (Leppik et al., 1989). Felbamate yielded a similar, statistically significant reduction in seizure frequency at each of the two sites. In the second study, an intensive three-period crossover design conducted at the National Institutes of Health, a similar reduction in seizure frequency was observed, but the statistical significance is still being evaluated (Theodore et al., 1989). In the latter study, a lowering of carbamazepine levels (the only concomitant drug in this investigation) may have decreased the apparent efficacy of felbamate in these highly refractory patients. Further studies at somewhat higher doses are warranted at this stage of development.

2. *LY201116.* Extensive structure-activity studies have been carried out by Clark and his collaborators on the anticonvulsant activity of aminobenzamides of arylalkylamines and arylamines (Clark et al., 1984, 1985, 1986). Of the compounds examined, LY201116 (fig. 19) proved to be the most potent in the maximal electroshock test (2.6 mg/kg, i.p., in mice) (Clark, 1988; Leander et al., 1988b). The protective index for LY201116 was 5.8 which is slightly lower than the corresponding value for phenytoin (6.9). Like phenytoin, LY201116 was inactive in the pentylenetetrazol test. A prodrug of LY201116 with a longer duration of action N-(2,6-dimethylphenyl)-4-{[(diethylamino)-acetyl]amino}benzamide has been described (Parli et al., 1988). Whether these compounds will provide advantages over phenytoin and other currently available drugs remains to be determined.

3. *Gabapentin.* Gabapentin [1-(aminomethyl) cyclohexaneacetic acid; fig. 19] is a conformationally restricted analog of GABA that has a higher lipid solubility than the naturally occuring inhibitory transmitter. As a consequence, it is able to effectively penetrate the blood-brain barrier (Ojemann et al., 1988; Ben-Menachem et al., 1990). Gabapentin was designed to serve as a centrally active GABA agonist that might have useful therapeutic properties and, in fact, was found to be protective in a variety of animal seizure models. However, gabapentin does not interact with GABA receptors, and the mechanism of its anticonvulsant activity is unknown. The data summarized below are taken primarily from Bartoszyk et al. (1986b).

Gabapentin has a broad spectrum of anticonvulsant activity that is similar to that of valproate. Like valproate, gabapentin is effective in preventing tonic seizures induced by various chemoconvulsants including bicuculline, picrotoxin, 3-mercaptopropionic acid, isonicotinic acid, semicarbazide, strychnine, and pentylenetetrazol with ED_{50} values of 5–57 mg/kg, p.o., in mice. Gabapentin is also effective in the maximal electroshock test in rats (ED_{50}, 9.4 mg/kg, p.o.), although the drug was reported to be inactive in mice. In addition to its effect on tonic seizures, gabapentin is weakly effective against clonic seizures induced by pentylenetetrazol in mice (147 mg/kg, p.o.). Gabapentin blocks reflex seizures in DBA/2 mice, Mongolian gerbils (Bartoszyk and Hamer, 1987), and genetically epilepsy-prone rats (Naritoku et al., 1988) and produced a minimal prolongation of the latency to seizure onset and death following intraperitoneal injection of NMDA. Studies to date have failed to show effectiveness against seizures in photosensitive baboons or in the kindling model. Despite its wide spectrum of anticonvulsant activity, gabapentin is surprisingly free of neurological side effects, although at doses of 400 mg/kg, p.o., the drug does produce sedation and ataxia in mice. (At lower doses the drug has a baclofen-like antispasticity effect that could be of clinical utility.)

Despite its structural similarity to GABA, gabapentin fails to bind to $GABA_A$ receptors labeled with [^{3}H] muscimol or $GABA_B$ receptors labeled with [^{3}H]baclofen. The drug does not inhibit synaptosomal GABA uptake. Gabapentin is a weak inhibitor of GABA-T, comparable in potency to valproate (IC_{50}, 6 mM) although this is unlikely to contribute to the anticonvulsant activity of the drug because sufficient levels are not achieved during therapy [blood levels in rats treated with a 100-mg/kg, p.o., dose are 24 μg/ml (139 μM) and plasma levels in humans are much lower, approximately 2–4 μg/ml after a 200- to 300-mg dose; gabapentin is not bound to serum proteins and CSF to plasma ratios range from 0.056- 0.34 (Ben-Menachem et al., 1990)]. Unlike valproate, anticonvulsant doses of gabapentin have not been shown to elevate synaptosomal GABA content in mice pretreated with the drug. Submillimolar concentrations of gabapentin can

inhibit the stimulation-evoked release of various neurotransmitters from brain slices (Reimann, 1983; Schlicker et al., 1985). This action is not blocked by the $GABA_A$ receptor antagonist bicuculline and is additive with baclofen, indicating that it is not due to activation of either $GABA_A$ or $GABA_B$ receptors as expected from the binding studies. Therefore, at present, the most attractive preliminary hypothesis to explain gabapentin's mechanism of anticonvulsant action is that the drug can interact with an undetermined presynaptic site to inhibit transmitter release. Obviously, this hypothesis is likely to be revised as more information is collected.

Gabapentin is well tolerated by normal volunteers in doses up to 3600 mg/day (Bartoszyk et al., 1986b) and the drug has progressed rapidly to the stage of controlled clinical trials in epileptic patients. The first of these to be reported is the study by Crawford et al. (1987a) in which 25 patients with uncontrolled partial and generalized epilepsies were evaluated. The study was a double-blind crossover design with add-on therapy. Doses ranged from 300–900 mg/day. The drug caused a significant, dose-related decrease in seizure frequency. The most prominent effect was on tonic-clonic seizures. No evidence of tolerance to the drug was apparent on long-term follow-up. Several other double-blind, placebo-controlled studies of gabapentin in patients with partial seizures have been completed. Schmidt (1989a) reported a study of 110 patients with severe refractory partial seizures in whom gabapentin (1200 mg/day) was compared to placebo. The active drug caused a statistically significant reduction in the frequency of seizures. In a short-term study of 43 patients, Kälviainen et al. (1989b) found gabapentin to be effective in a dose-related manner. Sivenius et al. (1989) evaluated 45 patients in a double-blind, placebo-controlled trial of gabapentin as add-on therapy; the drug appeared to be effective in partial seizures. Ojemann et al. (1990) successfully maintained several patients with medically unresponsive partial and secondarily generalized tonic-clonic seizures on a regimen of gabapentin monotherapy for up to 12 months without adverse side effects. In additional recent open studies, the drug has been found to be safe and effective, even for durations of up to several years (Bauer et al., 1989; Chadwick, 1989).

In a study of absence seizures utilizing 24-hour intensive monitoring, Rowan et al. (1989) showed a decrease in seizure frequency and generalized spike wave complexes after introduction of gabapentin. Gabapentin is now in multiple clinical trials in both Europe and the United States; it may be marketed as early as 1991 in some countries.

4. Eterobarb. Eterobarb (N,N′-dimethoxymethylphenobarbital; fig. 20) is an anticonvulsant barbiturate with attenuated sedative and hypnotic activity compared to phenobarbital. Although eterobarb is eventually converted completely to phenobarbital, the dealkylated metabolite MMP accumulates in the brain because the first dealkylation occurs much more rapidly than the second (fig. 20). Eterobarb itself does not appear to enter the brain and can be considered a prodrug for MMP and phenobarbital which are the active anticonvuusant species (Rapport and Kupferberg, 1973; Baumel et al., 1976). Eterobarb has a somewhat different anticonvulsant profile from phenobarbital, which presumably reflects the unique properties of MMP. Thus, eterobarb is more active against maximal electroshock seizures (ED_{50}, 14 mg/kg, p.o., in mice) than in the pentylenetetrazol test (ED_{50}, 47 mg/kg), whereas the reverse is true for phenobarbital (Gallagher, 1989). Of particular interest, however, is the relative lack of sedation caused by eterobarb. In rats, the hypnotic dose (expressed as the HD_{50} for loss of righting reflex) of eterobarb is 700 mg/kg, p.o., compared to 102 mg/kg for phenobarbital, and a similar lack of sedation has been observed in human subjects (Gallagher et al., 1975). The more favorable side effect profile of eterobarb is believed to reflect an interaction between MMP and phenobarbital because the hypnotic activity of MMP alone is close to that of phenobarbital (Gallagher, 1989). Thus, the combination of MMP and phenobarbital in some way leads to the development of functional tolerance to the hypnotic but not to the anticonvulsant effects of the metabolites.

Although it was originally thought that the antiepileptic action of eterobarb in man could be fully explained by its metabolic conversion to phenobarbital (Goldberg, 1982), recent clinical studies appear to support the animal behavioral evidence suggesting that eterobarb is less hypnotic than phenobarbital (Smith et al., 1986). Thus, Gobbi et al. (1989) compared phenobarbital with eterobarb in a single-blind crossover study in 19 patients. Eterobarb showed good antiepileptic activity and was less sedating than phenobarbital. In another recent study, Bernardina et al. (1989) studied eterobarb in 25 children with a variety of seizure types. The drug seemed efficacious and appeared to cause less severe hyperactivity than phenobarbital. However, a determination of whether the drug truly represents a substantial improvement over phenobarbital and other presently available barbiturates awaits the outcome of controlled clinical trials that are currently in progress (K. D. Wolter, personal communication).

5. U-54494A. In the course of studying a series of benzamide κ-opioid agonists with anticonvulsant properties, U-54494A (fig. 19) was identified which lacks the analgesic and sedative properties of κ-agonists yet retains their anticonvulsant activity (VonVoigtlander et al., 1987). U-54494A is effective as an antagonist of maximal electroshock seizures (ED_{50}, 36 mg/kg, i.p, in

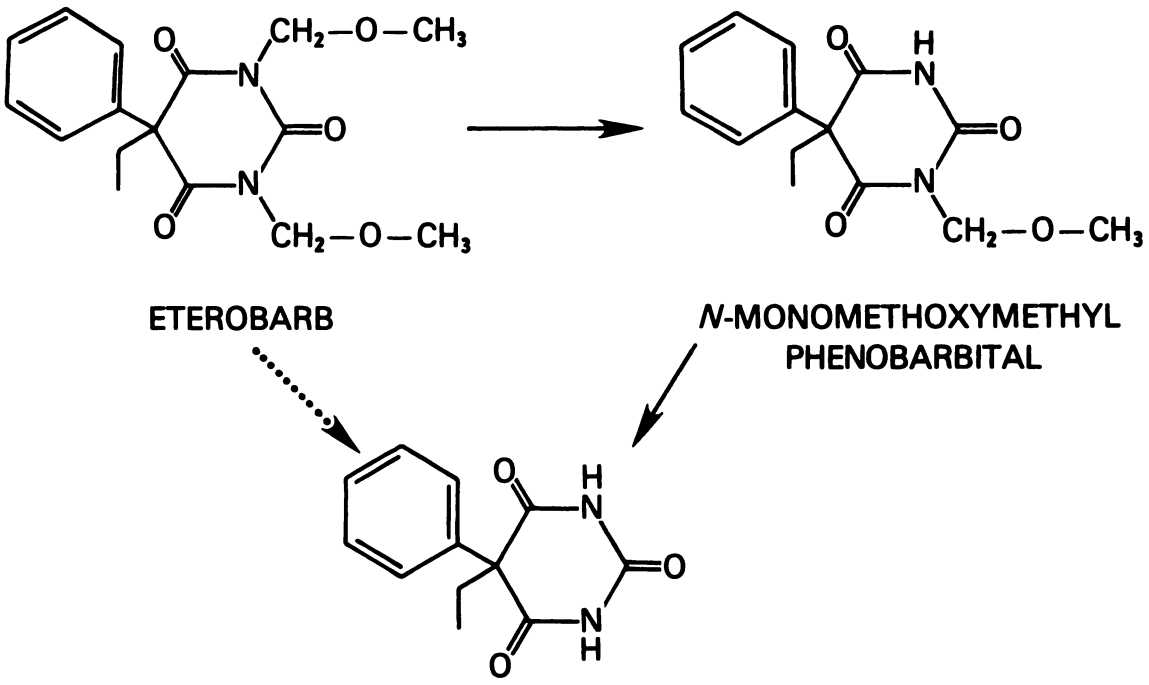


FIG. 20. Metabolism of eterobarb.

mice) but is relatively inactive against pentylenetetrazol-, bicuculline-, or picrotoxin-induced clonic seizures; its TD_{50} in the rotarod ataxia test is 97 mg/kg (P. F. VonVoigtlander, personal communication). Like phenytoin, U-54494A is able to protect against sound-induced convulsions in DBA/2 mice and to block PTP in a nerve-muscle preparation. However, U-54494A has a number of unique pharmacological properties that distinguish it from other anticonvulsants. At relatively low doses, U-54494A is able to block seizures induced by administration of the excitatory amino acid agonists kainate (ED_{50}, 28 mg/kg, s.c., in mice), NMDA (79 mg/kg), and quisqualate (28 mg/kg), an action shared by very high doses of carbamazepine (section V, E, 4), but not by phenytoin or phenobarbital. Like carbamazepine, U-54494A does not discriminate among seizures induced by agonists of the various excitatory amino acid receptor subtypes, perhaps suggesting that the drug may not act as a conventional receptor antagonist. In fact, in preliminary studies, U-54494A failed to block NMDA responses in voltage-clamp recordings from cultured hippocampal neurons (N. Hershkowitz and M. A. Rogawski, unpublished observations). Surprisingly, high doses of the opiate antagonist naltrexone can block the ability of U-54494A to protect against maximal electroshock seizures as well as those produced by excitatory amino acids. Naltrexone is also able to block the anticonvulsant activity of the structurally related κ-opioid agonist U-54498H. However, at least in vivo, U-54494A does not appear to have pharmacological actions characteristic of κ-agonists.

Several lines of evidence suggest that active metabolites may contribute to the anticonvulsant activity of U-54494A. The drug is a racemic mixture, but each of its enantiomers has approximately equal intrinsic anticonvulsant activity (VonVoigtlander et al., 1989). Nevertheless, the racemate is more potent than either enantiomer when the drugs are administered orally, perhaps as a result of an interaction of the enantiomers during metabolism. (The potency advantage of the racemate is maintained to some extent even when the drugs are administered intracerebroventricularly, suggesting that pharmacodynamic factors may also be of importance.) In addition, orally administered U-54494A has a long duration of action even in the absence of detectable brain levels of the drug, strongly suggesting the existence of active metabolites. U-54494A is currently undergoing phase I clinical trials. Single oral doses as high as 200 mg have been well tolerated (P. F. VonVoigtlander, personal communication).

6. D-19274. The structurally novel pyridine-oxazolidinone D-19274 (fig. 19) is an effective anticonvulsant in the maximal electroshock test (ED_{50}, 28 mg/kg, i.p., in mice; Emig et al., 1990). The drug has relatively low motor toxicity (rotarod TD_{50}, 150 mg/kg). D-19274 has also been reported to suppress spontaneous spike and wave discharges in rats at doses as low as 10 mg/kg, and it has been proposed that the drug might have activity against absence seizures.

7. AHR-12245. Another potential antiabsence drug

is the imidazopyridine AHR-12245 (fig. 19). AHR-12245 attracted attention in a drug-screening program when it was found to be an effective antagonist of pentylenetetrazol-induced clonic seizures (ED_{50}, 29 mg/kg, i.p., in mice; Johnson et al., 1988), being ninefold more potent (on a molar basis) than ethosuximide. Moreover, the drug failed to cause motor toxicity even at doses as high as 2000 mg/kg so that its protective index is >69 (compared to a protective index for ethosuximide of 3.4 under the same experimental conditions). AHR-12245 is also protective against bicuculline- and picrotoxin-induced clonic seizures (174 and 211 mg/kg, respectively) and prevents maximal electroshock seizures at higher doses (329 mg/kg). Like ethosuximide, AHR-12245 fails to alter seizures in amygdaloid-kindled rats. AHR-12245 is orally active: serum concentrations providing 50% protection in the pentylenetetrazol test were 17.4 μM and brain levels were 57% of serum concentrations (Osman et al., 1988). AHR-12245 binds weakly to the benzodiazepine receptor and not at all to other sites on the $GABA_A$ receptor-Cl^- channel complex. Its mechanism of action is unknown.

Conclusion

As is apparent from this review, there is a wide array of new, effective anticonvulsant compounds of potential usefulness for the treatment of partial seizures and generalized tonic-clonic seizures in man. The new understanding of cellular physiological mechanisms in absence epilepsy has provided important insights into the way in which presently available drugs operate, and this should enhance the search for new therapeutic agents against this seizure type as well. Moreover, recent advances in neuroscience have suggested a host of potential cellular targets for antiepileptic drugs that are not exploited by presently available compounds, including various sites on the NMDA receptor-channel complex and on voltage-dependent K^+ channels. It can be expected that compounds targeted at these sites will be emerging from the preclinical pipeline in the coming years. The real challenge for the future will be to carry out well-controlled clinical trials to validate the efficacy and safety of these compounds in the treatment of human seizure disorders.

REFERENCES

ABDUL-GHANI, A. S., NORRIS, P. J., SMITH, C. C., AND BRADFORD, H. F.: Effects of γ-acetylenic GABA and γ-vinyl GABA on synaptosomal release and uptake of GABA. Biochem. Pharmacol. **30:** 1203–1209, 1981.

ADLER, E. M., YAARI, Y., DAVID, G., AND SELZER, M.: Frequency-dependent action of phenytoin on lamprey spinal axons. Brain Res. **362:** 271–280, 1986.

AICKIN, C. C., DEISZ, R. A., AND LUX, H. D.: On the action of the anticonvulsant 5,5-diphenylhydantoin and the convulsant picrotoxin in crayfish stretch receptor. J. Physiol. (Lond.) **315:** 157–173, 1981.

AIKIA, M., SIVENIUS, J., KERANEN, T., YLINEN, A., KALVIAINEN, R., AND RIEKKINEN, P. J.: Oxcarbazepine vs. phenytoin in monotherapy for newly diagnosed epilepsy with a special reference to memory function. *In* Book of Abstracts, 18th International Epilepsy Congress, New Delhi, India, p. 91, 1989.

AIRAKSINEN, E. M., KOIVISTO, K., KERÄNEN, T., PITKÄNEN, A., RIEKKINEN, P. J., OJA, S. S., MARNELA, K.-M., PARTANEN, J. V., TOKOLA, O., GOTHÓNI, G., NEUVONEN, P. J., AND AIRAKSINEN, M. M.: Biochemical and clinical studies on epileptic patients during two phase I trials with the novel anticonvulsant taltrimide. Epilepsy Res. **1:** 308–311, 1987.

AKAIKE, N., HATTORI, K., INOMATA, N., AND OOMURA, Y.: γ-Aminobutyric-acid- and pentobarbitone-gated chloride currents in internally perfused frog sensory neurones. J. Physiol. (Lond.) **360:** 367–386, 1985.

AKAIKE, N., MARUYAMA, T., AND TOKUTOMI, N.: Kinetic properties of the pentobarbitone-gated chloride current in frog sensory neurones. J. Physiol. (Lond.) **394:** 85–98, 1987.

ALBERTSON, T. E., BOWYER, J. F., AND PAULE, M. G.: Modification of the anticonvulsant efficacy of diazepam by Ro-15–1788 in the kindled amygdaloid seizure model. Life Sci. **31:** 1597–1601, 1982.

ALBERTSON, T. E., JOY, R. M., AND STARK, L. G.: Caffeine modification of kindled amygdaloid seizures. Pharmacol. Biochem. Behav. **19:** 339–343, 1983b.

ALBERTSON, T. E., JOY, R. M., AND STARK, L. G.: Carbamazepine. A pharmacological study in the kindling model of epilepsy. Neuropharmacology **23:** 1117–1123, 1984a.

ALBERTSON, T. E., STARK, L. G., AND JOY, R. M.: The effect of a glycine derivative (CP 1552 S) on kindled seizures in rats. Neuropharmacology **23:** 967–970, 1984a

ALBERTSON, T. E., STARK, L. G., JOY, R. M., AND BOWYER, J. F.: Aminophylline and kindled seizures. Exp. Neurol. **81:** 703–713, 1983b

ALBERTSON, T. E., AND WALBY, W. F.: The anticonvulsant action of nafimidone on kindled amygdaloid seizures in rats. Epilepsy Res. **2:** 20–26, 1988.

ALBRIGHT, P. S., AND BRUNI, J.: Effects of carbamazepine and its epoxide metabolite on amygdala-kindled seizures in rats. Neurology **34:** 1383–1386, 1984.

ALGER, B. E.: GABA and glycine: postsynaptic actions. *In* Neurotransmitter Actions in the Vertebrate Nervous System, ed. by M. A. Rogawski and J. L. Barker, pp. 33–69, Plenum Press, New York, 1985.

ALLAN, A. M., AND HARRIS, R. A.: Anesthetic and convulsant barbiturates alter gamma-aminobutyric acid-stimulated chloride flux across brain membranes. J. Pharmacol. Exp. Ther. **238:** 763–768, 1986.

ALLEN, H. L., AND IVERSEN, L. L.: Phencyclidine, dizocilpine, and cerebrocortical neurons. Science (Wash. DC) **247:** 221, 1990.

ALTAFULLA, I., TALWAR, D., LOEWENSON, R., OLSON, K., AND LOCKMAN, L. A.: Factors influencing serum levels of carbamazepine and carbamazepine-10,11-epoxide in children. Epilepsy Res. **4:** 72–80, 1989.

ALVING, J., KRISTENSEN, O., TSIROPOULOS, I., AND MONDRUP, K.: Double-blind placebo-controlled evaluation of flunarizine as adjunct therapy in epilepsy with complex partial seizures. Acta Neurol. Scand. **79:** 128–132, 1989.

ANDERSON, R. E., HOWARD, R. A., AND WOODBURY, D. M.: Correlation between effects of acute acetazolamide administration to mice on electroshock seizure threshold and maximal electroshock seizure pattern, and on carbonic anhydrase activity in subcellular fractions of brain. Epilepsia **27:** 504–509, 1986.

ANDERSON, W. W., SWARTZWELDER, H. S., AND WILSON, W. W.: The NMDA receptor antagonist 2-amino-5-phosphonovalerate blocks stimulus train-induced epileptogenesis but not epileptiform bursting in the rat hippocampal slice. J. Neurophysiol. **57:** 1–21, 1987.

ANDREWS, R. V., RITTER, F. J., AND MIMS, J.: Spectrum of efficacy of methsuximide in pediatric epilepsy. Epilepsia **30:** 736, 1989.

ANIS, N. A., BERRY, S. C., BURTON, N. R., AND LODGE, D.: The dissociative anesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. Br. J. Pharmacol. **79:** 565–575, 1983.

ANLEZARK, G., HORTON, R. W., MELDRUM, B. S., AND SAWAYA, M. C. B.: Anticonvulsant action of ethanolamine-*o*-sulphate and di-*n*-propylacetate and the metabolism of γ-aminobutyric acid (GABA) in mice with audiogenic seizures. Biochem. Pharmacol. **25:** 413–417, 1976.

ANONYMOUS: Vigabatrin (editorial). Lancet **1:** 532–533, 1989.

ARAM, J. A., MARTIN, D., TOMCZYK, M., ZEMAN, S., MILLAR, J., POHLER, G., AND LODGE, D.: Neocortical epileptogenesis *in vitro*: studies with N-methyl-D-aspartate, phencyclidine, *sigma* and dextromethorphan receptor ligands. J. Pharmacol. Exp. Ther. **248:** 320–328, 1989.

ASHTON, D., REID, K., WILLEMS, R., MARRANNES, R., AND WAUQUIER, A.: Comparative action of flunarizine, phenytoin, carbamazepine and two calcium-entry blockers on spontaneous epileptiform bursts in the low calcium-hippocampal slice preparation. Drug Dev. Res. **8:** 397–405, 1986.

ASHTON, D., AND WAUQUIER, A.: Effects of some anti-epileptic, neuroleptic and gabaminergic drugs on convulsions induced by D,L-allylglycine. Pharmacol. Biochem. Behav. **11:** 221–226, 1979a.

ASHTON, D., AND WAUQUIER, A.: Behavioural analysis of the effects of 15 anticonvulsants in amygdaloid kindled rats. Psychopharmacology **65:** 7–13, 1979b.

AYALA, G. F., AND JOHNSTON, D.: The influence of phenytoin on the fundamental electrical properties of simple neural systems. Epilepsia **18:** 299–307, 1977.

BAILLIE, T. A., AND RETTENMEIER, A. W.: Valproate. Biotransformation. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 601–619, Raven Press, New York, 1989.

BALDINO, F., JR., AND GELLER, H. M.: Sodium valproate enhancement of γ-

aminobutyric acid (GABA) inhibition: electrophysiological evidence for anticonvulsant activity. J. Pharmacol. Exp. Ther. **217:** 445–450, 1981.

BARALDI, M., GRANDISON, L., AND GUIDOTTI, A.: Distribution and metabolism of muscimol in the brain and other tissues of the rat. Neuropharmacology **18:** 57–62, 1979.

BARKER, J. L., AND MCBURNEY, R. N.: Phenobarbitone modulation of postsynaptic GABA receptor function on cultured mammalian neurons. Proc. R. Soc. Lond. B **206:** 319–327, 1979.

BARKER, J. L., AND RANSOM, B. R.: Amino acid pharmacology of mammalian central neurones grown in tissue culture. J. Physiol. (Lond.) **280:** 331–354, 1978a

BARKER, J. L., AND RANSOM, B. R.: Pentobarbitone pharmacology of mammalian central neurones grown in tissue culture. J. Physiol. (Lond.) **280:** 355–372, 1978b

BARNES, D. M., AND DICHTER, M. A.: Effects of ethosuximide and tetramethylsuccinimide on cultured cortical neurons. Neurology **34:** 620–625, 1984.

BARRACO, R. A., SWANSON, T. H., PHILLIS, J. W., AND BERMAN, R. F.: Anticonvulsant effects of adenosine analogues on amygdaloid-kindled seizures in rats. Neurosci. Lett. **46:** 317–322, 1984.

BARTOSZYK, G. D., DOOLEY, FRITSCHI, E., AND SATZINGER, G.: Ralitoline: a thiazolidinone. *In* New Anticonvulsant Drugs, ed. by B. S. Meldrum and R. J. Porter, pp. 309–311, John Libbey, London, 1986a.

BARTOSZYK, G. D., AND HAMER, M.: The genetic animal model of reflex epilepsy in the mongolian gerbil: differential efficacy of new anticonvulsive drugs and prototype antiepileptics. Pharmacol. Res. Commun. **19:** 429–440, 1987.

BARTOSZYK, G. D., MEYERSON, N., REIMANN, W., SATZINGER, G., AND VON HODENBERG, A.: Gabapentin. *In* New Anticonvulsant Drugs, ed. by B. S. Meldrum and R. J. Porter, pp. 147–163, John Libbey, London, 1986b.

BARUZZI, A., MICHELUCCI, R., AND TASSINARI, C. A.: Benzodiazepines. Nitrazepam. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 785–804, Raven Press, New York, 1989.

BARZAGHI, F., FOURNEX, R., AND MANTEGAZZA, P.: Pharmacological and toxicological properties of clobazam (1-phenyl-5-methyl-8-chloro-1,2,4,5-tetrahydro-2,4-diketo-3H-1,5-benzodiazepine), a new psychotherapeutic agent. Arzneim. Forsch. **23:** 683–696, 1973.

BASILE, A. S., BOLGER, G. T., LUEDDENS, H. W. M., AND SKOLNICK, P.: Electrophysiological actions of Ro5–4864 on cerebellar Purkinje neurons: evidence for "peripheral" benzodiazepine receptor-mediated depression. J. Pharmacol. Exp. Ther. **248:** 463–469, 1989.

BATTAGLIA, A., FERRARI, A. R., TOLER, M. T., AND GUERRINI, R.: Double-blind placebo-controlled trial of funarizine in therapy resistant epilepsy. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 84, New Delhi, India, 1989.

BAUER, G., DEISENHAMMER, E., KLINGLER, D., AND MAMOLI, B.: Gabapentin in the long-term treatment of drug resistant epileptic patients. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 41, New Delhi, India, 1989.

BAUMEL, I. P., GALLAGHER, B. B., DIMICCO, J., AND DIONNE, R.: Metabolism, distribution and anticonvulsant properties of N,N′-dimethoxymethyl-phenobarbital in the rat. J. Pharmacol. Exp. Ther. **196:** 180–187, 1976.

BAXTER, M. G., MILLER, A. A., AND WEBSTER, R. A.: Some studies on the convulsant action of folic acid. Br. J. Pharmacol. **48:** 350P-351P, 1973.

BENASSI, E., BESIO, G., BO, G. P., COCITO, L., MAFFINI, M., MAINARDI, P., MORSELLI, P. L., AND LOEB, C.: Preliminary observations on the activity of progabide, administered as monotherapy in complex partial seizures. Int. J. Clin. Pharmacol. Res. **8:** 353–361, 1988b.

BENASSI, E., COCITO, L., MAFFINI, M., BO, G. P., AND LOEB, C.: Preliminary note on the effect of denzimol in partial epilepsy. Ital. J. Neurol. Sci. **9:** 331–335, 1988a.

BÉNAVIDÈS, J., GUILLOUX, F., ALLAM, D. E., UZAN, A., MIZOULE, J., RENAULT, C., DUBROEUCQ, M. C., GUEREMY, C., AND LE FUR, G.: Opposite effects of an agonist, RO5–4864, and an antagonist, PK 11195, of the peripheral type benzodiazepine sites on audiogenic seizures in DBA/2J mice. Life Sci. **34:** 2613–2620, 1984.

BEN-MENACHEM, E., HEDNER, T., PERSSON, L. I., AND SÖDERFELDT, B.: Seizure frequency and CSF gabapentin, GABA, and monoamine metabolite concentrations after 3 months' treatment with 900 mg or 1,200 mg gabapentin daily in patients with intractable complex partial seizures. Neurology **40** (suppl. 1): 158, 1990.

BEN MENACHEM, E., PERSSON, L. I., SCHECHTER, P. J., HAEGELE, K. D., HUEBERT, N., HARDENBERG, J., DAHLGREN, L., AND MUMFORD, J. P.: Effects of single doses of vigabatrin on CSF concentrations of GABA, homocarnosine, homovanillic acid and 5-hydroxyindoleacetic acid in patients with complex partial epilepsy. Epilepsy Res. **2:** 96–101, 1988.

BENNETT, D. A., BERNARD, P. S., AND AMRICK, C. I.: A comparison of PCP-like compounds for NMDA antagonism in two *in vivo* models. Life Sci. **42:** 447–454, 1988.

BENNETT, D. A., BERNARD, P. S., AMRICK, C. L., WILSON, D. E., LIEBMAN, J. M., AND HUTCHISON, A. J.: Behavioral pharmacological profile of CGS 19755, a competitive antagonist at *N*-methyl-D-aspartate receptors. J. Pharmacol. Exp. Ther. **250:** 454–460, 1989.

BENVENGA, M. J., AND SPAULDING, T. C.: Amnestic effect of the novel anticonvulsant MK-801. Pharmacol. Biochem. Behav. **30:** 205–207, 1988.

BENVENISTE, M., AND MAYER, M. L.: Kinetic experiments with competitive NMDA receptor antagonists. Biophys. J. **57:** 121a, 1990.

BERNARD, P., BROWN, W., WILLIAMS, M., LEHMANN, J., KAPEGHIAN, J., LIEBMAN, J., AND ROBSON, R.: CGS 18416A: pharmacological and neurochemical profile of a novel anticonvulsant. Abstracts of The First Princeton Drug Research Symposium, ed. M. Williams, p. 42, 1989.

BERNARDINA, B. D., FONTANA, E., SGRO, V., CELLINO, R., AND SIMEONI, M.: Eterobarb (Antilon™, dimethoxymethylphenobarbital) treatment in children with epilepsy. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 156, New Delhi, India, 1989.

BERNASCONI, R., KLEIN, M., MARTIN, P., CHRISTEN, P., HAFNER, T., PORTET, C., AND SCHMUTZ, M.: γ-Vinyl GABA: comparison of neurochemical and anticonvulsant effects in mice. J. Neural Transm. **72:** 213–233, 1988.

BESSER, R., AND KRAMER, G.: Long term efficacy and safety of vigabatrin in epileptic patients. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 155, New Delhi, India, 1989.

BETTS, T., GRACE, E., AND PIGOTT, C.: Clinical experience with lamotrigine (Lamictal®): results of an open trial of 70 patients with one year follow up. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 144, New Delhi, India, 1989.

BINNIE, C. D.: Potential antiepileptic drugs: flunarizine and other calcium entry blockers. *In* Antiepileptic Drugs, 3rd ed., ed. by R. J. Levy, F. E. Dreifuss, R. H. Mattson, B. S. Meldrum, and J. K. Penry, pp. 971–982, Raven Press, New York, 1989a.

BINNIE, C. D., DEBETS, R. M. C., ENGELSMAN, M., MEIJER, J. W. A., MEINARDI, H., OVERWEG, J., PECK, A. W., VAN WIERINGEN, A., AND YUEN, W. C.: Double-blind crossover trial of lamotrigine lamictal as add-on therapy in intractable epilepsy. Epilepsy Res. **4:** 222–229, 1989.

BIRCH, P. J., GROSSMAN, C. J., AND HAYES, A. G.: 6,7-Dinitro-quinoxaline-2,3-dion and 6-nitro,7-cyano-quinoxaline-2,3-dion antagonise responses to NMDA in the rat spinal cord via an action at the strychnine-insensitive glycine receptor. Eur. J. Pharmacol. **156:** 177–180, 1988.

BLAIR, L. A. C., LEVITAN, E. S., MARSHALL, J., DIONNE, V. E., AND BARNARD, E. A.: Single subunits of the $GABA_A$ receptor form ion channels with properties of the native receptor. Science (Wash. DC) **242:** 577–579, 1988.

BLAUSTEIN, M. P., AND ECTOR, A. C.: Barbiturate inhibition of calcium uptake by depolarized nerve terminals *in vitro*. Mol. Pharmacol. **11:** 369–378, 1975.

BOOKER, H. E.: Trimethadione. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 715–720, Raven Press, New York, 1989.

BOURGEOIS, B. F. D.: Primidone. Biotransformation and mechanisms of action. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 401–412, Raven Press, New York, 1989.

BOURGEOIS, B. F. D., DODSON, W. E., AND FERRENDELLI, J. A.: Primidone, phenobarbital and PEMA: I. Seizure protection, neurotoxicity and therapeutic index of individual compounds in mice. Neurology **33:** 283–290, 1983.

BOURGEOIS, B. F. D., AND WAD, N.: Individual and combined antiepileptic and neurotoxic activity of carbamazepine and carbamazepine-10,11-epoxide in mice. J. Phrarmacol. Exp. Ther. **231:** 411–415, 1984.

BOURN, W. M., GARRETT, R. L., REIGEL, C. E., AND RISINGER, F. O.: Reduction of flurazepam convulsive threshold by Ro 15–1788. Psychopharmacology **85:** 267–270, 1985.

BOURN, W. M., YANG, D. J., AND DAVISSON, J. N.: Effect of ketamine enantiomers on sound-induced convulsions in epilepsy prone rats. Pharmacol. Res. Commun. **15:** 815–824, 1983.

BOWERY, N. G., HILL, D. R., AND HUDSON, A. L.: Evidence that SL75102 is an agonist at $GABA_B$ as well as $GABA_A$ receptors. Neuropharmacology **21:** 391–395, 1982.

BRAESTRUP, C., NIELSEN, E. B., SONNEWALD, U., KNUTSEN, L. J., ANDERSEN, K. E., JANSEN, J. A., FREDERIKSEN, K., ANDERSEN, P. H., MORTENSEN, A., AND SUZDAK, P. D.: (R)-N-[4,4-bis(3-methyl-2-thienyl)but-3-en-1-yl]nipecotic acid binds with high affinity to the brain γ-aminobutyric acid uptake carrier. J. Neurochem. **54:** 639–647, 1990.

BRAESTRUP, C., AND SQUIRES, R. F.: Pharmacological characterization of benzodiazepine receptors in the brain. Eur. J. Pharmacol. **48:** 263–270, 1978.

BRENT, D. A., CRUMRINE, P. K., VARMA, R. E., ALLAN, M. AND ALLMAN, C.: Phenobarbital treatment and major depressive disorder in children with epilepsy. Pediatrics **80:** 909–917, 1987.

BROWNE, T. R.: Other succinimides. Methsuximide. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 707–714, Raven Press, New York, 1989.

BROWNE, T. R., DREIFUSS, F. E., DYKEN, P. R., GOODE, D. J., PENRY, J. K., PORTER R. J., WHITE, B. G., AND WHITE, P. T.: Ethosuximide in the treatment of absence (petit mal) seizures. Neurology **25:** 515–524, 1975.

BROWNE, T. R., MATTSON, R. H., PENRY, J. K., SMITH, D. B., TREIMAN, D. M., WILDER, B. J., BEN-MENACHEM, E., MIKETTA, R. M., SHERRY, K. M., AND SZABO, G. K.: A multicentre study of vigabatrin for drug-resistant epilepsy. Br. J. Pharmacol. **27** (suppl. 1): 95S-100S, 1989.

BUHLES, W. C., JR., WALLACH, M. B., CHAPLIN, M. D., AND TREIMAN, D. M.: Nafimidone. *In* New Anticonvulsant Drugs, ed. by B. S. Meldrum, and R. J. Porter, pp. 203–214, John Libbey, London, 1986.

BURLEY, E. S., AND FERRENDELLI, J. A.: Regulatory effects of neurotransmitters on electroshock and pentylenetetrazol seizures. Fed. Proc. **43:** 2521–2524, 1984.

BUTELMAN, E. R.: A novel NMDA antagonist, MK-801, impairs performance in a hippocampal-dependent spatial learning task. Pharmacol. Biochem. Behav. **34:** 13–16, 1989.

BUTLER, W. H.: The neuropathology of vigabatrin. Epilepsia **30** (suppl. 3): S15–17, 1989.

BUTLER, W. H., FORD, G. P., AND NEWBERNE, J. W.: A study of the effects of GVG on the central nervous system and retina of Sprague-Dawley and Lister-Hooded rats. Toxicol. Pathol. **15:** 143–148, 1987.

BUTLER, T. C., WADDELL, W. J., AND POOLE, D. T.: Demethylation of trimethadione and metharbital by rat liver microsomal enzymes: substrate concentration-yield relationships and competition between substrates. Biochem. Pharmacol. **14:** 937–942, 1965.

BYRD, L. D., STANDISH, L. J., AND HOWELL, L. L.: Behavioral effects of phencyclidine and ketamine alone and in combination with other drugs. Eur. J. Pharmacol. **144:** 331–341, 1987.

CALLAGHAN, D. A., AND SCHWARK, W. S.: Pharmacological modification of amygdaloid-kindled seizures. Neuropharmacology **19:** 1131–1136, 1980.

CANOLL, P. D., SMITH, P. R., GOTTESMAN, S., AND MUSACCHIO, J. M.: Autoradiographic localization of [^{3}H]dextromethorphan in guinea pig brain: allosteric enhancement by ropizine. J. Neurosci. Res. **24:** 311–328, 1989.

CARLSSON, M., AND CARLSSON, A.: Dramatic synergism between MK-801 and clonidine with respect to locomotor stimulatory effect in monoamine-depleted mice. J. Neural Transm. **77:** 65–71, 1989.

CARTER, C., RIVY, J. P., AND SCATTON, B.: Ifenprodil and SL 82.0715 are antagonists at the polyamine site of the N-methyl-D-aspartate (NMDA) receptor. Eur. J. Pharmacol. **164:** 611–612, 1989.

CARTER, C. A., HELMS, R. A., AND BOEHM, R.: Ethotoin in seizures of childhood and adolescence. Neurology **34:** 791–795, 1984.

CASALOTTI, S. O., STEPHENSON, F. A., AND BARNARD, E. A.: Separate subunits for agonist and benzodiazepine binding in the γ-aminobutyric acid$_A$ receptor oligomer. J. Biol. Chem. **261:** 15013–15016, 1986.

CELESIA, G. G., BAMFORTH, B. J., AND CHEN, R.-C.: Effects of ketamine in epileptics. Neurology **24:** 386, 1974.

CEPEDA, C., WORMS, P., LLOYD, K. G., AND NAQUET, R.: Action of progabide in the photosensitive baboon *Papio papio*. Epilepsia **24:** 463–470, 1982.

CEREGHINO, J. J., BROCK, J. T., VAN METER, J. C., PENRY, J. K., SMITH, L. D., AND WHITE, B. G.: Carbamazepine for epilepsy: a controlled prospective evaluation. Neurology **24:** 401–410, 1974.

CHADWICK, D.: Comparison of monotherapy with valproate and other antiepileptic drugs in the treatment of seizure disorders. Am. J. Med. **84:** 3–6, 1988.

CHADWICK, D.: Gabapentin as an anticonvulsant in long term therapy of partial epilepsy. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 54, New Delhi, India, 1989.

CHANG, T.: Ethosuximide. Absorption, distribution, and excretion. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 671–678, Raven Press, New York, 1989.

CHAPMAN, A. G., CROUCHER, M. J., AND MELDRUM, B. S.: Anticonvulsant activity of intracerebroventricularly administered valproate and valproate analogues. A dose-dependent correlation with changes in brain aspartate and GABA levels in DBA/2 mice. Biochem. Pharmacol. **33:** 1459–1463, 1984.

CHAPMAN, A. R., GRAHAM, J., AND MELDRUM, B. S.: Potent oral anticonvulsant action of CPP and CPPene in DBA/2 mice. Eur. J. Pharmacol. **178:** 97–99, 1990.

CHAPMAN, A. G., AND HART, G. P.: Anticonvulsant drug action and regional neurotransmitter amino acid changes. J. Neural Transm. **72:** 201–212, 1988.

CHAPMAN, A. G., HORTON, R. W., AND MELDRUM, B. S.: Anticonvulsant action of a 1,5-benzodiazepine, clobazam, in reflex epilepsy. Epilepsia **19:** 293–299, 1978.

CHAPMAN, A., KEANE, P. E., MELDRUM, B. S., SIMIAND, J., AND VERNIERES, J. C.: Mechanism of anticonvulsant action of valproate. Prog. Neurobiol. **19:** 315–359, 1982.

CHAPMAN, A., AND MELDRUM, B. S.: Non-competitive N-methyl-D-aspartate antagonists protect against sound-induced seizures in DBA/2 mice. Eur. J. Pharmacol. **166:** 201–211, 1989.

CHAPMAN, A. G., MELDRUM, B. S., AND MENDES, E.: Acute anticonvulsant activity of structural analogues of valproic acid and changes in brain GABA and aspartate content. Life Sci. **32:** 2023–2031, 1983.

CHAPMAN, A. G., MELDRUM, B. S., NANJI, N., AND WATKINS, J. C.: Anticonvulsant action and biochemical effects in DBA/2 mice of CPP (3-((±)-2-carboxypiperazin-4-yl)-propyl-1-phosphonate), a novel N-methyl-D-aspartate antagonist. Eur. J. Pharmacol. **139:** 91–96, 1987.

CHAUVEL, P., VIGNAL, J. P., TROTTIER, S., AND BEAUMONT, D.: Long-term follow-up of vigabatrin treated patients with partial seizures. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 140, New Delhi, India. 1989.

CHEN, G., AND BOHNER, B.: Anticonvulsant properties of 1-(1-phenylcyclohexyl) piperidine HCl and certain other drugs. Proc. Soc. Exp. Biol. Med. **106:** 632–635, 1961.

CHEN, G., ENSOR, C. R., AND BOHNER, B.: The neuropharmacology of 2-(*o*-chlorophenyl)-2-methylaminocyclohexanone hydrochloride. J. Pharmacol. Exp. Ther. **152:** 332–339, 1966.

CHEN, G., PORTMAN, R., ENSOR, C. R., AND BRATTON, A. C., JR.: The anticonvulsant activity of alpha-phenyl succinimides. J. Pharmacol. Exp. Ther. **103:** 54–61, 1951.

CHEN, G., WESTON, J. K., AND BRATTON, A. C., JR.: Anticonvulsant activity and toxicity of phensuximide, methsuximide and ethosuximide. Epilepsia **4:** 66–76, 1963.

CHIRON, C., DULAC, O., LUNA, D., PALACIOS, L., MONDRAGON, S., BEAUMOND, D., AND MUMFORD, J. P.: Vigabatrin in infantile spasms. Lancet **1:** 363–364, 1990.

CHOI, D. W., FARB, D. H., AND FISCHBACH, G. D.: Chlordiazepoxide selectively augments GABA action in spinal cord cell cultures. Nature (Lond.) **269:** 342–344, 1977.

CHOI, D. W., FARB, D. H., AND FISCHBACH, G. D.: Chlordiazepoxide selectively potentiates GABA conductance of spinal cord and sensory neurons in cell culture. J. Neurophysiol. **45:** 621–631, 1981.

CHURCH, J., LODGE, D., AND BERRY, S. C.: Differential effects of dextrorphan and levorphanol on the excitation of rat spinal neurons by amino acids. Eur. J. Pharmacol. **111:** 185–190, 1985.

CLARK, C. R.: Comparative anticonvulsant activity and neurotoxicity of 4-amino-N-(2,6-dimethylphenyl)benzamide and prototype antiepileptic drugs in mice and rats. Epilepsia **29:** 198–203, 1988.

CLARK, C. R., LIN, C. M., AND SANSOM, R. T.: Anticonvulsant activity of 2- and 3-aminobenzanilides. J. Med. Chem. **29:** 1534–1537, 1986.

CLARK, C. R., SANSON, R. T., LIN, C.-M., AND NORRIS, G. N.: Anticonvulsant activity of some 4-aminobenzanilides. J. Med. Chem. **28:** 1259–1262, 1985.

CLARK, C. R., WELLS, M. J. M., SANSON, R. T., NORRIS, G. N., DOCKENS, R. C., AND RAVIS, W. R.: Anticonvulsant activity of some 4-aminobenzamides. J. Med. Chem. **27:** 779–782, 1984.

CLINESCHMIDT, B. V., MARTIN, G. E., AND BUNTING, P. R.: Anticonvulsant activity of (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. Drug Dev. Res. **2:** 123–134, 1982a.

CLINESCHMIDT, B. V., MARTIN, G. E., BUNTING, P. R., AND PAPP, N. L.: Central sympathomimetic activity of (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. Drug. Dev. Res. **2:** 135–145, 1982b.

COCITO, L., MAFFINI, M., PERFUMO, P., RONCALLO, F., AND LOEB, C.: Vigabatrin in complex partial seizures: a long-term study. Epilepsy Res. **3:** 160–166, 1989.

COENEN, A. M., AND VAN LUIJTELAAR, E. L.: Effects of diazepam and two beta-carbolines on epileptic activity and on EEG and behavior in rats with absence seizures. Pharmacol. Biochem. Behav. **32:** 27–35, 1989.

COKER, S. B., HOLMES, E. W., AND EGEL, R. T.: Phenacemide therapy of complex partial epilepsy in children: determination of plasma drug concentrations. Neurology **37:** 1861–1866, 1987.

COLE, A. E., ECCLES, C. U., ARYANPUR, J. J., AND FISHER, R. S.: Selective depression of *N*-methyl-D-aspartate-mediated responses by dextrorphan in the hippocampal slice in rat. Neuropharmacology **28:** 249–254, 1989.

COLEMAN-RIESE, D., AND CUTLER, R. W. P.: Inhibition of gamma-aminobutyric acid release from rat cerebral cortex slices by barbiturate anesthesia. Neurochem. Res. **3:** 423–429, 1978.

COLLABORATIVE STUDY GROUP (BOURGEOIS, B., BEAUMANOIR, A., BLAJEV, B., DE LA CRUZ, N., DESPLAND, P. A., EGLI, M., GEUDELIN, B., KASPAR, U., KETZ, E., KRONAUER, C., MEYER, C., SCOLLO-LAVIZZARI, G., TOSI, C., VASSELLA, F., AND ZAGURY, S.): Monotherapy with valproate in primary generalized epilepsies. Epilepsia **28** (suppl. 2): S8–S11, 1987.

COLLINGRIDGE, G. L., AND LESTER, R. A. J.: Excitatory amino acid receptors in the vertebrate central nervous system. Pharmacol. Rev. **40:** 143–210, 1989.

COMMISSION ON CLASSIFICATION AND TERMINOLOGY OF THE INTERNATIONAL LEAGUE AGAINST EPILEPSY: Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia **22:** 489–501, 1981.

COMMISSION ON CLASSIFICATION AND TERMINOLOGY OF THE INTERNATIONAL LEAGUE AGAINST EPILEPSY: Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia **30:** 389–399, 1989.

COMPTON, R. P., CONTRERAS, P. C., O'DONOHUE, T. L., AND MONAHAN, J. B.: The N-methyl-D-aspartate antagonist, 2-amino-7-phosphonoheptanoate, produces phencyclidine-like behavioral effects in rats. Eur. J. Pharmacol. **136:** 133–134, 1987.

CONNORS, B. W.: A comparison of the effects of pentobarbital and diphenylhydantoin on the GABA sensitivity and excitability of adult sensory ganglion cells. Brain Res. **207:** 357–369, 1981.

CORBETT, D.: Possible abuse potential of the NMDA antagonist MK-801. Behav. Brain Res. **34:** 239–246, 1989.

COSI, V., CALLIECO, R., GALIMBERTI, C. A., MANNI, R., TARTARA, A.,

MUMFORD, J., AND PERUCCA, E.: Effects of vigabatrin on evoked potentials in epileptic patients. Br. J. Clin. Pharmacol. **27** (Suppl. 1): 61S–68S, 1989.
COTE, I. L., ZBICZ, K. L., AND WILSON, W. A.: Barbiturate-induced slow outward currents in *Aplysia* neurones. Nature (Lond.) **274:** 594–596, 1978.
COULTER, D. A., HUGUENARD, J. R., AND PRINCE, D. A.: Differential effects of anticonvulsant and convulsant succinimides on GABA responses of thalamic neurons. Epilepsia **30:** 734, 1989a.
COULTER, D. A., HUGUENARD, J. R., AND PRINCE, D. A.: Calcium currents in rat thalamocortical relay neurones: kinetic properties of the transient, low-threshold current. J. Physiol. (Lond.) **414:** 587–604, 1989b.
COULTER, D. A., HUGUENARD, J. R., AND PRINCE, D. A.: Characterization of ethosuximide reduction of low-threshold calcium current in thalamic neurons. Ann. Neurol. **25:** 582–593, 1989c.
COULTER, D. A., HUGUENARD, J. R., AND PRINCE, D. A.: Specific petit mal anticonvulsants reduce calcium currents in thalamic neurons. Neurosci. Lett. **98:** 74–78, 1989d.
COULTER, D. A., HUGUENARD, J. R., AND PRINCE, D. A.: Differential effects of petit mal anticonvulsants and convulsants on thalamic neurones. I. calcium current reduction. Br. J. Pharmacol., in press, 1990.
COURTNEY, K. R., AND ETTER, E. F.: Modulated anticonvulsant block of sodium channels in nerve and muscle. Eur. J. Pharmacol. **88:** 1–9, 1983.
COUTINHO-NETTO, J., ABDUL-GHANI, A. S., COLLINS, J. F., AND BRADFORD, H. F.: Is glutamate a triger factor in epileptic hyperactivity? Epilepsia **22:** 289–296, 1981.
CRAIG, C. R., AND SHIDEMAN, F. E.: Metabolism and anticonvulsant properties of mephobarbital and phenobarbital in rats. J. Pharmacol. Exp. Ther. **176:** 35–41, 1971.
CRAVISO, G. L., AND MUSACCHIO, J. M.: High-affinity dextromethorphan binding sites in guinea pig brain. I. Initial characterization. Mol. Pharmacol. **23:** 619–628, 1983a.
CRAVISO, G. L., AND MUSACCHIO, J. M.: High-affinity dextromethorphan binding sites in guinea pig brain. II. Competition experiments. Mol. Pharmacol. **23:** 629–640, 1983b.
CRAWFORD, P., GHADIALI, E., LANE, R., BLUMHARDT, L., AND CHADWICK, D.: Gabapentin as an antiepileptic drug in man. J. Neurol. Neurosurg. Psychiatry **50:** 682–686, 1987a.
CRAWFORD, T. O., MITCHELL, W. G. AND SNODGRASS, S. R.: Lorazepam in childhood status epilepticus and serial seizures: effectiveness and tachyphylaxis. Neurology **37:** 190–195, 1987b.
CROUCHER, M. J., COLLINS, J. F., AND MELDRUM, B. S.: Anticonvulsant action of excitatory amino acid antagonists. Science (Wash. DC) **216:** 899–901, 1982.
CROWDER, J. M., AND BRADFORD, H. F.: Common anticonvulsants inhibit Ca^{2+} uptake and amino acid neurotransmitter release in vitro. Epilepsia **28:** 378–382, 1987.
CURTIS, D. R., AND LODGE, D.: Phenobarbitone enhancement of the inhibitory action of GABA. Nature (Lond.) **270:** 543–544, 1977.
CZUCZWAR, S. J., AND MELDRUM, B. S.: Protection against chemically induced seizures by 2-amino-7-phosphonoheptanoic acid. Eur. J. Pharmacol. **83:** 335–338, 1982.
DAM, M.: Long-term evaluation of vigabatrin (gamma vinyl GABA) in epilepsy. Epilepsia **30** (suppl. 3): S26–30, 1989.
DAM, M., EKBERG, R., LÖYNING, Y., WALTIMO, O., AND JAKOBSEN, K.: A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed previously untreated epilepsy. Epilepsy Res. **3:** 70–76, 1989.
DAM, M., GRAM, L., PHILBERT, A., HANSEN, B. S., BLATT-LYON, B., CHRISTIENSEN, J. M., AND ANGELO, H. R.: Progabide: a controlled trial in partial epilepsy. Epilepsia **24:** 127–135, 1983.
DAM, M., AND JENSEN, P. K.: Potential antiepileptic drugs. Oxcarbazepine. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 913–924, Raven Press, New York, 1989.
DANYSZ, W., FADDA, E., WROBLEWSKI, J. T., AND COSTA, E.: Different modes of action of 3-amino-1-hydroxy-2-pyrrolidone (HA-966) and 7-chlorokynurenic acid in the modulation of *N*-methyl-D-aspartate-sensitive glutamate receptors. Mol. Pharmacol. **36:** 912–916, 1989.
DANYSZ, W., WROBLEWSKI, J. T., AND COSTA, E.: Learning impairment in rats by *N*-methyl-D-aspartate receptor antagonists. Neuropharmacology **27:** 653–656, 1988.
DAVAL, J.-L., DECKERT, J., WEISS, S. R. B., POST, R. M., AND MARANGOS, P. J.: Upregulation of adenosine A1 receptors and forskolin binding sites following chronic treatment with caffeine or carbamazepine: a quantitative autoradiographic study. Epilepsia **30:** 26–33, 1989.
DAVID, J., AND GREWAL, R. S.: Effect of carbamazepine (Tegretol) on seizure and EEG patterns in monkeys with alumina-induced focal motor and hippocampal foci. Epilepsia **17:** 415–422, 1976.
DAVIES, J., EVANS, R. H., HERRLING, P. L., JONES, A. W., OLVERMAN, H. J., POOK, P., AND WATKINS, J. C.: CPP, a new potent and selective NMDA antagonist. Depression of central neuron responses, affinity for [^{3}H]D-AP5 binding sites on brain membranes and anticonvulsant activity. Brain Res. **382:** 169–173, 1986.
DAVIES, S. N., MARTIN, D., MILLAR, J. D., CHURCH, J., AND LODGE, D.: Differences in results from in vivo and in vitro studies on the use-dependency of N-methylaspartate antagonism by MK-801 and other phencyclidine receptor ligands. Eur. J. Pharmacol. **145:** 141–151, 1988.
DAVIS, R. W., AND TOLSTOSHEV, G. C.: Ketamine—use in severe febrile convulsions. Med. J. Aust. **2:** 465–466, 1976.
DEAN, J. C., AND PENRY, J. K.: Valproate monotherapy in 30 patients with partial seizures. Epilepsia **29:** 140–144, 1988.
DEISZ, R. A., AND LUX, H. D.: Diphenylhydantoin prolongs postsynaptic inhibition and iontophoretic GABA action in the crayfish stretch receptor. Neurosci. Lett. **5:** 199–203, 1977.
DE LORENZO, R. J.: Phenytoin. Mechanisms of Action. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 143–158, Raven, Press, New York, 1989.
DEPAULIS, A., VERGNES, M., MARESCAUX, C., LANNES, B., AND WARTER, J. M.: Evidence that activation of GABA receptors in the substantia nigra suppresses spontaneous spike-and-wave discharges in the rat. Brain Res. **448:** 20–29, 1988.
DESARMENIEN, M., FELZ, P., HEADLEY, P. M., AND SANTANGELO, F.: SL 75102 as a γ-aminobutyric acid agonist: experiments on dorsal root ganglion neurones *in vitro*. Br. J. Pharmacol. **72:** 355–364, 1981.
DE SARRO, G. B., LIBRI, V., ASCIOTI, C., TESTA, R., AND NISTICO, G.: Anticonvulsant effect of denzimol in DBA/2 mice. Neuropharmacology **26:** 1425–1429, 1987.
DE SARRO, G. B., MELDRUM, B. S., AND NISTICÓ, G.: Anticonvulsant effects of some calcium entry blockers in DBA/2 mice. Br. J. Pharmacol. **93:** 247–256, 1988.
DE SARRO, G., MELDRUM, B. S., AND REAVILL, C.: Anticonvulsant action of 2-amino-7-phosphonoheptanoic acid in the substantia nigra. Eur. J. Pharmacol. **106:** 175–179, 1984.
DE SARRO, G. B., NISTICÓ, G., AND MELDRUM, B. S.: Anticonvulsant properties of flunarizine on reflex and generalized models of epilepsy. Neuropharmacology **25:** 695–701, 1986.
DESMEDT, L. K., NIEMEGEERS, C. J., AND JANSSEN, P. A.: Anticonvulsive properties of cinnarizine and flunarizine in rats and mice. Arzneim. Forsch. Drug Res. **25:** 1408–1413, 1975.
DEVORE, G. R., MCQUEEN, J. K., AND WOODBURY, D. M.: Ketamine hydrochloride and its effect on a chronic cobalt epileptic cortical focus. Epilepsia **17:** 111–117, 1976.
DINGLEDINE, R., HYNES, M. A., AND KING, G. L.: Involvement of *N*-methyl-D-aspartate receptors in epileptiform bursting in the rat hippocampal slice. J. Physiol. (Lond.) **380:** 175–189, 1986.
DOMINO, E. F., CHODOFF, P., AND CORSSEN, G.: Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. Clin. Pharmacol. Ther. **6:** 279–291, 1965.
DREJER, J., SHEARDOWN, M., NIELSEN, E. O., AND HONORÉ, T.: Glycine reverses the effect of HA-966 on NMDA responses in cultured rat cortical neurones and in chick retina. Neurosci. Lett. **98:** 333–338, 1989.
DUBROEUCQ, M. C., GUÉRÉMY, C., AND LE FUR, G.: Opposite effects of an agonist, RO5-4864, and an antagonist, PK 11195, of the peripheral benzodiazepine binding sites on audiogenic seizures in DBA/2J mice. Life Sci. **34:** 2613–2620, 1984.
DUNWIDDIE, T. V.: Endogenously released adenosine regulates excitability in the in vitro hippocampus. Epilepsia **21:** 541–548, 1980.
DUNWIDDIE, T. V.: The physiological role of adenosine in the central nervous system. Int. Rev. Neurobiol. **27:** 63–139, 1985.
DUNWIDDIE, T. V., AND FREDHOLM, B. B.: Adenosine A_1 receptors inhibit adenylate cyclase activity and neurotransmitter release and hyperpolarize pyramidal neurons in rat hippocampus. J. Pharmacol. Exp. Ther. **249:** 31–37, 1989.
DUNWIDDIE, T. V., AND WORTH, T.: Sedative and anticonvulsant effects of adenosine analogs in mouse and rat. J. Pharmacol. Exp. Ther. **220:** 70–76, 1982.
EADIE, M. J.: Other barbiturates. Methylphenobartibal and metharbital. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 357–378, Raven Press, New York, 1989.
EADIE, M. J., AND TRYER, J. H.: Anticonvulsant Therapy. Pharmacological Basis and Practice, 3rd ed. Churchill Livingstone, Edinburgh, 1989.
ECCLES, J. C., SCHMIDT, R. F., AND WILLIS, W. D.: Pharmacological studies on presynaptic inhibition. J. Physiol. (Lond.) **168:** 500–530, 1963.
EDMONDS, H. L., JR., STARK, L. G., STARK, D. M., MCCORMACK, C. R., SYLVESTER, D. M., AND BELLIN, S. I.: The anticonvulsant activity ropizine in the rat. J. Pharmacol. Exp. Ther. **208:** 236–242, 1979.
EMIG, P., ENGEL, J., NICKEL, B., SZELENYI, I., AND WERNER, U.: D-19274. Drugs Future **15:** 223–225, 1990.
EMSON, P. C.: Effects of chronic treatment with amino oxyacetic acid or sodium *n*-dipropylacetate on brain GABA levels and the development and regression of cobalt epileptic foci in rats. J. Neurochem. **27:** 1489–1494, 1976.
ENGSTROM, F. L., WHITE, H. S., KEMP, J. W., AND WOODBURY, D. M.: Acute and chronic acetazolamide administration in DBA and C57 mice: effects of age. Epilepsia **27:** 19–26, 1986.
ESPLIN, D. W.: Effects of diphenylhydantoin on synaptic transmission in cat spinal cord and stellate ganglion. J. Pharmacol. Exp. Ther. **120:** 301–323, 1957.
ESPLIN, D. W., AND CARTO, E. W.: Effect of trimethadione on synaptic transmission in the spinal cord: antagonism of trimethadione and pentylene-tetrazole. J. Pharmacol. Exp. Ther. **121:** 457–467, 1957.
EVERETT, G. M., AND RICHARDS, R. K.: Comparative anticonvulsive action

of 3,5,5-trimethyloxazolidine-2,4-dione (Tridone), Dilantin and phenobarbital. J. Pharmacol. Exp. Ther. **81:** 402–407, 1944.

FAEDDA, M. T., IANI, C., FUSCO, L., MATTIA, D., GIALLONARDO, A. T., MANFREDI, M., IUDICE, A., AND MUMFORD, J. P.: Long term effect of vigabatrin (VGB) in refractory epilepsies. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 80, New Delhi, India, 1989.

FAGG, G. E., OLPE, H.-R., POZZA, M. F., BAUD, J., STEINMANN, M., SCHMUTZ, M., PORTET, C., BAUMANN, P., THEDINGA, K., BITTIGER, H., ALLGEIER, H., HECKENDORN, R., ANGST, C., BRUNDISH, D., AND DINGWALL, J. G.: CGP 37849 and CGP 39551: novel and potent competitive N-methyl-D-aspartate receptor antagonists with oral activity. Br. J. Pharmacol. **99:** 791–797, 1990.

FARIELLO, R. G., AND GOLDEN, G. T: The THIP-induced model of bilateral synchronous spike and wave in rodents. Neuropharmacology **26:** 161–165, 1987.

FARIELLO, R. G., GOLDEN, G. T., AND BLACK, J. A.: Activating effects of homotaurine and taurine on corticoreticular epilepsy. Epilepsia **22:** 217–224, 1981.

FARIELLO, R., AND SMITH, M. C.: Valproate. Mechanisms of action. *In* Antiepileptic Drugs, 3rd ed., R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 567–575, Raven Press, New York, 1989.

FARIELLO, R. G., AND TICKU, M. K.: The perspective of GABA replenishment therapy in the epilepsies: a critical evaluation of hopes and concerns. Life Sci. **33:** 1629–1640, 1983.

FARWELL, J. R., LEE, Y. J., HIRTZ, D. G., SULZBACHER, S. I., ELLENBERG, J. H., NELSON, K. B.: Phenobarbital for febrile seizures—effects on intelligence and on seizure recurrence. N. Engl. J. Med. **322:** 364–369, 1990.

FARWELL, J. R., LEVY, R. H., AND ANDERSON, G.: An open trial of stiripentol in atypical absence seizures. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 109, New Delhi, India, 1989.

FEESER, H. R., KADIS, J. L., AND PRINCE, D. A.: Dextromethorphan, a common antitussive, reduces kindled amygdala seizures in the rat. Neurosci. Lett. **86:** 340–345, 1988.

FERKANY, J. W., BOROSKY, S. A., CLISSOLD, D. B., AND PONTECORVO, M. J.: Dextromethorphan inhibits NMDA-induced convulsions. Eur. J. Pharmacol. **151:** 151–154, 1988.

FERKANY, J. W., KYLE, D. J., WILLETS, J., RZESZOTARSKI, W. J., GUZEWSKA, M. E., ELLENBERGER, S. R., JONES, S. M., SACAAN, A. I., SNELL, L. D., BOROSKY, S., JONES, B. E., JOHNSON, K. M., BALSTER, R. L., BURCHETT, K., KAWASAKI, K., HOCH, D. B., AND DINGLEDINE, R.: Pharmacological profile of NPC 12626, a novel, competitive N-methyl-D-aspartate receptor antagonist. J. Pharmacol. Exp. Ther. **250:** 100–109, 1989.

FERRENDELLI, J. A., HOLLAND, K. D., MCKEON, A. C., AND COVEY, D. F.: Comparison of the anticonvulsant activities of ethosuximide, valproate, and a new anticonvulsant, thiobutyrolactone. Epilepsia **30:** 617–622, 1989.

FERRER-ALLADO, T., BRECHNER, V. L., DYMOND, A., COZEN, H., AND CRANDALL, P.: Ketamine-induced electroconvulsive phenomena in the human limbic and thalamic regions. Anesthesiology **38:** 333–344, 1973.

FFRENCH-MULLEN, J. M. H., AND ROGAWSKI, M. A.: Interaction of phencyclidine with voltage-dependent potassium channels in cultured rat hippocampal neurons: comparison with block of the NMDA receptor-ionophore complex. J. Neurosci. **9:** 4051–4061, 1989.

FILE, S. E.: Pro- and anticonvulsant properties of PK 11195, a ligand for benzodiazepine binding sites: development of tolerance. Br. J. Pharmacol. **83:** 471–476, 1984.

FILE, S. E., AND PELLOW, S.: Intrinsic actions of benzodiazepine receptor antagonist Ro 15–1788. Psychopharmacology (Berl.) **88:** 1–11, 1986.

FISHER, R. S.: Animal models of the epilepsies. Brain Res. Rev. **14:** 245–278, 1989.

FISHER, R. S., CYSYK, B. J., LESSER, R. P., PONTECORVO, M. J., FERKANY, J. T., SCHWERDT, P. R., HART, J., AND GORDON, B.: Dextromethorphan for treatment of complex partial seizures. Neurology **40:** 547–549, 1990.

FLETCHER, E. J., AND LODGE, D.: Glycine reverses antagonism of N-methyl-D-aspartate (NMDA) by 1-hydroxy-3-aminopyrrolidone-2 (HA-966) but not by D-2-amino-5-phosphonovalerate (D-AP5) on rat cortical slices. Eur. J. Pharmacol. **151:** 161–162, 1988.

FLOREN, K. L., GRAVES, N. M., LEPPIK, I. E., REMMEL, R. P., MARGUL, B. L., AND DOOSE, D. R.: Pharmacokinetics of topiramate in patients with partial epilepsy receiving phenytoin or valproate. Epilepsia **30:** 646, 1989.

FOHLMEISTER, J. F., ADELMAN, W. J., JR., AND BRENNAN, J. J.: Excitable channel currents and gating times in the presence of anticonvulsants exthosuximide and valproate. J. Pharmacol. Exp. Ther. **230:** 75–81, 1984.

FOSTER, A. C., AND KEMP, J. A.: HA-966 antagonizes *N*-methyl-D-aspartate receptors through a selective interaction with the glycine modulatory site. J. Neurosci. **9:** 2191–2196, 1989.

FOSTER, A. C., AND WONG, E. H. F.: The novel anticonvulsant MK-801 binds to the activated state of the N-methyl-D-aspartate receptor in rat brain. Br. J. Pharmacol. **91:** 403–409, 1987.

FOUTZ, A. S., CHAMPAGNAT, J., AND DENAVIT-SAUBIÉ, M.: Respiratory effects of the N-methyl-D-aspartate (NMDA) antagonist MK-801, in intact and vagotomized chronic cats. Eur. J. Pharmacol. **154:** 179–184, 1988.

FOWLER, L. J., BECKFORD, J., AND JOHN, R. A.: An analysis of the kinetics of inhibition of rabbit brain gamma-aminobutyrate aminotransferase by sodium n-dipropylacetate and some other simple carboxylic acids. Biochem. Pharmacol. **24:** 1267–1270, 1975.

FRANCE, C. P., WOODS, J. H., AND ORNSTEIN, P.: The competitive N-methyl-D-aspartate (NMDA) antagonist CGS 19755 attenuates the rate-decreasing effects of NMDA in rhesus monkeys without producing ketamine-like discriminative stimulus effects. Eur. J. Pharmacol. **159:** 133–139, 1989.

FREEMAN, A. S., AND BUNNEY, B. S.: The effects of phencyclidine and *N*-allylnormetazocine on midbrain dopamine neuronal activity. Eur. J. Pharmacol. **104:** 287–293, 1984.

FREEMAN, F. G., JARVIS, M. F., AND DUNCAN, P. M.: Phencyclidine raises kindled seizure thresholds. Pharmacol. Biochem. Behav. **16:** 1009–1011, 1982.

FROMM, G. H., SHIBUYA, T., AND TERRENCE, C. F.: Effect of zonisamide (CI-912) on a synaptic system model. Epilepsia **28:** 673–679, 1987.

FROSHER, W., BULAU, P., BURR, W., PENIN, H., RAO, M. L., AND DE BEUKELAAR, F.: Double-blind placebo controlled trial with flunarizine in therapy-resistant epileptic patients. Clin. Neuropharmacol. **3:** 232–240, 1988.

FUJIWARA, Y., SATO, M., AND OTSUKI, S.: Interaction of carbamazepine and other drugs with adenosine (A_1 and A_2) receptors. Psychopharmacology **90:** 332–335, 1986.

GAGE, P. W., LONERGAN, M., AND TORDA, T. A.: Presynaptic and postsynaptic depressant effects of phenytoin sodium at the neuromuscular junction. Br. J. Pharmacol. **69:** 119–121, 1980.

GAGE, P. W., AND MCKINNON, D.: Effects of pentobarbitone on acetylcholine-activated channels in mammalian muscle. Br. J. Pharmacol. **85:** 229–235, 1985.

GAGE, P. W., MCKINNON, D., AND ROBERTSON, B.: The influence of anesthetics on postsynaptic ion channels. *In* Molecular and Cellular Mechanisms of Anesthetics, ed. by S. H. Roth, and K. W. Miller, pp. 139–153, Plenum, New York, 1986.

GALLAGHER, B. B.: Eterobarb. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 103–115, Raven Press, New York, 1989.

GALLAGHER, B. B., BAUMEL, I. P., WOODBURY, S. G., AND DIMICCO, J. A.: Clinical evaluation of eterobarb, a new anticonvulsant drug. Neurology **25:** 399–404, 1975.

GALLAGHER, J. P., INOKUCHI, H., NAKAMURA, J., AND SHINNICK-GALLAGHER, P.: Effects of anticonvulsants on excitability and GABA sensitivity of cat dorsal root ganglion cells. Neuropharmacology **20:** 427–433, 1981.

GALLAGER, D. W., LAKOSKI, J. M., GONSALVES, S. F., AND RAUCH, S. L.: Chronic benzodiazepine treatment decreases postsynaptic GABA sensitivity. Nature (Lond.) **308:** 74–77, 1984.

GALLAGER, D. W., MALLORGA, P., AND TALLMAN, J. F.: Interaction of diphenylhydantoin and benzodiazepines in the CNS. Brain Res. **189:** 209–220, 1980.

GARFIELD, J. M., GARFIELD, F. B., STONE, J. G., HOPKINS, D., AND JOHNS, L. A.: A comparison of psychologic responses to ketamine and thiopental-nitrous oxide-halothane anesthesia. Anesthesiology **36:** 329–338, 1972.

GARRATT, J. C., GENT, J. P., FEELY, M., AND HAIGH, J. R.: Can benzodiazepines be classified by characterising their anticonvulsant tolerance-inducing potential? Eur. J. Pharmacol. **145:** 75–80, 1988.

GASTAUT, H.: Dictionary of Epilepsy. World Health Organization, Geneva, 1973.

GEAN, P.-W., AND SHINNICK-GALLAGHER, P.: Epileptiform activity induced by magnesium-free solutions in slices of rat amygdala: antagonism by *N*-methyl-D-aspartate receptor antagonists. Neuropharmacology **27:** 557–562, 1988.

GEE, K. W.: Phenylquinolines PK 8165 and PK 9084 allosterically modulate [^{35}S]t-butylbicyclophosphorothionate binding to a chloride ionophore in rat brain via a novel Ro5 4864 binding site. J. Pharmacol. Exp. Ther. **240:** 747–753, 1987.

GEE, K. W., BRINTON, R. E., AND MCEWEN, B. S.: Regional distribution of a Ro5 4864 binding site that is functionally coupled to the γ-aminobutyric acid/benzodiazepine receptor complex in rat brain. J. Pharmacol. Exp. Ther. **244:** 379–383, 1988.

GELLER, E. B., ADLER, L. H., WOJNO, C., AND ADLER, M. W.: The anticonvulsant effect of phencyclidine in rats. Psychopharmacology **74:** 97–98, 1981.

GENT, J. P., HAIGH, J. R. M., MEHTA, A., AND FEELY, M.: Studies of the nature of tolerance to the anticonvulsant effects of a 1,5-benzodiazepine, clobazam, in mice. Drugs Exp. Clin. Res. **10:** 867–875, 1984.

GENT, J. P., AND PHILLIPS, N. I.: Sodium di-n-propylacetate (valproate) potentiates responses to GABA and muscimol on single central neurons. Brain Res. **197:** 275–278, 1980.

GIBBS, F. A., EVERETT, G. M., AND RICHARDS, R. K.: Phenurone in epilepsy. Dis. Nerv. Syst. **10:** 47–49, 1949.

GILBERT, M. E.: The NMDA-receptor antagonist, MK-801, suppresses limbic kindling and kindled seizures. Brain Res. **463:** 90–99, 1988.

GLOOR, P.: Electrophysiology of generalized epilepsy. *In* Electrophysiology of Epilepsy, ed. by P. A. Schwartzkroin and H. V. Wheal, pp. 109–136, Academic Press, London, 1984.

GOBBI, G., MAGLIETTA, E. P., STANZANI, P., COSTANZO, M. G., FOLEGANI, P., SANTUCCI, M., AND ROSSI, P. G.: Clinical trial of a new antiepileptic drug: eterobarb. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 79, New Delhi, India, 1989.

GODFRAIND, T.: Classification of calcium antagonists. Am. J. Cardiol. **59:** 11B-23B, 1987.
GODIN, Y., HEINER, L., MARK, J., AND MANDEL, P.: Effects of di-*n*-propylacetate, an anticonvulsive compound, on GABA metabolism. J. Neurochem. **16:** 869–873, 1969.
GODSCHALK, M., DZOLJIC, M. R., AND BONTA, I. L.: Antagonism of gamma-hydroxybutyrate-induced hypersynchronization in the ECoG of the rat by anti-petit mal drugs. Neurosci. Lett. **3:** 145–150, 1976.
GOLDBERG, M. A: Eterobarb. Absorption, distribution, biotransformation and excretion. *In* Antiepileptic Drugs, ed. by D. M. Woodbury, J. K. Penry, and C. E. Pippenger, pp. 803–811, Raven Press, New York, 1982.
GOLDBERG, M. A., AND CRANDALL, P. H.: Human brain binding of phenytoin. Neurology **28:** 881–885, 1978.
GOLDEN, G. T., AND FARIELLO, R. G.: Penicillin spikes in rats. Limitations of a simple model for the study of anticonvulsants. Neuropharmacology **23:** 1001–1007, 1984.
GOLDRING, J. M., AND BLAUSTEIN, M. P.: Effect of pentobarbital on Na and Ca action potentials in an invertebrate neuron. Brain Res. **240:** 273–283, 1982.
GOODMAN, L. S., GREWAL, M. S., BROWN, W. C., AND SWINYARD, E. A.: Comparison of maximal electroshock seizures evoked by pentylenetetrazole (Metrazol) and electroshock in mice, and their modification by anticonvulsants. J. Pharmacol. Exp. Ther. **108:** 168–176, 1953.
GOODMAN, R. R., COOPER, M. J., GAVISH, M., AND SNYDER, S. H.: Guanine nucleotide and cation regulation of the binding of [^{3}H]cyclohexyladenosine and [^{3}H]diethylphenylxanthine to adenosine A_1 receptors in brain membranes. Mol. Pharmacol. **21:** 329–335, 1982.
GORZ, A. M., FERRAZ, E., BIGARELLA, M. M., SEIXAS, R. R., MAZER, S., MARCOURAKIS, T., FERREIRA, Z. S., AND BITTENCOURT, P. R. M.: Efficacy and tolerability of vigabatrin. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 150, New Delhi, India, 1989.
GOULD, R. J., MURPHY, K. M. M., AND SNYDER, S. H.: Tissue heterogeneity of calcium channel antagonist binding sites labeled by [^{3}H]nitrendipine. Mol. Pharmacol. **25:** 235–241, 1984.
GRAHAM, D. G.: Neuropathology of vigabatrin. Br. J. Clin. Pharmacol. **27** (suppl.): 43–45, 1989.
GRAM, L., LARSSON, O. M., JOHNSEN, A. H., AND SCHOUSBOE, A.: Effects of valproate, vigabatrin and aminooxyacetic acid on release of endogenous and exogenous GABA from cultured neurons. Epilepsy Res. **2:** 87–95, 1988.
GRAM, L., LYON, B. B., AND DAM, M.: Gamma-vinyl-GABA: a single blind trial in patients with epilepsy. Acta Neurol. Scand. **68:** 34–39, 1983.
GRAM, L., AND PHILBERT, A.: Oxcarbazepine. *In* New Anticonvulsant Drugs, ed. by B. S. Meldrum and R. J. Porter, pp. 229–235, John Libbey, London, 1986.
GRAVES, N. M., AND KRIEL, R. L.: Rectal administration of antiepileptic drugs in children. Pediatr. Neurol. **3:** 321–326, 1984.
GRAZIANI, G., TIRONE, F., BARBADORO, E., AND TESTA, R.: Denzimol, a new anticonvulsant drug. Arzneim. Forsch. Drug Res. **33:** 1155–1160, 1983.
GREENBERG, D. A., COOPER, E. C., AND CARPENTER, C. L.: Phenytoin interacts with calcium channels in brain membranes. Ann. Neurol. **16:** 616–617, 1984.
GRIFFITH, W. H., AND TAYLOR, L.: Phenytoin reduces excitatory synaptic transmission and post-tetanic potentiation in the *in vitro* hippocampus. J. Pharmacol. Exp. Ther. **246:** 851–858, 1988a.
GRIFFITH, W. H., AND TAYLOR, L.: Sodium valproate decreases synaptic potentiation and epileptiform activity in hippocampus. Brain Res. **474:** 155–164, 1988b.
GRIMA, M., SCHWARTZ, J., SPACH, M. O., AND VELLY, J.: Anti-anginal arylalkylamines and sodium channels: [^{3}H]-batrachotoxinin-A 20-α-benzoate and [^{3}H]-tetracaine binding. Br. J. Pharmacol. **89:** 641–646, 1986.
GROSS, R. A., AND MACDONALD, R. L.: Barbiturates and nifedipine have different and selective effects on calcium currents of mouse DRG neurons in culture: a possible basis for differing clinical actions. Neurology **38:** 443–451, 1988.
GUBERMAN, A., GLOOR, P., AND SHERWIN, A. L.: Response of generalized penicillin epilepsy in the cat to ethosuximide and diphenylhydantoin. Neurology **25:** 785–764, 1975.
GUNDERSEN, C. B., UMBACH, J. A., AND SWARTZ, B. E.: Barbiturates depress currents through human brain calcium channels studied in *Xenopus* oocytes. J. Pharmacol. Exp. Ther. **247:** 824–829, 1988.
HAAN, J.: Gamma-vinyl-gaba (vigabatrin) in pharmaco-resistent epilepsies. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 160, New Delhi, India, 1989.
HAEFELY, W.: The biological basis of benzodiazepine actions. J. Psychoact. Drugs **15:** 19–39, 1983.
HAEFELY, W.: Benzodiazepines: mechanisms of action. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 721–734, Raven Press, New York, 1989.
HAEFELY, W., KULCSAR, A., MÖHLER, H., PIERI, L., POLC, P., AND SCHAFFNER, R.: Possible involvement of GABA in the central actions of benzodiazepines. Adv. Biochem. Psychopharmacol. **14:** 131–151, 1975.
HAIGH, J. R., AND FEELY, M.: RO 16–6028, a benzodiazepine receptor partial agonist, does not exhibit anticonvulsant tolerance in mice. Eur. J. Pharmacol. **147:** 283–285, 1988.
HAIGH, J. R., PULLAR, T., GENT, J. P., DAILLEY, C., AND FEELY, M.: N-Desmethylclobazam: a possible alternative to clobazam in the treatment of refractory epilepsy? Br. J. Clin. Pharmacol. **23:** 213–218, 1987.
HALLIWELL, R. F., PETERS, J. A., AND LAMBERT, J. J.: The mechanism of action and pharmacological specificity of the anticonvulsant NMDA antagonist MK-801: a voltage clamp study on neuronal cells in culture. Br. J. Pharmacol. **96:** 480–494, 1989.
HARRIS, K. M., AND MILLER, R. J.: CNQX (6-cyano-7-nitroquinoxaline-2,3-dione) antagonizes NMDA-evoked [^{3}H]GABA release from cultured cortical neurons via an inhibitory action at the strychnine-insensitive glycine site. Brain Res. **489:** 185–189, 1989.
HARRISON, N. L., AND SIMMONDS, M. A.: Sodium valproate enhances responses to GABA receptor activation only at high concentrations. Brain Res. **250:** 201–204, 1982.
HARRISON, N. L., AND SIMMONDS, M. A.: Quantitative studies of some antagonists of N-methyl D-aspartate in slices of rat cerebral cortex. Br. J. Pharmacol. **84:** 381–391, 1985.
HARVEY, P. K. P., BRADFORD, H. F., AND DAVIDSON, A. N.: The inhibitory effect of sodium n-dipropylacetate on the degradative enzymes of the GABA shunt. FEBS Lett. **52:** 251–254, 1975.
HASBANI, M., PINCUS, J. H., AND LEE, S. H.: Diphenylhydantoin and calcium movement in lobster nerves. Arch. Neurol. **31:** 250–254, 1974.
HAYASHI, T.: Effects of sodium glutamate on the nervous system. Keio J. Med. **3:** 183–192, 1954.
HAYCOCK, J. W., LEVY, W. B., AND COTMAN, C. W.: Phenobarbital depression of stimulus-secretion coupling in brain-selective inhibition of depolarization-induced calcium-dependent release. Biochem. Pharmacol. **26:** 159–161, 1977.
HAYES, B. A., AND BALSTER, R. L.: Anticonvulsant properties of phencyclidine-like drugs in mice. Eur. J. Pharmacol. **117:** 121–125, 1985.
HELLER, A. H., DICHTER, M. A., AND SIDMAN, R. L.: Anticonvulsant sensitivity of absence seizures in the *tottering* mutant mouse. Epilepsia **25:** 25–34, 1983.
HELLER, A. J., RING, H. A., AND REYNOLDS, E. H.: Factors relating to dramatic response to clobazam therapy in refractory epilepsy. Epilepsy Res. **2:** 276–280, 1988.
HENINGER, C., AND GALLAGER, D. W.: Altered γ-aminobutyric acid/benzodiazepine interaction after chronic diazepam exposure. Neuropharmacology **27:** 1073–1076, 1988.
HENRY, T. R., LEPPIK, I. E., GUMNIT, R. J., AND JACOBS, M.: Progressive myoclonus epilepsy treated with zonisamide. Neurology **38:** 928–931, 1988.
HENTSCHEL, B.: Clobazam in the Treatment of Epilepsy, Hoechst Aktiengesellschaft, Frankfurt, Germany, 1987.
HERBERG, L. J., AND ROSE, I. C.: The effect of MK-801 and other antagonists of NMDA-type glutamate receptors on brain-stimulation reward. Psychopharmacology **99:** 87–90, 1989.
HERNÁNDEZ-CRUZ, A., AND PAPE, H.-C.: Identification of two calcium currents in acutely dissociated neurons from the rat lateral geniculate nucleus. J. Neurophysiol. **61:** 1270–1283, 1989.
HERRANZ, J. L., ARTEAGA, R., ARMIJO, J. A., AND FARR, I. N.: Single-blind, dose modification study of vigabatrin in children with refractory partial epilepsy. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 117, New Delhi, India, 1989.
HERRLING, P. L., AEBISCHER, B., FREY, P., OLIVERMAN, H. J., AND WATKINS, J. C.: NMDA-antagonist properties of the enantiomers of 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP) and its unsaturated analogue 3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid (CPP-ene). Soc. Neurosci. Abst. **15:** 327, 1989.
HERRON, C. E., WILLIAMSON, R., AND COLLINGRIDGE, G. L.: A selective *N*-methyl-D-aspartate antagonist depresses epileptiform activity in rat hippocampal slices. Neurosci. Lett. **61:** 255–260, 1985.
HERSHKOWITZ, N., AND AYALA, G. F.: Effects of phenytoin on pyramidal neurons of the rat hippocampus. Brain Res. **208:** 487–492, 1981.
HERSHKOWITZ, N., DRETCHEN, K. L., AND RAINES, A.: Carbamazepine suppression of post-tetanic potentiation at the neuromuscular junction. J. Pharmacol. Exp. Ther. **207:** 810–816, 1978.
HERSHKOWITZ, N., AND ROGAWSKI, M. A.: Cycloleucine blocks NMDA responses in cultured hippocampal neurones under voltage clamp: antagonism at the strychnine-insensitive glycine receptor. Br. J. Pharmacol. **98:** 1005–1013, 1989.
HERSHKOWITZ, N., AND ROGAWSKI, M. A.: Tetrahydroaminoacridine is an open channel blocker of N-methyl-D-aspartate gated cation channels. Neurology **17** (part 2): 17, 1990.
HEYER, E. J., AND MACDONALD, R. L.: Barbiturate reduction of calcium-dependent action potentials: correlation with anesthetic action. Brain Res. **236:** 157–171, 1982.
HINDMARCH, I.: Some aspects of the effects of clobazam on human psychomotor performance. Br. J. Clin. Pharmacol. **7** (suppl. 1): 77S-82S, 1979.
HINDMARCH, I., AND STONIER P. D. (EDS.): Clobazam. International Congress and Symposium Series (43), Royal Society of Medicine, London, 1981.
HOFFMEISTER, F., BENZ, U., HEISE, A., KRAUSE, H. P., AND NEUSER, V.: Behavioral effects of nimodipine in animals. Arzneim. Forsch. Drug Res. **32:** 347–360, 1982.
HOMAN, R. W., AND UNWIN, D. H.: Benzodiazepines. Lorazepam. *In* Antie-

pileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 841–854, Raven Press, New York, 1989.
HOMAN, R. W., AND WALKER, J. E.: Clinical studies of lorazepam in status epileppicus. Adv. Neurol. **34:** 493–498, 1983.
HOMMES, O. R., AND OBBENS, E. A. M. T.: The epileptogenic action of Nafolate in the rat. J. Neurol. Sci. **16:** 271–281, 1972.
HÖNACK, D., AND LÖSCHER, W.: Amygdala-kindling as a model for chronic efficacy studies on antiepileptic drugs: experiments with carbamazepine. Neuropharmacology **28:** 599–610, 1989.
HONDA, H., AND ALLEN, M. B.: The effect of an iminostilbene derivative (G32 883) on peripheral nerves. J. Med. Assoc. Ga. **62:** 38–42, 1973.
HONEY, C. R., MILJKOVIC, Z., AND MACDONALD, J. F.: Ketamine and phencyclidine cause a voltage-dependent block of responses to L-aspartic acid. Neurosci. Lett. **61:** 135–139, 1985.
HOOD, W. F., SUN, E. T., COMPTON, R. P., AND MONAHAN, J. B.: 1-Aminocyclobutane-1-carboxylate (ACBC): a specific antagonist of the N-methyl-D-aspartate receptor coupled glycine receptor. Eur. J. Pharmacol. **161:** 281–282, 1989.
HORNE, A. L., HARRISON, N. L., TURNER, J. P., AND SIMMONDS, M. A.: Spontaneous paroxysmal activity induced by zero magnesium and bicuculline: suppression by NMDA antagonists and GABA mimetics. Eur. J. Pharmacol. **122:** 231–238, 1986.
HOUTKOOPER, M. A., LAMMERTSMA, A., MEYER, J. W., GOEDHART, D. M., MEINARDI, H., VAN OORSCHOT, C. A., BLOM, G. F., HÖPPENER, R. J., AND HULSMAN, J. A.: Oxcarbazepine (GP 47.680): a possible alternative to carbamazepine? Epilepsia **28:** 693–698, 1987.
HOUTKOOPER, M. A., VAN OORSCHOT, C. A. E. H., RENTMEESTER, T. W., HOPPENER, P. J. E. A., AND ONKELINX, C.: Double-blind study of milacemide in hospitalized therapy-resistant patients with epilepsy. Epilepsia **27:** 255–262, 1986.
HUETTNER, J. E.: Indole-2-carbyxylic acid: a competitive antagonist of potentiation by glycine at the NMDA receptor. Science (Wash. DC) **243:** 1611–1613, 1989.
HUETTNER, J. E., AND BEAN, B. P.: Block of N-methyl-D-aspartate-activated current by the anticonvulsant MK-801: selective binding to open channels. Proc. Natl. Acad. Sci. USA **85:** 1307–1311, 1988.
HUGUENARD, J. R., AND WILSON, W. A.: Barbiturate-induced alterations in the kinetic parameters of slow outward current in *Aplysia* giant neurons. J. Pharmacol. Exp. Ther. **234:** 821–829, 1985.
HUIDOBRO-TORO, J. P., BLECK, V., ALLAN, A. M., AND HARRIS, R. A.: Neurochemical actions of anesthetic drugs on the γ-aminobutyric acid receptor-chloride channel complex. J. Pharmacol. Exp. Ther. **242:** 963–969, 1987.
HUXTABLE, R. J.: Taurine in the central nervous system and the mammalian actions of taurine. Prog. Neurobiol. **32:** 471–533, 1989.
HWA, G. G. C., AND AVOLI, M.: NMDA receptor antagonists CPP and MK-801 partially supress the epileptiform discharges induced by the convulsant drug bicuculline in the rat neocortex. Neurosci. Lett. **98:** 189–193, 1989.
IADAROLA, M. J., AND GALE, K.: Cellular compartments of GABA in brain and their relationship to anticonvulsant activity. Mol. Cell Biochem. **39:** 305–330, 1981.
ICHIMARU, Y., GOMITA, Y., AND MORIYAMA, M.: Effects of clobazam on amygdaloid and hippocampal kindled seizures in rats. J. Pharmacobio-Dyn. **10:** 189–194, 1987.
IINUMA, K., HANDA, I., FUEKI, N., YAMAMOTO, K., KOJIMA, A., AND HAGINOYA, K.: Effects of zonisamide (AD-801) on refractory epilepsy in children: special reference to temporal lobe abnormalities. Curr. Ther. Res. Clin. Exp. **43:** 281–290, 1988.
IIVANAINEN, M., WALTIMO, O., TOKOLA, O., PARANTAINEN, J., ALLONEN, H., AND NEUVONEN, P. J.: A controlled clinical trial of a new anti-epileptic drug, taltrimide. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 29, New Delhi, India, 1989.
IKEMOTO, Y., MITSUIYE, T., AND ISHIZUKA, S.: Reduction of the voltage-dependent calcium current in *Aplysia* neurons by pentobarbital. Cell. Mol. Neurobiol. **6:** 293–305, 1986.
ITO, T., HORI, M., AND KADOKAWA, T.: Effects of zonisamide (AD-810) on tungstic acid gel-induced thalamic generalized seizures and conjugated estrogen-induced cortical spike-wave discharges in cats. Epilepsia **27:** 367–374, 1986.
ITO, T., HORI, M., MASUDA, Y., YOSHIDA, K., AND SHIMIZU, M.: 3-Sulfamoylmethyl-1,2-benzisoxazole, a new type of anticonvulsant drug. Electroencephalographic profile. Arzneim. Forsch. Drug Res. **30:** 603–609, 1980.
JAHNSEN, H., AND LLINÁS, R.: Electrophysiological properties of guinea-pig thalamic neurones: an *in vitro* study. J. Physiol. (Lond.) **349:** 205–226, 1984a.
JAHNSEN, H., AND LLINÁS, R.: Ionic basis for the electroresponsiveness and oscillatory properties of guinea-pig thalamic neurons *in vitro*. J. Physiol. (Lond.) **349:** 227–247, 1984b.
JANSSENS DE VAREBEKE, P., CAVALIER, R., DAVID-REMACLE, M., AND YOUDIM, M. B. H.: Formation of the neurotransmitter glycine from the anticonvulsant milacemide is mediated by brain monoamine oxidase B. J. Neurochem. **50:** 1011–1016, 1988.
JANSSENS DE VAREBEKE, P., NIEBES, P., PAUWELS, G., ROBA, J., AND KORF, J.: Effect of milacemide, a glycinamide derivative, on the rat brain γ-aminobutyric acid system. Biochem. Pharmacol. **32:** 2751–2755, 1983.
JANSSENS DE VAREBEKE, P., PAUWELS, G., BUYSE, C., DAVID-REMACLE, M., DE MEY, J., ROBA, J., AND YOUDIM, M. B. H.: The novel neuropsychotropic agent milacemide is a specific enzyme-activated inhibitor of brain monoamine oxidase B. J. Neurochem. **53:** 1109–1116, 1989.
JAVITT, D. C., AND ZUKIN, S. R.: Biexponential kinetics of [^{3}H]MK-801 binding: evidence for access to closed and open *N*-methyl-D-aspartate receptor channels. Mol. Pharmacol. **35:** 387–393, 1989.
JAWAD, S., RICHENS, A., GOODWIN, G., AND YUEN W. C.: Controlled Trial of lamotrigine (Lamictal) for refractory partial seizures. Epilepsia **30:** 356–363, 1989.
JOBE, P. C., AND LAIRD, H. E., II: Neurotransmitters and Epilepsy, Humana Press, Clifton, NJ, 1987.
JOHANNESSEN, A. C., AND NIELSON, O. A.: Hyponatremia induced by oxcarbazepine. Epilepsy Res. **1:** 155–156, 1987.
JOHNSON, D. N., TAYLOR, C. R., JR., TOMCZUK, B. E., AND SWINYARD, E. A.: AHR-11245: a potential drug for treatment of absence seizures. Epilepsia **29:** 694, 1988.
JOHNSON, J. W., AND ASCHER, P.: Glycine potentiates the NMDA response in cultured mouse brain neurons. Nature (Lond.) **325:** 529–531, 1987.
JOHNSON, K. M., AND JONES, S. M.: Neuropharmacology of phencyclidine: basic mechanisms and therapeutic potential. Annu. Rev. Pharmacol. Toxicol. **30:** 707–750, 1990.
JONES, K. J., LACRO, R. V., JOHNSON, K. A., AND ADAMS, J.: Pattern of malformations in the children of women treated with carbamazepine during pregnancy. N. Engl. J. Med. **320:** 1661–1666, 1989.
JONES, S. M., SNELL, L. D., AND JOHNSON, K. M.: Phencyclidine selectively inhibits N-methyl-D-aspartate-induced hippocampal [^{3}H]norepinephrine release. J. Pharmacol. Exp. Ther. **240:** 492–497, 1987.
JOY, R. M., ALBERTSON, T. E., AND STARK, L. G.: An analysis of the actions of progabide, a specific GABA receptor agonist, on kindling and kindled seizures. Exp. Neurol. **83:** 144–154, 1984.
JULIEN, R. M., AND HOLLISTER, R. P.: Carbamazepine: mechanism of action. Adv. Neurol. 11: 263–276, 1975.
JUNG, M. T., LIPPERT, B., METCALF, B. W., BOHLEN, P., AND SCHECHTER, P. J.: γ-Vinyl GABA (4-amino-hex-5-enoic acid), a selective irreversible inhibitor of GABA-T: effects on brain GABA metabolism in mice. J. Neurochem. **29:** 797–802, 1977.
KALANT, H., AND GROSE, W.: Effects of ethanol and pentobarbital on release of acetylcholine from cerebral cortex slices. J. Pharmacol. Exp. Ther. **158:** 386–393, 1967.
KALICHMAN, M. W., BURNHAM, W. M., AND LIVINGSTON, K. E.: Pharmacological investigation of gamma-aminobutyric acid (GABA) and fully-developed generalized seizures in the amygdala-kindled rat. Neuropharmacology **21:** 127–131, 1982.
KÄLVIAINEN, R., PARTANEN, J., SAKSA, M., SIVENIUS, J., AND RIEKKINEN, P. J.: VEPS and SEPS in gamma-vinyl GABA monotherapy. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 90, New Delhi, India, 1989a.
KÄLVIAINEN, R., SIVENIUS, J., YLINEN, A., AND RIEKKINEN, P. J.: A double-blind study of gabapentin in treatment of partial seizures. Epilepsia, **30:** 661, 1989b.
KAMEI, C., OKA, M., MASUDA, Y., YOSHIDA, K., AND SHIMIZU, M.: Effects of 3-sulfamoylmethyl-1,2-benzisoxazole (AD-810) and some antiepileptics on the kindled seizures in the neocortex, hippocampus and amygdala in rats. Arch. Int. Pharmacodyn. Ther. **249:** 164–176, 1981.
KANEKO, S., HIRANO, T., KONDO, T., OTANI, K., FUKUSHIMA, Y., HISHIDA, R., AND MATSUNAGA, M.: Antiepileptic drug phenytoin potentiates GABA in the rat cuneate nucleus. Jpn. J. Psychiatry Neurol. **42:** 643–645, 1988.
KAPETANOVIC, I. M., AND KUPFERBERG, H. J.: Nafimidone, an imidazole anticonvulsant, and its metabolite as potent inhibitors of microsomal metabolism of phenytoin and carbamazepine. Drug Metab. Dispos. **12:** 560–564, 1984.
KAPETANOVIC, I. M., AND KUPFERBERG, H. J.: Inhibition of microsomal phenytoin metabolism by nafimidone and related imidazoles. Potency and structural considerations. Drug Metab. Dispos. **13:** 430–437, 1985.
KEANE, P. E., SIMIAND, J., MENDES, E., SANTUCCI, V., AND MORRE, M.: The effects of analogues of valproic acid on seizures induced by pentylenetetrazol and GABA content in brain of mice. Neuropharmacology **22:** 875–879, 1983.
KEMP, J. A., FOSTER, A. C., LEESON, P. D., PRIESTLY, T., TRIDGETT, R., IVERSEN, L. L., AND WOODRUFF, G. N.: 7-Chlorokynurenic acid is a selective antagonist at the glycine modulatory site of the N-methyl-D-aspartate receptor complex. Proc. Natl. Acad. Sci. USA **85:** 6547–6550, 1988.
KENDALL, D. A., FOX, D. A., AND ENNA, S. J.: Effect of γ-vinyl GABA on bicuculline-induced seizures. Neuropharmacology **20:** 351–355, 1981.
KERR, B. M., AND LEVY, R. H.: Carbamazepine. Carbamazepine epoxide. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 505–520, Raven Press, New York, 1989.
KERWIN, R. W., AND TABERNER, P. V.: The mechanism of action of sodium valproate. Gen. Pharmacol. **12:** 71–75, 1981.
KESSLER, M., BAUDRY, M., AND LYNCH, G.: Quinoxaline derivatives are high-affinity antagonists of the NMDA receptor-associated glycines sites. Brain Res. **489:** 377–382, 1989.

KILLAM, E. K.: Measurement of anticonvulsant activity in the *Papio papio* model of epilepsy. Fed. Proc. **35:** 2264–2269, 1976.

KING, R. G., NIELSEN, M., STAUBER, G. B., OLSEN, R. W.: Convulsant/barbiturate activities on the soluble GABA/benzodiazepine receptor complex. Eur. J. Biochem. **169:** 555–562, 1987.

KLECKNER, N. W., AND DINGLEDINE, R.: Requirement for glycine in activation of NMDA-receptor expressed in *Xenopus* oocytes. Science (Wash. DC) **241:** 835–837, 1988.

KLECKNER, N. W., AND DINGLEDINE, R.: Selectivity of quinoxalines and kynurenines as antagonists of the glycine site on *N*-methyl-D-aspartate receptors. Mol. Pharmacol. **36:** 430–436, 1989.

KLEIN, M., PATURZO, J. J., AND MUSACCHIO, J. M.: The effects of prototypic σ ligands on the binding of [^{3}H]dextromethorphan to guinea pig brain. Neurosci. Lett. **97:** 175–180, 1989.

KLOOG, Y., HARING, R., AND SOKOLOVSKY, M.: Kinetic characterization of the phencyclidine-*N*-methyl-D-aspartate receptor interaction: evidence for a steric blockade of the channel. Biochemistry **27:** 843–848, 1988a.

KLOOG, Y., NADLER, V., AND SOKOLOVSKY, M.: Mode of binding of [^{3}H] dibenzocycloalkenimine (MK-801) to the *N*-methyl-D-aspartate (NMDA) receptor and its therapeutic implication. FEBS Lett. **230:** 167–170, 1988b.

KOE, B. K.: Enhancement of benzodiazepine binding by progabide (SL 76002) and SL 75102. Drug Dev. Res. **3:** 421–432, 1983.

KOEK, W., AND COLPAERT, F. C.: Selective blockade of N-methyl-D-aspartate (NMDA)-induced convulsions by NMDA antagonists and putative glycine antagonists: relationship with phencyclidine-like behavioral effects. J. Pharmacol. Exp. Ther. **252:** 349–357, 1990.

KOEK, W., WOODS, J. H., AND WINGER, G. D.: MK-801, a proposed noncompetitive antagonist of excitatory amino acid neurotransmission, produces phencyclidine-like behavioral effects in pigeons, rats and rhesus monkeys. J. Pharmacol. Exp. Ther. **245:** 969–974, 1988.

KOIVISTO, K., SIVENIUS, J., KERÄNEN, T., PARTANEN, J., RIEKKINEN, P., GOTHÓNI, G., TOKOLA, O., AND NEUVONEN, P. J.: Clinical trial with an experimental taurine derivative, taltrimide, in epileptic patients. Epilepsia **27:** 87–90, 1986.

KONTRO, P., AND OJA, S. S.: Effects of the anticonvulsant taurine derivative, taltrimide, on membrane transport and binding of GABA and taurine in the mouse cerebellum. Neuropharmacology **26:** 19–23, 1987a.

KONTRO, P., AND OJA, S. S.: Co-operativity in sodium-independent taurine binding to brain membranes in the mouse. Neuroscience **23:** 567–570, 1987b.

KRISHTAL, O. A., OSIPCHUK, Y. V., AND VRUBLEVSKY, S. V.: Properties of glycine-activated conductances in rat brain neurones. Neurosci. Lett. **84:** 271–276, 1988.

KRUPP, P., BIANCHI, C. P., AND SUAREZ-KURTZ, G.: On the local anesthetic effect of barbiturates. J. Pharm. Pharmacol. **21:** 763–768, 1969.

KUKO, T., AND WADA, J. A.: Antiepileptic effect of dextromethorphan on amygdaloid-kindled seizure in cats. Epilepsia **30:** 669, 1989.

KULKARNI, S. K., AND TICKU, M. K.: Interaction between GABAergic anticonvulsants and the NMDA receptor antagonist MK 801 against MES- and picrotoxin-induced convulsions in rats. Life Sci. **44:** 1317–1323, 1989.

KUPFERBERG, H. J.: Antiepileptic drug development program: a cooperative effort of government and industry. Epilepsia **30** (suppl. 1): S51-S56, 1989a.

KUPFERBERG, H. J.: Other hydantoins. Mephenytoin and ethotoin. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 257–265, Raven Press, New York, 1989b.

KUPFERBERG, H. J., LUST, W. D. AND PENRY, J. K.: Anticonvulsant activity of dipropyl-acetic acid (DPA) in relation to GABA and cGMP brain levels in mice. Fed. Proc **34:** 283–287, 1975.

KUPFERBERG, H. J., YONEKAWA, W. D., NEWMARK, M. E., PORTER, R. J., AND PENRY, J. K.: Measurement of mephenytoin and its demethylated metabolite, Nirvanol, by mass fragmentography in epileptic patients. *In* Abstracts of the 7th International Congress of Pharmacology, Paris, p. 181, 1978.

KURUMAJI, A., NEHLS, D. G., PARK, C. K., AND MCCULLOCH, J.: Effects of NMDA antagonists, MK-801 and CPP, upon local cerebral glucose use. Brain Res. **496:** 268–284, 1989.

KUTT, H.: Carbamazepine. Chemistry and methods of determination. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 457–471, Raven Press, New York, 1989.

LAPIN, I. P.: Antagonism of L-glycine to seizures induced by L-kynurenine, quinolinic acid and strychnine in mice. Eur. J. Pharmacol. **71:** 495–498, 1981.

LARSSON, O. M., GRAM, L., SCHOUSBOE, I., AND SCHOUSBOE, A.: Differential effect of gamma-vinyl GABA and valproate on GABA-transaminase from cultured neurons and astrocytes. Neuropharmacology **25:** 617–625, 1986.

LEACH, M. J., MARDEN, C. M., AND MILLER, A. A.: Pharmacological studies on lamotrigine, a novel potential antiepileptic drug: II. Neurochemical studies on the mechanism of action. Epilepsia **27:** 490–497, 1986.

LEAL, K. W., RAPPORT, R. L., WILENSKY, A. J., AND FRIEL, P. N.: Single dose pharmacokinetics and anticonvulsant efficacy of primidone in mice. Ann. Neurol. **5:** 470–474, 1979.

LEANDER, J. D.: Evaluation of dextromethorphan and carbetapentane as anticonvulsants and *N*-methyl-D-aspartic acid antagonists in mice. Epilepsy Res. **4:** 28–33, 1989.

LEANDER, J. D., LAWSON, R. R., ORNSTEIN, P. L., AND ZIMMERMAN, D. M.: *N*-methyl-D-aspartic acid-induced lethality in mice: selective antagonism by phencyclidine-like drugs. Brain Res. **448:** 115–120, 1988a.

LEANDER, J. D., LAWSON, R. R., AND ROBERTSON, D. W.: Anticonvulsant effects of a novel aminobenzamide (LY201116) in mice. Neuropharmacology **27:** 623–628, 1988b.

LEANDER, J. D., RATHBUN, R. C., AND ZIMMERMAN, D. M.: Anticonvulsant effects of phencyclidine-like drugs: relation to *N*-methyl-D-aspartic acid antagonism. Brain Res. **454:** 368–372, 1988c.

LECCESE, A. P., MARQUIS, K. L., MATTIA, A., AND MORETON, J. E.: The convulsant and anticonvulsant effects of phencyclidine (PCP) and PCP analogues in the rat. Behav. Brain Res. **19:** 163–169, 1986.

LEHMANN, J., HUTCHISON, A. J., MCPHERSON, S. E., MONDADORI, C., SCHMUTZ, M., SINTON, C. M., TSAI, C., MURPHY, D. E., STEEL, D. J., WILLIAMS, M., CHENEY, D. L., AND WOOD, P. L.: CGS 19755, a selective and competitive N-methyl-D-aspartate-type excitatory amino acid receptor antagonist. J. Pharmacol. Exp. Ther. **246:** 65–75, 1988.

LEHMANN, J., SCHNEIDER, J., MCPHERSON, S., MURPHY, D. E., BERNARD, P., TSAI, C., BENNETT, D. A., PASTOR, G., STEEL, D. J., BOEHM, C., CHENY, D. L., LIEBMAN, J. M., WILLIAMS, M., AND WOOD, P. L.: CPP, a selective N-methyl-D-aspartate (NMDA)-type receptor antagonist: characterization *in vitro* and *in vivo*. J. Pharmacol. Exp. Ther. **240:** 737–746, 1987.

LENNOX, W. G.: The petit mal epilepsies: their treatment with Tridione. J. Am. Med. Assoc. **129:** 1069–1074, 1945.

LEPPIK, I. E., DREIFUSS, F. E., PLEDGER, G. W., GRAVES, N. M., SANTILLI, N., DRURY, I., TSAY, J. Y., JACOBS, M. P., BERTRAM, E., CEREGHINO, J. J., COOPER, G., SHERIDAN, P., AND ASHWORTH, M.: Felbamate in partial seizures: results of phase II clinical trial. Epilepsia **30:** 661, 1989.

LEPPIK, I. E., DREIFUSS, F. E., PORTER, R. J., BOWMAN, T., SANTILLI, N., JACOBS, M. K, CROSBY, C., CLOYD, J., STACKMAN, J., GRAVES, N., SUTULA, T., WELTY, T., VICKERY, J., BRUNDAGE, R., GATES, J., AND GUMNIT, R. J.: A controlled study of progabide in partial seizures: methodology and results. Neurology **37:** 963–968, 1987.

LEPPIK, I. E., AND GRAVES, N. M.: Potential antiepileptic drugs. Felbamate. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 983–990, Raven Press, New York, 1989.

LEPPIK, I. E,. MARIENAU, K., GRAVES, N. M., AND RASK, C. A.: MK-801 for epilepsy: a pilot study. Neurology **38:** 405, 1988.

LESLIE, S. W., FRIEDMAN, M. B., WILCOX, R. E., AND ELROD, S. V.: Acute and chronic effects of barbiturates on depolarization-induced calcium influx into rat synaptosomes. Brain Res. **185:** 409–417, 1980.

LEVITAN, E. S., BLAIR, L. A. C., DIONNE, V. E., AND BARNARD, E. A.: Biophysical and pharmacological properties of cloned $GABA_A$ receptor subunits expressed in *Xenopus* oocytes. Neuron **1:** 773–781, 1988a.

LEVITAN, E. S., SCHOFIELD, P. R., BURT, D. R., RHEE, L. M., WISDEN, W., KÖHLER, M., FUJITA, N., RODRIGUEZ, H. F., STEPHENSON, A., DARLISON, M. G., BARNARD, E. A., AND SEEBURG, P. H.: Structural and functional basis for $GABA_A$ receptor heterogeneity. Nature (Lond.) **335:** 76–79, 1988b.

LEVY, R. H., KERR, B. M., FARWELL, J., ANDERSON, G. D., MARTINEZ-LAGE, J. M., AND TOR, J.: Carbamazepine/stiripentol interaction in adult and pediatric patients. Epilepsia **30:** 701, 1989.

LEVY, R. H., AND SHEN, D. D.: Valproate. Absorption, distribution, and excretion. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 583–599, Raven Press, New York, 1989.

LEWIN, E., AND BLECK, B.: Cyclic AMP accumulation in cerebral cortical slices: effect of carbamazepine, phenobarbital, and phenytoin. Epilepsia **18:** 237–242, 1977.

LEYSEN, J. M., AND GOMMEREN, W.: *In vitro* binding profile of drugs used in migraine. *In* The Pharmacological Basis of Migraine Therapy, ed. by W. K. Amery, J. M. Van Nueten, and A. Wauquier, pp. 255–267, Pitman, London, 1984.

LIEGEOIS-CHAVEL, C., MARQUIS, P., GISSELBRECHT, D., PANTIERI, R., BEAUMONT, D., AND CHAUVEL, P.: Effects of long term vigabatrin on somatosentory-evoked potentials in epileptic patients. Epilepsia **30** (suppl. 3): S23–25, 1989.

LIPICKY, R. J., GILBERT, D. L., AND STILLMAN, I. M.: Diphenylhydantoin inhibition of sodium conductance in squid giant axon. Proc. Natl. Acad. Sci. USA **69:** 1758–1760, 1972.

LIPPERT, B., METCALF, B. W., JUNG, M. J., AND CASARA, P.: 4-Amino-hex-5-enoic acid, a selective catalytic inhibitor of 4-aminobutyric-acid aminotransferase in mammalian brain. Eur. J. Biochem. **74:** 441–445, 1977.

LIVINGSTON, J. H., BEAUMONT, D., ARZIMANOGLOU, A., AND AICARDI, J.: Vigabatrin in the treatment of epilepsy in children. Br. J. Clin. Pharmacol. **27** (suppl.): 109–112, 1989.

LLOYD, K. G., ARBILLA, S., BEAUMONT, K., BRILEY, M., DE MONTIS, G., SCATTON, B., LANGER, S. Z., AND BARTHOLINI, G.: γ-Aminobutyric acid (GABA) receptor stimulation. I. Specificity of progabide (SL 76002) and SL 75102 for the GABA receptor. J. Pharmacol. Exp. Ther. **220:** 672–677, 1982.

LOCKARD, J. S., LEVY, R. H., RHODES, P. H., AND MOORE, D. F.: Stiripentol in acute/chronic efficacy tests in monkey model. Epilepsia **26:** 704–712, 1985.

LODGE, D., JONES, M., AND FLETCHER, E.: Non-competitive antagonists of

N-methyl-D-aspartate. *In* The NMDA Receptor, ed. by J. C. Watkins and G. L. Collingridge, pp. 37–51, IRL Press, Oxford, 1989.

LOHSE, M. J., LENSCHOW, V., AND SCHWABE, U.: Two affinity states of R_i adenosine receptors in brain membranes. Analysis of guanine nucleotide and temperature effects on radioligand binding. Mol. Pharmacol. **26:** 1–9, 1984.

LOISEAU, P., BES, A., MENAGER, T., DUCHE, B., AND ARNE-BES, M. C.: Double-blind placebo controlled cross-over study of (lamotrigine*) as add-on therapy in patients with refractory partial seizures. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 144, New Delhi, India, 1989.

LOISEAU, P., BOSSI, L., GUYOT, M., OROFIAMMA, B., AND MORSELLI, P. L.: Double blind cross-over trial of progabide versus placebo in severe epilepsies. Epilepsia **24:** 703–715, 1983.

LOISEAU, P., AND DUCHE, B.: Carbamazepine. Clinical use. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 533–554, Raven Press, New York, 1989a.

LOISEAU, P., AND DUCHE, B.: Potential antiepileptic drugs. Stiripentol. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 955–969, Raven Press, New York, 1989b.

LOISEAU, P., HARDENBERG, J.P., PESTRE, M., GUYOT, M., SCHECHTER, P.J., AND TELL, G. P.: Double-blind placebo controlled study of vigabatrin (gamma-vinyl GABA) in drug-resistant epilepsy. Epilepsia **27:** 115–120, 1986.

LOISEAU, P., STRUBE, E., TOR, J., LEVY R. H., AND DODRILL, C.: Evaluation neuropsychologique et therapeutique du stiripentol dans l'epilepsie. Resultats preliminaries. Rev. Neurol. (Paris) **144:** 165–172, 1988.

LÖSCHER, W.: Anticonvulsant action of GABA agonists and prodrugs on minor and major seizures in epileptic gerbils. Arch. Int. Pharmacodyn. Ther. **276:** 263–270, 1985.

LÖSCHER, W.: Comparative study of the inhibition of GABA aminotransferase by different anticonvulsant drugs. Arch. Int. Pharmacodyn. Ther. **243:** 48–55, 1980.

LÖSCHER, W.: Valproate induced changes in GABA metabolism at the subcellular level. Biochem. Pharmacol. **30:** 1364–1366, 1981a.

LÖSCHER, W.: Relationship between drug-induced changes in seizure thresholds and the GABA content of brain and brain nerve endings. Naunyn-Schmiedebergs Arch. Pharmacol. **317:** 131–134, 1981b.

LÖSCHER, W.: Influence of pharmacological manipulation of inhibitory and exitatory neurotransmitter systems on seizure behavior in the mongolian gerbil. J. Pharmacol. Exp. Ther. **233:** 204–213, 1985.

LÖSCHER, W.: Valproate enhances GABA turnover in the substantia nigra. Brain Res. **501:** 198–203, 1989.

LÖSCHER, W., JÄCKEL, R., AND MLLER, F.: Anticonvulsant and proconvulsant effects of inhibitors of GABA degredation in the amygdala-kindling model. Eur. J. Pharmacol. **163:** 1–14, 1989.

LÖSCHER, W., AND NAU, H.: Valproic acid: metabolite concentrations in plasma and brain, anticonvulsant activity, and effects on GABA metabolism during subacute treatment in mice. Arch. Int. Pharmacodyn. Ther. **257:** 20–31, 1982.

LÖSCHER, W., AND NAU, H.: Pharmacological evaluation of various metabolites and analogues of valproic acid. Anticonvulsant and toxic potencies in mice. Neuropharmacology **24:** 427–435, 1985.

LÖSCHER, W., NAU, H., MARESCAUX, C., AND VERGNES, M.: Comparative evaluation of anticonvulsant and toxic potencies of valproic acid and 2-en-valproic acid in different animal models of epilepsy. Eur. J. Pharmacol. **99:** 211–218, 1984.

LÖSCHER, W., NAU, H., AND SIEMES, H.: Penetration of valproate and its active metabolites into cerebrospinal fluid of children with epilepsy. Epilepsy **29:** 311–316, 1988a.

LÖSCHER, W., NOLTING, B., AND HÖNACK, D.: Evaluation of CPP, a selective NMDA antagonist, in various rodent models of epilepsy. Comparison with other NMDA antagonists, and with diazepam and phenobarbital. Eur. J. Pharmacol. **152:** 9–17, 1988b.

LÖSCHER, W., AND SCHMIDT, D.: Increase in human plasma GABA by sodium valproate. Epilepsia **21:** 611–615, 1980.

LÖSCHER, W., AND SCHMIDT, D.: Plasma GABA levels in neurological patients under treatment with valproic acid. Life Sci. **23:** 2383–2388, 1981.

LÖSCHER, W., AND SCHMIDT, D.: Which animal models should be used in the search for new antiepileptic drugs? A proposal based on experimental and clinical considerations. Epilepsy Res. **2:** 145–181, 1988.

LÖSCHER, W., AND SCHWARK, W. S.: Evaluation of different GABA receptor agonists in the kindled amygdala seizure model in rats. Exp. Neurol. **89:** 454–460, 1985.

LÖSCHER, W., AND SIEMES, H.: Valproic acid increases gamma-aminobutyric acid in CSF of epileptic children. Lancet **2:** 225, 1984.

LOTHMAN, E. W., SALERNO, R. A., PERLIN, J. B., AND KAISER, D. L.: Screening and characterization of antiepileptic drugs with rapidly recurring hippocampal seizures in rats. Epilepsy Res. **2:** 367–379, 1988.

LUBY, E. D., COHEN, B. D., ROSENBAUM, G., GOTTLIEB, J. S., AND KELLEY, R.: Study of a new schizophrenomimetic drug–Sernyl. AMA Arch. Neurol. Psychiatry **81:** 363–369, 1959.

LUNA, D., DULAC, O., PAJOT, N., AND BEAUMONT, D.: Vigabatrin in the treatment of childhood epilepsies: a single-blind placebo-controlled study. Epilepsia **30:** 430–437, 1989.

MACDONALD, J. F., MILJKOVIC, Z., AND PENNEFATHER, P.: Use-dependent block of excitatory amino acid currents in cultured neurons by ketamine. J. Neurophysiol. **58:** 251–266, 1987.

MACDONALD, J. F., AND NOWAK, L. M.: Mechanisms of blockade of excitatory amino acid receptor channels. Trends Neurosci. **11:** 167–172, 1990.

MACDONALD, R., AND BARKER, J. L.: Benzodiazepines specifically modulate GABA-mediated postsynaptic inhibition in cultured mammalian neurones. Nature (Lond.) **271:** 563–564, 1978a.

MACDONALD, R. L., AND BARKER, J. L.: Different actions of anticonvulsant and anesthetic barbiturates revealed by use of cultured mammalian neurons. Science (Wash. DC) **200:** 775–777, 1978b.

MACDONALD, R. L., AND BERGEY, G. K.: Valproic acid augments GABA-mediated postsynaptic inhibition in cultured mammalian neurons. Brain Res. **170:** 558–562, 1979.

MACDONALD, R. L., ROGERS, C. J., AND TWYMAN, R. E.: Barbiturate regulation of kinetic properties of the $GABA_A$ receptor channel of mouse spinal neurones in culture. J. Physiol. (Lond.) **417:** 483–500, 1989.

MAITRE, M., CHESIELSKI, L., LEHMANN, A., KEMPF, E., AND MANDEL, P.: Protective effect of adenosine and nicotinamide against audiogenic seizure. Biochem. Pharmacol. **23:** 2807–2816, 1974.

MAJKOWSKI, J., SOBIESZEK, A., BILINSKA-NIGOT, B., AND KARLINSKI, A.: EEG and clinical studies of the development of alumina cream epileptic focus in split-brain cats. Epilepsia **17:** 257–269, 1976.

MALMINEN, O., AND KONTRO, P.: γ-aminobutyric acid and benzodiazepine receptors in cultured cerebellar granule cells: effects of taurine and its lipophilic derivatives. Neuropharmacology **28:** 907–912, 1989.

MANGANO, T. J., PATEL, J., SALAMA, A. I., AND KEITH, R. A.: Glycine-evoked neurotransmitter release from rat hippocampal brain slices: evidence for the involvement of glutaminergic transmission. J. Pharmacol. Exp. Ther. **252:** 574–580, 1990.

MANOHAR, S., MAXWELL, D., AND WINTERS, W. D.: Development of EEG seizure activity during and after chronic ketamine administration in the rat. Neuropharmacology **11:** 819–826, 1972.

MARANGOS, P. J., MONTGOMERY, P., WEISS, S. R. B., PATEL, J., AND POST, R. M.: Persistent upregulation of brain adenosine receptors in response to chronic carbamazepine tretment. Clin. Neuropharmacol. **10:** 443–448, 1987.

MARANGOS, P. J., PATEL, J., SMITH, K. D., AND POST, R. M.: Adenosine antagonist properties of carbamazepine. Epilepsia **28:** 387–394, 1987.

MARANGOS, P. J., POST, R. M., PATEL, J., ZANDER, K., PARMA, A., AND WEISS, S.: Specific and potent interactions of carbamazepine with brain adenosine receptors. Eur. J. Pharmacol. **93:** 175–182, 1983.

MARANGOS, P. J., WEISS, S. R. B., MONTGOMERY, P., PATEL, J., NARANG, P. K., CAPPABIANCA, A. M., AND POST, R. M.: Chronic carbamazepine treatment increases brain adenosine receptors. Epilepsia **26:** 493–498, 1985.

MARESCAUX, C., MICHELETTI, G., VERGNES, M., DEPAULIS, A., RUMBACH, L., AND WARTER, J. M.: A model of chronic spontaneous petit mal-like seizures in the rat: comparison with pentylenetetrazole-induced seizures. Epilepsia **25:** 326–331, 1984.

MARESCAUX, C., MICHELETTI, G., VERGNES, M., RUMBACH, L., AND WARTER, J.-M.: Diazepam antagonizes gabamimetics in rats with spontaneous petit mal-like epilepsy. Eur. J. Pharmacol. **113:** 19–24, 1985.

MARLEY, R. J., AND GALLAGER, D. W.: Chronic diazepam treatment produces regionally specific changes in GABA-stimulated chloride flux. Eur. J. Pharmacol. **159:** 217–223, 1989.

MARTIN, D., AND LODGE, D.: Ketamine acts as a non-competitive N-methyl-D-aspartate antagonist on frog spinal cord in vitro. Neuropharmacology **24:** 999–1003, 1985.

MARTIN, G. E., AND PAPP, N. L.: Blockade of MK-801 induced ipsiversive turning in 6-OHDA lesioned rats by α_1-adrenoceptor antagonists. Pharmacol. Biochem. Behav. **20:** 893–897, 1984.

MARTINEZ-LAGE, J. M., BOSSI, L., MORALES, G., MARTINEZ-VILA, E., OROFIAMMA, B., AND VITERI, C.: Progabide treatment in severe epilepsy: a double-blind cross-over trial versus placebo. Epilepsia **25:** 586–593, 1984.

MARTINEZ-LAGE, M., LEVY, R. H., GONZALEZ, I., VITERI, C., TOR, J., AND BLEHAUT, H.: Stiripentol in therapy-resistant and severe epileptic patients: a long-term open trial in bitherapy. *In* Advances in Epileptology, vol. 16, ed. by P. Wolf, M. Dam, D. Janz, and F. E. Dreifuss, pp. 541–546, Raven Press, New York, 1987.

MARYANOFF, B. E., NORTEY, S. O., GARDOCKI, J. F., SHANK, R. P., AND DODGSON, S. P.: Anticonvulsant *O*-alkyl sulfamates. 2,3:4,5-Bis-*O*-(1-methylidene)-β-D-fructopyranose sulfamate and related compounds. J. Med. Chem. **30:** 880–887, 1987.

MASUDA, Y., KARASAWA, T., SHIRAISHI, Y., HORI, M., YOSHIDA, K., AND SHIMIZU, M.: 3-Sulfamoylmethyl-1,2-benzisoxazole, a new type of anticonvulsant drug. Pharmacological profile. Arzneim. Forsch. Drug Res. **30:** 477–483, 1980.

MATHERS, D. A.: Pentobarbital promotes bursts of γ-aminobutyric acid-activated single channel currents in cultured mouse central neurons. Neurosci. Lett. **60:** 121–126, 1985.

MATHERS, D. A.: The $GABA_A$ receptor: new insights from single-channel recording. Synapse **1:** 96–101, 1987.

MATHERS, D. A., AND BARKER, J. L.: (−)Pentobarbital opens ion channels

of long duration in cultured mouse spinal neurons. Science (Wash. DC) **209:** 507–509, 1980.

MATHERS, D. A., GREWAL, A., AND WANG, Y. H.: Membrane channels activated by taurine in cultured mouse spinal cord neurons. Neurosci. Lett. **98:** 229–233, 1989.

MATILAINEN, R., PITKÄNEN, A., RUUTIAINEN, T., MERVAALA, E., AND RIEKKINEN, P.: Vigabatrin in epilepsy in mentally retarded patients. Br. J. Clin. Pharmacol. **27:** (suppl. 1): 113S–118S, 1989.

MATSUKI, N., QUANDT, F. N., TEN EICK, R. E., AND YEH, J. Z.: Characterization of the block of sodium channels by phenytoin in mouse neuroblastoma cells. J. Pharmacol. Exp. Ther. **228:** 523–530, 1984.

MATSUO, F., MADSEN, J., GAY, P., BASS, J., WARGIN, W., VALAKAS, A., AND GORODETZKY, C.: One-year safety evaluation of lamotrigine in epileptic outpatients. Epilepsia **30:** 662, 1989.

MATTHEWS, W. D., AND CONNOR, J. D.: Actions of iontophoretic phenytoin and midazepam on hippocampal neurons. J. Pharmacol. Exp. Ther. **201:** 613–621, 1977.

MATTSON, R. H., CRAMER, J. A., COLLINS, J. F., SMITH, D. B., DELGADO-ESCUETA, A. V., BROWNE, T. R., WILLIAMSON, P. D., TREIMAN, D. M., MCNAMARA, J. O., MCCUTCHEN, C. B., HOMAN, R. W., CRILL, W. E., LUBOZYNSKI, M. F., ROSENTHAL, N. P., AND MAYERSDORF, A.: Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generated tonic-clonic seizures. N. Engl. J. Med. **313:** 145–151, 1985.

MCLEAN, M. J: *In vitro* electrophysiological evidence predicting anticonvulsant efficacy of memantine and flunarizine. Pol. J. Pharmacol. Pharm. **39:** 513–525, 1987.

MCLEAN, M. J., AND MACDONALD, R. L.: Multiple actions of phenytoin on mouse spinal cord neurons in cell culture. J. Pharmacol. Exp. Ther. **227:** 779–789, 1983.

MCLEAN, M. J., AND MACDONALD, R. L.: Carbamazepine and 10,11-epoxy carbamazepine produce use- and voltage-dependent limitation of rapidly firing action potentials of mouse central neurons in cell cultures. J. Pharmacol. Exp. Ther. **238:** 727–738, 1986a.

MCLEAN, M. J., AND MACDONALD, R. L.: Sodium valproate, but not ethosuximide, produces use- and voltage-dependent limitation of high frequency repetitive firing of action potentials of mouse central neurons in cell culture. J. Pharmacol. Exp. Ther. **237:** 1001–1011, 1986b.

MCNAMARA, J. O., PEPER, A. M., AND PATRONE, V.: Repeated seizures induce long-term increase in hippocampal benzodiazepine receptors. Proc. Natl. Acad. Sci. USA **77:** 3029–3032, 1980.

MCNAMARA, J. O., RIGSBEE, L. C., BUTLER, L. S., AND SHIN, C.: Intravenous phenytoin is an effective anticonvulsant in the kindling model. Ann. Neurol. **26:** 675–678, 1989.

MCNAMARA, J. O., RUSSELL, R. D., RIGSBEE, L., AND BONHAUS, D. W.: Anticonvulsant and antiepileptogenic actions of MK-801 in the kindling and electroshock models. Neuropharmacology **27:** 563–568, 1988.

MCNEAL, E. T., LEWANDOWSKI, G. A., DALY, J.W., AND CREVELING, C. R.: [^{3}H]Batrachotoxinin A 20α-benzoate binding to voltage-sensitive sodium channels: a rapid and quantitative assay for local anesthetic activity in a variety of drugs. J. Med. Chem. **28:** 381–388, 1985.

MEADOR, K. J., LORING, D. W., HUH, K., GALLAGER, B. B., AND KING, D. W.: Comparative cognitive effects of anticonvulsants. Neurology **40:** 391–394, 1990.

MEHTA, A. K., AND TICKU, M. K.: Interactions of pentobarbital and phenobarbital with GABAergic drugs against chemoconvulsants in rats. Pharmacol. Biochem. Behav. **30:** 995–1000, 1988.

MELDRUM, B. S.: Preclinical test systems for evaluation of novel compounds. *In* New Anticonvulsant Drugs, ed. by B. S. Meldrum and R. J. Porter, pp. 31–48, John Libbey, London, 1986.

MELDRUM, B. S., CHAPMAN, A. G., PATEL, S., AND SWAN, J.: Competitive NMDA antagonists as drugs. *In* The NMDA Receptor, ed. J. C. Watkins and G. L. Collingridge, pp. 207–216, IRL Press, Oxford, 1989.

MELDRUM, B. S., AND CROUCHER, M. J.: Anticonvulsant action of clobazam and desmethyl-clobazam in reflex epilepsy in rodents and baboons. Drug Dev. Res. **1** (suppl.): 33–38, 1982.

MELDRUM, B., AND HORTON, R.: Blockade of epileptic responses in the photosensitive baboon, Papio papio, by two irreversible inhibitors of GABA-transaminase, γ-acetylenic GABA (4-amino-hex-5-ynoic acid) and γ-vinyl GABA (4-amino-5-enoic acid). Psychopharmacology **59:** 47–50, 1978.

MELDRUM, B., AND HORTON, R.: Effects of the bicyclic GABA agonist, THIP, on myoclonic and seizure responses in mice and baboons with reflex epilepsy. Eur. J. Pharmacol. **61:** 231–237, 1980.

MELDRUM, B. S., HORTON, R. W., AND TOSELAND, P. A.: A primate model for testing anticonvulsant drugs. Arch. Neurol. **32:** 289–294, 1975.

MELDRUM, B. S., AND MURUGAIAH, K.: Anticonvulsant action in mice with sound-induced seizures of the optical isomers of gamma-vinyl GABA. Eur. J. Pharmacol. **89:** 149–152, 1983.

MENNINI, T., GOBBI, M., AND TESTA, R.: Effects of denzimol on benzodiazepine receptors in the CNS: relationship between the enhancement of diazepam activity and benzodiazepine binding sites induced by denzimol in the rat. Life Sci. **35:** 1811–1820, 1984.

MERRITT, H. H., AND PUTNAM, T. J.: A new series of anticonvulsant drugs tested by experiments on animals. Arch. Neurol. Psychiatry **39:** 1003–1015, 1938.

MESSING, R. O., CARPENTER, C. L., AND GREENBERG, D. A.: Mechanism of calcium channel inhibition by phenytoin: comparison with classical calcium channel antagonists. J. Pharmacol. Exp. Ther. **235:** 407–411, 1985.

MEYER, F. B., ANDERSON, R. E., AND SUNDT, T. M., JR.: Anticonvulsant effects of dihydropyridine Ca^{2+} antagonists in electrocortical shock seizures. Epilepsia **31:** 68–74, 1990.

MICHELUCCI, R., AND TASSINARI, C. A.: Response to vigabatrin in relation to seizure type. Br. J. Clin. Pharmacol. **27** (suppl. 1): 119S–124S, 1989.

MIKATI, M. A., SCHACHTER, S. C., SCHOMER, D. L., KEALLY, M., OSBORNE-SHAFER, P., SEAMAN, C. A., SHERIDAN, P. H., ASHWORTH, M., KUPFERBERG, H., VALAKAS, A., CLOUTIER, G., AND GORODETZKY, C.: Long-term tolerability, pharmacokinetic and preliminary efficacy study of lamotrigine in patients with resistant partial seizures. Clin. Neuropharmacol. **12:** 312–321, 1989.

MILJKOVIC, Z., AND MACDONALD, J. F.: Voltage-dependent block of excitatory amino acid currents by pentobarbital. Brain Res. **376:** 396–399, 1986.

MILLER, A. A., SAWYER, D. A., ROTH, B., PECK, A. W., LEACH, M. J., WHEATLY, P. L., PARSONS, D. N, AND MORGAN, R. J. I.: Lamotrigine. *In* New Anticonvulsant Drugs, ed. by B. S. Meldrum and R. J. Porter, pp. 125–134, John Libbey, London, 1986a.

MILLER, A. A., WHEATLEY, P., SAWYER, D. A., BAXTER, M. G., AND ROTH, B.: Pharmacological studies on lamotrigine, a novel potential antiepileptic drug: I. Anticonvulsant profile in mice and rats. Epilepsia **27:** 483–489, 1986b.

MILLER, L. G., GREENBLATT, D. J., BARNHILL, J. G., AND SCHADER, R. I.: Chronic benzodiazepine administration. I. Tolerance is associated with benzodiazepine receptor downregulation and decreased γ-aminobutyric $acid_A$ receptor function. J. Pharmacol. Exp. Ther. **246:** 170–176, 1988a.

MILLER, L. G., GREENBLATT, D. J., ROY, R. B., SUMMER, W. R., AND SHADER, R. I.: Chronic benzodiazepine administration. II. Discontinuation syndrome is associated with upregulation of γ-aminobutyric $acid_A$ receptor complex binding and function. J. Pharmacol. Exp. Ther. **246:** 177–182, 1988b.

MILLER, R.J.: Multiple calcium channels and neuronal function. Science (Wash. DC) **235:** 46–52, 1987.

MIMAKI, T., SUZUKI, Y., TAGAWA, T., TANAKA, J., ITOH, N., AND YABUUCHI, H.: [^{3}H]Zonisamide binding in rat brain. Jpn. J. Psychiatry Neurol. **42:** 640–642, 1988.

MITCHELL, W. G., AND CHAVEZ, J. M.: Carbamazepine versus phenobarbital for partial onset seizures in children. Epilepsia **28:** 56–60, 1987.

MIYAHARA, J. T., ESPLIN, D. W., AND ZABLOCKA, B.: Differential effects of depressant drugs on presynaptic inhibition. J. Pharmacol. Exp. Ther. **154:** 119–127, 1966.

MÖHLER, H., BATTERSBY, M. K., AND RICHARDS, J. G.: Benzodiazepine receptor protein identified and visualized in brain tissue by a photoaffinity label. Proc. Natl. Acad. Sci. USA **77:** 1666–1670, 1980.

MÖHLER, H., AND OKADA, T.: Benzodiazepine receptor: demonstration in the central nervous system. Science (Wash. DC) **198:** 849–851, 1977.

MONAGHAN, D. T., BRIDGES, R. J., AND COTMAN, C. W.: The excitatory amino acid receptors: their classes, pharmacology, and distinct properties in the function of the central nervous system. Annu. Rev. Pharmacol. Toxicol. **29:** 365–401, 1989.

MORÓN, M. A., STEVENS, C. W., AND YAKSH, T. L.: Diltiazem enhances and flunarizine inhibits nimodipine's antiseizure effects. Eur. J. Pharmacol. **163:** 299–307, 1989.

MORÓN, M. A., STEVENS, C. W., AND YAKSH, T. L.: The antiseizure activity of dihydropyridine calcium channel antagonists in the conscious rat. J. Pharmacol. Exp. Ther. **252:** 1150–1155, 1990.

MORRELL, F., BRADLEY, W., AND PTASHNE, M.: Effects of drugs on discharge characteristics of chronic epileptogenic lesions. Neurology **9:** 492–498, 1959.

MORRIS, R. G. M., ANDERSON, E., LYNCH, G. S., AND BAUDRY, M.: Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature (Lond.) **319:** 774–776, 1986.

MORRIS, R. G. M., DAVIS, S., AND BUTCHER, S. P.: The role of NMDA receptors in learning and memory. *In* The NMDA Receptor, ed. by J. C. Watkins and G. L. Collingridge, pp. 137–151, IRL Press, Oxford, 1989.

MORSELLI, P. L.: Carbamazepine. Absorption, distribution and excretion. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 473–490, Raven Press, New York, 1989.

MORSELLI, P. L., BARTHOLINI, G., AND LLOYD, K. G.: Progabide. *In* New Anticonvulsant Drugs, ed. by B. S. Meldrum and R. J. Porter, pp. 237–253, John Libbey, London, 1986.

MURPHY, D. E., SCHNEIDER, J., BOEHM, C., LEHMANN, J., AND WILLIAMS, M.: Binding of [^{3}H]3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid to rat brain membranes: a selective, high-affinity ligand for N-methyl-D-aspartate receptors. J. Pharmacol. Exp. Ther. **240:** 778–784, 1987.

MUSACHIO, J. M., KLEIN, M., AND PATURZO, J. J.: Effects of dextromethorphan site ligands and allosteric modifiers on the binding of (+)-[^{3}H]3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine. Mol. Pharmacol. **35:** 1–5, 1989.

MUSACCHIO, J. M., KLEIN, M., AND SANTIAGO, L. J.: High affinity dextro-

methorphan binding sites in guinea pig brain: further characterization and allosteric interactions. J. Pharmacol. Exp. Ther. **247:** 424–431, 1988.

MYSLOBODSKY, M. S., ACKERMANN, R. F., AND ENGEL, J., JR.: Effects of γ-acetylenic GABA and γ-vinyl GABA on metrazol-activated, and kindled seizures. Pharmacol. Biochem. Behav. **11:** 265–271, 1979.

MYSLOBODSKY, M. S., GOLOVCHINSKY, V., AND MINTZ, M.: Ketamine: convulsant or anticonvulsant? Pharmacol. Biochem. Behav **14:** 27–33, 1981.

NAKAGAWA, K., AND HUXTABLE, R. J.: The anticonvulsive actions of two lipophilic taurine derivatives. Neurochem. Int. **7:** 819–824, 1985.

NARDI, D., TAJANA, A., LEONARDI, A., PENNINI, R., PORTIOLI, F., MAGISTRETTI, M. J., AND SUBISSI, A.: Synthesis and anticonvusant activity of N-(benzoylalkyl)imidazoles and N-(φ-phenyl-φ-hydroxyalkyl)imdazoles. J. Med. Chem. **24:** 727–731, 1981.

NARITOKU, D. K., STRYKER, M. T., MECOZZI, L. B., COPLEY, C. A., AND FAINGOLD, C. L.: Gabapentin reduces the severity of audiogenic seizures in the genetically epilepsy-prone rat. Epilepsia **29:** 693, 1988.

NAU, H., AND LÖSCHER, W.: Valproic acid: brain and plasma levels of the drug and its metabolites, anticonvulsant effects and γ-aminobutyric acid (GABA) metabolism in the mouse. J. Pharmacol. Exp. Ther. **220:** 654–659, 1982.

NEAL, M. J., CUNNINGHAM, J. R., SHAH, M. A., AND YAZULLA, S.: Immunocytochemical evidence that vigabatrin in rats causes GABA accumulation in glial cells of the retina. Neurosci. Lett. **98:** 29–32, 1989.

NEHLS, D. G., KURUMAJI, A., PARK, C. K., AND MCCULLOCH, J.: Differential effects of competitive and non-competitive *N*-methyl-D-aspartate antagonists on glucose use in the limbic system. Neurosci. Lett. **91:** 204–210, 1988.

NEWBERRY, N. R., AND NICOLL, R. A.: Comparison of the action of baclofen with gamma-aminobutyric acid on rat hippocampal pyramidal cells *in vitro*. J. Physiol. (Lond.) **360:** 161–185, 1985.

NICOLL, R. A.: The effect of anaesthetics on synaptic excitation and inhibition in the olfactory bulb. J. Physiol. (Lond.) **223:** 803–814, 1972.

NICOLL, R. A.: Pentobarbital: action on frog motoneurons. Brain Res. **96:** 119–123, 1975.

NICOLL, R. A.: Pentobarbital: differential postsynaptic actions on sympathetic ganglion cells. Science (Wash. DC) **199:** 451–452, 1978.

NICOLL, R. A., ECCLES, J. C., OSHIWA, T., AND RUBIA, F.: Prolongation of hippocampal postsynaptic potentials by barbiturates. Nature (Lond.) **258:** 625–627, 1975.

NICOLL, R. A., AND IWAMOTO, E. T.: Action of pentobarbital on sympathetic ganglion cells. J. Neurophysiol. **41:** 977–986, 1978.

NICOLL, R. A., AND WOJTOWICZ, J. M.: The effects of pentobarbital and related compounds on frog motoneurons. Brain Res. **191:** 225–237, 1980.

NIEDERMEYER, E.: The Epilepsies. Diagnosis and Management. Urban & Schwarzenberg, Baltimore, 1990.

NIELSEN, O. A., JOHANNESSEN, A. C., AND BARDRUM, B.: Oxcarbazepine-induced hyponatremia, a cross-sectional study. Epilepsy Res. **2:** 269–271, 1988.

NISHI, K., AND OYAMA, Y.: Accelerating effects of pentobarbitone on the inactivation process of the calcium current in Helix neurones. Br. J. Pharmacol. **79:** 645–654, 1983a.

NISHI, K., AND OYAMA, Y.: Barbiturates increase the rate of voltage-dependent inactivation of the calcium current in snail neurones. Br. J. Pharmacol. **80:** 761–765, 1983b.

NISTRI, A.: Glutamate. *In* Neurotransmitter Actions in the Vertebrate Nervous System, ed. by M. A. Rogawski and J. L. Barker, pp. 101–123, Plenum Press, New York, 1985.

NORTON, L. C., LAXER, K. D., SCHOMER, D., AND OSBORN, P.: Phase II study to evaluate the efficacy and safety of milacemide (CP 1552S) in the treatment of complex partial seizures in adult patients. Epilepsia **27:** 648, 1986.

NOVACK, G. D., STARK, L. G., AND PETERSON, S. L.: Anticonvulsant effects of benzhydryl piperazines on maximal electroshock seizures in rats. J. Pharmacol. Exp. Ther. **208:** 480–484, 1979.

NOWYCKY, M. C., FOX, A. P., AND TSIEN, R. W.: Three types of neural calcium channels with different calcium agonist sensitivity. Nature (Lond.) **316:** 440–443, 1985.

NUTT, D. J., COWEN, P. J., AND LITTLE, H. J.: Unusual interactions of benzodiazepine receptor antagonists. Nature (Lond.) **295:** 426–438, 1982.

OBBENS, E. A. M. T., AND HOMMES, O. R.: The epileptogenic effects of folate derivatives in the rat. J. Neurol. Sci. **20:** 223–229, 1973.

OGITA, K., SUZUKI, T., AND YONEDA, Y.: Strychnine-insensitive binding of [^{3}H]glycine to synaptic membranes in rat brain, treated with Triton X-100. Neuropharmacology **28:** 1263–1270, 1989.

OGUNI, H., HAYAKAWA, T., AND FUKAYAMA, Y: Clinical trial of zonisamide, a new antiepileptic drug, in cases of refractory childhood epilepsy. J. Jpn. Epilepsy Soc. **7:** 43–50, 1989.

OJEMANN, L. M., FRIEL, P. N., AND OJEMANN, G. A.: Gabapentin concentrations in human brain. Epilepsia **29:** 694, 1988.

OJEMANN, L. M., WILENSKY, A. J., TEMKIN, N., CHMELIR, T., AND RICKER, B.: Gabapentin extended follow-up for medically unresponsive partial and secondarily generalized tonic-clonic seizures. Neurology **40** (suppl. 1)**:** 158, 1990.

OKAMOTO, K., AND SAKAI, Y.: Localization of sensitive sites to taurine, γ-aminobutyric acid, glycine and β-alanine in the molecular layer of guinea-pig cerebellar slices. Br. J. Pharmacol. **69:** 407–413, 1980.

OLAFSSON, E., LEPPIK, I. E., NAKHLEH, R., SUNG, J., MAXWELLL, R. E., GATES, J. R., AND FIOL, M. E.: Histopathology of vigabatrin in human brain. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 100, New Delhi, India, 1989.

OLIVERMAN, H. J., AND WATKINS, J. C.: NMDA agonists and competitive antagonists. *In* The NMDA Receptor, ed. by J. C. Watkins and G. L. Collingridge, pp. 19–36, IRL Press, Oxford, 1989.

OLNEY, J. W., LABRUYERE, J., AND PRICE, M. T.: Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science (Wash. DC) **244:** 1360–1362, 1989.

OLNEY, J. W., LABRUYERE, J., AND PRICE, M. T.: Phencyclidine, dizocilpine, and cerebrocortical neurons. Science (Wash. DC) **247:** 221, 1990.

OLPE, H.-R., BAUDRY, M., AND JONES, R. S. G.: Electrophysiological and neurochemical investigations on the action of carbamazepine on the rat hippocampus. Eur. J. Pharmacol. **110:** 71–80, 1985.

OLSEN, R. W.: Barbiturates. Int. Anesthesiol. Clin. **26:** 254–261, 1988.

OLSEN, R. W., AND TOBIN, A. J.: Molecular biology of $GABA_A$ receptors. FASEB J. **4:** 1469–1480, 1990.

ONDRUSEK, M. G., BELKNAP, J. K., AND LESLIE, S. W.: Effects of acute and chronic barbiturate administration on synaptosomal calcium accumulation. Mol. Pharmacol. **15:** 386–395, 1979.

ORMANDY, G. C., JOPE, R. C., AND SNEAD, O. C., 3RD: Anticonvulsant actions of MK-801 on the lithium-pilocarpine model of status epilepticus in rats. Exp. Neurol. **106:** 172–180, 1989.

OSMAN, M. A., CHENG, L. K., JOHNSON, D. N., AND WRIGHT, G. J.: Relationship between antiepileptic activities and plasma and brain concentrations of AHR-12245, a potential antiepileptic. Epilepsia **29:** 694, 1988.

OVERWEG, J., BINNIE, C. D., MEIJER, J. W. A., MEINARDI, H., NEIJTEN, S. T. M., SCHMALTZ, S., AND WAUQUIER, A.: Double-blind placebo-controlled trial of flunarizine as add-on therapy in epilepsy. Epilepsia **25:** 217–222, 1984.

PAINTER, M. J.: Phenobarbital. Clinical use. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 329–340, Raven Press, New York, 1989.

PALFREYMAN, M. G., SCHECHTER, P. J., BUCKETT, W. R., TELL, G. P., AND KOCH-WESER, J.: The pharmacology of GABA-transaminase inhibitors. Biochem. Pharmacol. **30:** 817–824, 1981.

PALJÄRVI, L., VAPALAHTI, M., SIVENIUS, J., AND RIEKKINEN, P.: Neuropathological findings in 5 patients with vigabatrin treatment. Neurology **40** (suppl. 1)**:** 157, 1990.

PALMER, G. C., HARRIS, E. W., NAPIER, J. J., STAGNITTO, M. L., GARSKE, G. E., GRIFFITH, R. C., AND SWINYARD, E. A.: Status of PR 934–423*, a novel anticonvulsant targeted for generalized tonic/clonic seizures (*new designation is FPL 12924AA). *In* Current and Future Trends in Anticonvulsant, Anxiety and Stroke Therapy (Princeton Drug Research Symposium, vol. 1), ed. by M. Williams, Wiley-Liss, New York, pp. 435–442, 1990.

PARLI, C. J., EVENSON, E., POTTS, B. D., BEEDLE, E., LAWSON, R., ROBERTSON, D. W., AND LEANDER, J. D.: Metabolism of the prodrug DEGA (N-(2,6-dimethylphenyl)-4-[[(diethylamino)acetyl]amino]benzamide) to the potent anticonvulsant LY201116 in mice. Effect of *bis*-(*p*-nitrophenyl)phosphate. Drug Metab. Dispos. **16:** 707–711, 1988.

PATEL, S., CHAPMAN, S. G., MILLAN, M. H., AND MELDRUM, B. S.: Epilepsy and excitatory amino acid antagonists. *In* Excitatory Amino Acids in Health and Disease, ed. by D. Lodge, pp. 353–378, John Wiley & Sons, Chichester, 1988.

PATSALOS, P. N., STEPHENSON, T.J., KRISHNA, S., ELYAS, A. A., LASCELLES, P. T., AND WILES, C. M.: Side-effects induced by carbamazepine-10,11-epoxide. Lancet **2:** 496, 1985.

PAUL, S. M., AND SKOLNICK, P.: Rapid changes in brain benzodiazepine receptors after experimental seizures. Science (Wash. DC) **202:** 892–894, 1978.

PAUL, S. M., SYAPIN, P. J., PAUGH, B. A., MONCADA, V., AND SKOLNICK, P.: Correlation between benzodiazepine receptor occupation and anticonvulsant effects of diazepam. Nature (Lond.) **281:** 688–689, 1979.

PEDDER, S. C. J., WILCOX, R., TUCHEK, J. M., CRAWFORD, R. D., AND JOHNSON, D. D.: Benzodiazepine antagonist Ro 15–1788 (flumazenil) attenuates the anticonvulsant activity of diazepam in epileptic fowl. Brain Res. **424:** 139–143, 1987.

PEDDER, S. C. J., WILCOX, R., TUCHEK, J. M., JOHNSON, D. D., AND CRAWFORD, R. D.: The relationship between anticonvulsant activity and receptor affinity of N-methyl-D-aspartate antagonists in epileptic fowl. Neuropharmacology **28:** 753–756, 1989.

PEDLEY, T. A., HORTON, R. W., AND MELDRUM, B. S.: Electroencephalographic and behavioral effects of a GABA agonist (muscimol) on photosensitive epilepsy in the baboon, *Papio papio*. Epilepsia **20:** 409–416, 1979.

PEET, M. J., CURRY, K., MAGNUSON, D. S., AND MCLENNAN, H.: Ca^{2+}-dependent depolarization and burst firing of rat CA1 pyramidal neurones induced by *N*-methyl-D-aspartic acid and quinolinic acid: antagonism by 2-amino-5-phosphonovaleric and kynurenic acids. Can. J. Physiol. Pharmacol. **64:** 163–168, 1986a.

PEET, M. J., CURRY, K., MAGNUSON, D. S., AND MCLENNAN, H.: The *N*-methyl-D-aspartate receptor and burst firing of CA1 hippocampal pyramidal neurons. Neuroscience **22:** 563–571, 1987.

PEET, M. J., GREGERSEN, H., AND MCLENNAN, H.: 2-Amino-5-phosphonovalerate and Co^{2+} selectively block depolarization and burst firing of rat hippocampal CA1 pyramidal neurones by *N*-methyl-D-aspartate. Neuroscience **17:** 635–641, 1986b.

PENFIELD, W., AND JASPER, H.: Epilepsy and the Functional Anatomy of the Human Brain. Little, Brown and Co., Boston, 1954.

PENRY, J. K., PORTER, R. J., SATO, S., REDDENBOUGH, J., AND DREIFUSS, F. E.: Effect of sodium valproate on generalised spike-wave paroxysms in the electroencephalogram. *In* Clinical and Pharmacological Aspects of Sodium Valproate (Epilim) in the Treatment of Epilepsy, ed. by N. J. Legg, pp. 158–164, MCS Consultants, Tunbridge Wells, 1976.

PERHACH, J. L., WELIKY, I., NEWTON, J. J., SOFIA, R. D., ROMANYSHYN, W. M., AND ARDNT, W. F., JR.: Felbamate. *In* New Anticonvulsant Drugs, ed. by B. S. Meldrum, and R. J. Porter, pp. 117–113, John Libbey, London, 1986.

PERRY, T. L., KISH, S. J., AND HANSEN, S.: γ-vinyl GABA: Effects of chronic administration on the metabolism of GABA and other amino compounds in rat brain. J. Neurochem. **32:** 1641–1645, 1979.

PETERSON, D. W., COLLINS, J. F., AND BRADFORD, H. F.: The kindled model of epilepsy: anticonvulsant action of amino acid antagonists. Brain Res. **275:** 169–172, 1983.

PHILLIPS, N. I., AND FOWLER, L. J.: The effects of sodium valproate on gamma-aminobutyrate metabolism and behaviour in naive and ethanolamine-*O*-sulphate pretreated rats and mice. Biochem. Pharmacol. **31:** 2257–2261, 1982.

PHILLIS, J. W.: Interactions of the anticonvulsants diphenylhydantoin and carbamazepine with adenosine on cerebral cortical neurons. Epilepsia **25:** 765–772, 1984.

PICKLES, H. G., AND SIMMONDS, M. A.: Field potentials, inhibition and the effect of pentobarbitone in the rat olfactory cortex slice. J. Physiol. (Lond.) **275:** 135–148, 1978.

PIERCEY, M. F., HOFFMANN, W. E., AND KACZKOFSKY, P.: Functional evidence for PCP-like effects of the anti-stroke candidate MK-801. Psychopharmacology **96:** 561–562, 1988.

PINCUS, J. H., AND HSIAO, K.: Calcium uptake mechanisms affected by some convulsant and anticonvulsant drugs. Brain Res. **217:** 119–127, 1981.

PINCUS, J. H., AND LEE, S. H.: Diphenylhydantoin and calcium: relation to norepinephrine release from brain slices. Arch. Neurol. **29:** 239–244, 1973.

PITKÄNEN, A., MATILAINEN, R., RUUTIAINEN, T., LEHTINEN, M., AND RIEKKINEN, P.: Effect of vigabatrin (gamma-vinyl GABA) on amino acid levels in CSF of epileptic patients. J. Neurol. Neurosurg. Psychiatry **51:** 1395–1400, 1988.

POISSON, M., HUGUET, F., SAVATTIER, A., BAKRI-LOGEAIS, F., AND NARCISSE, G.: A new type of anticonvulsant, stiripentol: pharmacological profile and neurochemical study. Arzneim. Forsch. Drug Res. **34:** 199–204, 1984.

POLITI, D. M. T., SUZUKI, S., AND ROGAWSKI, M. A.: BRL 34915 (cromakalim) enhances voltage-dependent K^+ current in cultured rat hippocampal neurons. Eur. J. Pharmacol. **168:** 7–14, 1989.

POPOLI, A., PÉZZOLA, A., AND SCOTTI DE CAROLIS, A.: Effects of calcium antagonist nimodipine on pentylenetetrazole-induced seizures in rats and rabbits. Arch. Int. Pharmacodyn. Ther. **292:** 58–67, 1988.

PORTER R. J.: Epilepsy: One Hundred Elementary Principles, 2nd ed. W. B. Saunders Co., London, 1989.

PORTER, R. J.: New agents in epilepsy: strategies for drug development. Lancet, in press, 1990.

PORTER, R. J., CEREGHINO, J. J., GLADDING, G. D., HESSIE, B. J., KUPFERBERG, H. J., SCOVILLE, B., AND WHITE, B. G.: Antiepileptic drug development program. Cleveland Clin. Q. **51:** 293–305, 1984.

PORTER, R. J., PENRY, J. K., LACY, J. R., NEWMARK, M. E., AND KUPFERBERG, H. J.: Plasma concentrations of phensuximide, methsuximide, and their metabolites in relation to clinical efficacy. Neurology **29:** 1509–1513, 1979.

POTASHNER, S. J., LAKE, N., LANGLOIS, E. A., PLOUFFE, L., AND LECAVALIER, D.: Pentobarbital: differential effects on the depolarization-induced release of excitatory and inhibitory amino acids from cerebral cortex slices. Brain Res. Bull. **5:** 659–664, 1980.

PRADHAN, S. N.: Phencyclidine (PCP): some human studies. Neurosci. Biobehav. Rev. **8:** 493–501, 1984.

PREISENDÖRFER, U., ZEISE, M. L., AND KLEE, M. R.: Valproate enhances inhibitory postsynaptic potentials in hippocampal neurons in vitro. Brain Res. **435:** 213–219, 1987.

PRICHARD, J. W., AND RANSOM, B. R.: Phenobarbital: mechanisms of action. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J.K. Penry, and F.E. Dreifuss, pp. 267–282, Raven Press, New York, 1989.

PRIESTLEY, T., WOODRUFF, G. N., AND KEMP, J. N.: Antagonism of responses to excitatory amino acids on rat cortical neurones by the spinder toxin, argiotoxin$_{636}$. Br. J. Pharmacol. **97:** 1315–1323, 1989.

PRITCHETT, D. B., LÜDDENS, H., AND SEEBURG, P. H.: Type I and type II $GABA_A$-benzodiazepine receptors produced in transfected cells. Science (Wash. DC) **245:** 1389–1392, 1989a

PRITCHETT, D. B., SONTHEIMER, H., GORMAN, C. M., KETTENMANN, H., SEEBURG, P. H., AND SCHOFIELD, P. R.: Transient expression shows ligand gating and allosteric potentiation of $GABA_A$ receptor subunits. Science (Wash. DC) **242:** 1306–1308, 1988.

PRITCHETT, D. B., SONTHEIMER, H., SHIVERS, B. D., YMER, S., KETTENMANN, H., SCHOFIELD, P. R., AND SEEBURG, P. H.: Importance of a novel $GABA_A$ receptor subunit for benzodiazepine pharmacology. Nature (Lond.) **338:** 582–585, 1989b

PRZEGALINSKI, E.: Monoamines and the pathophysiology of seizure disorders. *In* Handbook of Experimental Pharmacology, vol. 74, ed. by H.-H. Frey and D. Janz, pp. 102–137, Springer-Verlag, Berlin, 1985.

PURDY, R. E., JULIEN, R. M., FAIRHURST, A. S., AND TERRY, M. D.: Effect of carbamazepine on the *in vitro* uptake and release of norepinephrine in adrenergic nerves of rabbit aorta and in whole brain synaptosomes. Epilepsia **18:** 251–257, 1977.

PUTNAM, T. J., AND MERRITT, H. H.: Experimental determination of the anticonvulsant properties of some phenyl derivatives. Science (Wash. DC) **85:** 525–526, 1937.

QUATTRONE, A., ANNUNZIATO, L., AGUGLIA, U., AND PREZIOSI, P.: Carbamazepine, phenytoin and phenobarbital do not influence brain catecholamine uptake, *in vivo*. Arch. Int. Pharmacodyn. Ther. **252:** 180–185, 1981.

RAABE, W., AND AYALA, G. F.: Diphenylhydantoin increases cortical postsynaptic inhibition. Brain Res. **105:** 597–601, 1976.

RAINES, A., AND STANDAERT, F. G.: Pre- and postjunctional effects of diphenylhydantoin at the cat soleus neuromuscular junction. J. Pharmacol. Exp. Ther. **153:** 361–366, 1966.

RAJA, S. N., AND GUYENET, P. G.: Effects of phencyclidine on the spontaneous activity of monoaminergic neurons. Eur. J. Pharmacol. **63:** 229–233, 1980.

RALL, T. W., AND SCHLEIFER, L. S.: Drugs effective in the therapy of epilepsies. *In* Goodman and Gilman's The Pharmacological Basis of Therapeutics, 6th ed., ed. by A. G. Gilman, L. S. Goodman, and A. Gilman, pp. 448–474, Macmillan Publishing Co., New York, 1980.

RAMSAY, R. E., WILDER, B. J., SACHELLARES, J. C., BROWNE, T., GUTERMAN, A., BARNES, D., MATHEWS, J., BERENT, S., DONOFRIO, P. D., ABOU-KHALIL, B., AND WAGNER, J. G.: Multicenter study on the efficacy of zonisamide in the treatment of medically refractory complex partial seizures. Epilepsia **25:** 673, 1984.

RANSOM, B. R., AND BARKER, J. L.: Pentobarbital modulates transmitter effects on mouse spinal neurones grown in tissue culture. Nature (Lond.) **254:** 703–705, 1975.

RANSOM, R. W., AND STEC, N. L.: Cooperative modulation of [^{3}H]MK-801 binding to the *N*-methyl-D-aspartate receptor-ion channel complex by L-glutamate, glycine, and polyamines. J. Neurochem. **51:** 830–836, 1988.

RAPPORT, R. L., 2D, AND KUPFERBERG, H. J.: Metabolism of dimethoxymethylphenobarbital in mice. Relationship between brain phenobarbital levels and anticonvulsant activity. J. Med. Chem. **16:** 599–602, 1973.

RASCOL, O., SQUALLI, A., MONTASTRUC, J-L, GARAT, A., HOUIN, G. L., LACHAU, S., TOR, J., BLEHAUT, H., AND RASCOL, A.: A pilot study of stiripentol, A new anticonvulsant drug, in complex partial seizures uncontrolled by carbamazepine. Clin. Neuropharmacol. **12:** 119–123, 1989.

REDER, B. S., TRAPP, L. D., AND TROUTMAN, K. C.: Ketamine suppression of chemically induced convulsions in the two-day-old white leghorn cockerel. Anesth. Analg. **59:** 406–409, 1980.

REIMANN, W.: Inhibition by GABA, baclofen and gabapentin of dopamine release from rabbit caudate nucleus: are there common or different sites of action? Eur. J. Pharmacol. **94:** 341–344, 1983.

REINHARD, J. F., AND REINHARD, J. F., JR.: Experimental evaluation of anticonvulsants. *In* Anticonvulsants, ed. by J. AAVida, pp. 57–111, Academic Press, New York, 1977.

REINIKAINEN, K. J., KERANEN, T., HALONEN, T., KOMULAINEN, H., AND RIEKKINEN, P. J.: Comparison of oxcarbazepine and carbamazepine: a double-blind study. Epilepsy Res. **1:** 284–289, 1987.

REMY, C., FAVEI, P., TELL, G., HARENERG, J., AND SCHECHTER, P. J.: Double-blind, placebo-controlled, cross-over study of GVC in drug resistant epilepsy of the adult. Boll. Lega. It. Epil. **54/55:** 241–243, 1986.

REYNOLDS, E. H.: Vigabatrin. Br. Med. J. **300:** 277–278, 1990.

REYNOLDS, E. H., RING, H., AND HELLER, A.: A controlled trial of gamma-vinyl-GABA (vigabatrin) in drug resistant epilepsy. Br. J. Clin. Pract. Symp. Suppl. **61:** 33, 1988.

REYNOLDS, I. J.: Arcaine is a competitive antagonist of the polyamine site on the NMDA receptor. Eur. J. Pharmacol. **177:** 215–216, 1990.

REYNOLDS, I. J., AND MILLER, R. J.: Ifenprodil is a novel type of *N*-methyl-D-aspartate receptor antagonist: interaction with polyamines. Mol. Pharmacol. **36:** 758–765, 1989.

RICHENS, A. AND YUEN, W. C: Meta-analysis of four controlled crossover trials of lamotrigine (Lamictal®) in refractory epilepsy. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 142, New Delhi, India, 1989.

RICHTER, J. A., AND WALLER, M. B.: Effects of pentobarbital on the regulation of acetylcholine content and release in different regions of rat brain. Biochem. Pharmacol. **26:** 609–615, 1977.

RIED, S., AND SCHMIDT, D.: Withdrawal seizures after discontinuation of vigabatrin. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 101, New Delhi, India, 1989.

RIEKKINEN, P. J., PITKANEN, A., YLINEN, A., SIVENIUS, J., AND HALONEN, T.: Specificity of vigabatrin for the GABAergic system in human epilepsy. Epilepsia **30** (suppl. 3): S18-S22, 1989.

RIMMER, E. M., AND RICHENS, A.: Double-blind study of gamma-vinyl GABA in patients with refractory epilepsy. Lancet 1: 189–190, 1984.
ROBA, J., CAVALIER, R., CORDI, A., GORISSEN, H., HERIN, M., JANSSENS DE VAREBEKE, P., ONKELINX, C., REMACLE, M., AND VAN DORSSER, W.: Milacemide. *In* New Anticonvulsant Drugs, ed. by B. S. Meldrum and R. J. Porter, pp. 179–190, John Libbey, London, 1986.
ROBERTSON, D. W., KRUSHINSKI, J. H., BEEDLE, E. E., LEANDER, J. D., WONG, D. T., AND RATHBUN, R. C.: Structure-activity relationships of (arylalkyl)imidazole anticonvulsants: comparison of the (fluorenylalkyl)imidazoles with nafimidone and denzimol. J. Med. Chem. 29: 1577–1586, 1986.
ROBICHAUD, L. J., BRAHCE, L. J., COUGHENOUR, L. L., AND BOXER, P. A.: Is ifenprodil an NMDA antagonist? Soc. Neurosci. Abst. 15: 200, 1989.
ROBINS, M. M.: Aplastic anemia secondary to anticonvulsants. Am. J. Dis. Child. 104: 614–624, 1962.
ROBINSON, G. S., JR., CROOKS, G. B., JR., SHINKMAN, P. G., AND GALLAGHER, M.: Behavioral effects of MK-801 mimic deficits associated with hippocampal damage. Psychobiology 17: 156–164, 1989.
ROCK, D. M., MACDONALD, R. L., AND TAYLOR, C. P.: Blockade of sustained repetitive action potentials in cultured spinal cord neurons by zonisamide (AD 810, CI 912), a novel anticonvulsant. Epilepsy Res. 3: 138–143, 1989.
RODIN, E. A., RIM, C. S., AND RENNICK, P. M.: The effects of carbamazepine on patients with psychomotor epilepsy: results of a double-blind study. Epilepsia 15: 547–561, 1974.
ROGAWSKI, M. A., HERSHKOWITZ, N., POLITI, D. M., SUZUKI, S., THURKAUF, A., AND YAMAGUCHI, S.: Novel research strategies for antiepileptic therapy. *In* Current and Future Trends in Anticonvulsant, Anxiety and Stroke Therapy (Princeton Drug Research Symposium, vol. 1), ed. by B. S. Meldrum and M. Williams, Wiley-Liss, New York, pp. 91–111 1990a.
ROGAWSKI, M. A., THURKAUF, A., MONN, J. A., YAMAGUCHI, S., AND JONES, S. M.: A novel anticonvulsant structurally related to the NMDA antagonist MK-801 and to carbamazepine. Epilepsia, in press, 1990b.
ROGAWSKI, M. A., THURKAUF, A., YAMAGUCHI, S., RICE, K. C., JACOBSON, A. E., AND MATTSON, M. V.: Anticonvulsant activities of 1-phenylcyclohexylamine and its conformationally restricted analog 1,1-pentamethylenetetrahydroisoquinoline. J. Pharmacol. Exp. Ther. 249: 708–712, 1989.
ROSENBERG, H. C., TIETZ, E. I., AND CHIU, T. H.: Tolerance to anticonvulsant effects of diazepam, clonazepam, and clobazam in amygdala-kindled rats. Epilepsia 30: 276–285, 1989.
ROWAN, A. J., SCHEAR, M. J., WIENER, J. A., AND LUCIANO, D.: Intensive monitoring and pharmacokinetic studies of gabapentin in patients with generalized spike-wave discharges. Epilepsia, 30: 661, 1989.
SAANO, V., RÄGO, L., AND RÄTY, M.: Peripheral benzodiazepine binding sites. Pharmacol. Ther. 41: 503–514, 1989.
SACAAN, A.I., AND JOHNSON, K.M.: Characterization of the stimulatory and inhibitory effects of polyamines on [^{3}H]*N*-(1-[thienyl]cyclohexyl)piperidine binding to the *N*-methyl-D-aspartate receptor ionophore complex. Mol. Pharmacol. 37: pp. 572–577, 1990.
SACHELLARES, J. C., DONOFRIO, P. D., WAGNER, J. G., ABOU-KHALIL, B., BERENT, S., AND AASVED-HOYT, K.: Pilot Study of zonisamide (1,2-benzisoxazole-3-methanesulfonamide) in patients with refractory partial seizures. Epilepsia 26: 206–211, 1985.
SAKAMOTO, K., KUROKAWA, T, TOMITA, S., KITAMOTO, I., MAEDA, Y., UEDA, K., HANI, T., AND NARAZAKI, O.: Effects of zonisamide in children with epilepsy. Curr. Ther. Res. 43: 378–383, 1988.
SANDER, J. W. A. S., TREVISOL-BITTENCOURT, P. C., PATSALOS, P. N., AND SHORVON, S. D.: The efficacy of lamotrigine (Lamictal®) as an add-on drug in the treatment of severe epilepsy. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 142, New Delhi, India, 1989.
SANGER, D. J., AND JACKSON, A.: Effects of phencyclidine and other N-methyl-D-aspartate antagonists on the schedule-controlled behavior of rats. J. Pharmacol. Exp. Ther. 248: 1215–1221, 1989.
SANGER, D. J., AND ZIVKOVIC, B.: The discriminative stimulus properties of antagonists of N-methyl-D-aspartate. Br. J. Pharmacol. 96: 86P, 1989.
SASA, M., OHNO, Y., UJIHARA, H., FUJITA, Y., YOSHIMURA, M., TAKAORI, S., SERIKAWA, T., AND YAMADA, J.: Effects of antiepileptic drugs on absence-like and tonic seizures in the spontaneously epileptic rat, a double mutant rat. Epilepsy 29: 505–513, 1988.
SASTRY, S. R., AND PHILLIS, J. W.: Antagonism of glutamate and acetylcholine excitation of rat cerebral cortical neurones by diphenylhydantoin. Gen. Pharmacol. 7: 411–413, 1976.
SATO, K., MORIMOTO, K., AND OKAMOTO, M.: Anticonvulsant action of a non-competitive antagonist of NMDA receptors (MK-801) in the kindling model of epilepsy. Brain Res. 463: 12–20, 1988.
SATO, S.: Benzodiazepines. Clonazepam. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 765–784, Raven Press, New York, 1989.
SATO, S., WHITE, B. G., PENRY, J. K., DREIFUSS, F. E., AND KUPFERBERG, H. J.: Double blind crossover study of sodium valproate acid and ethosuximide in the treatment of absence seizures. Neurology 32: 157–163, 1982.
SCHALLEK, W., AND KUEHN, A.: Effects of trimethadione, diphenylhydantoin, and chlordiazepoxide on after-discharges in brain of cat. Proc. Soc. Exp. Biol. Med. 112: 813–817, 1963.
SCHAUF, C. L.: Zonisamide enhances slow sodium inactivation in *Myxicola*. Brain Res. 413: 185–188, 1987.
SCHAUF, C. L., DAVIS, F. A., AND MARDER, J.: Effects of carbamazepine on ionic conductances of *Myxicola* giant axons. J. Pharmacol. Exp. Ther. 189: 538–543, 1974.
SCHECHTER, P. J., HANKE, N. F., GROVE, J., HUEBERT, N., AND SJOERDSMA, A.: Biochemical and clinical effects of gamma-vinyl GABA in patients with epilepsy. Neurology 34: 182–186, 1984.
SCHECHTER, P. J., TRANIER, Y., AND GROVE, J.: Effect of n-dipropylacetate on amino acid concentrations in mouse brain: correlation with anti-convulsant activity. J. Neurochem. 31: 1325–1327, 1978.
SCHECHTER, P. J., TRANIER, Y., JUNG, M. J., AND BOEHLEN, P.: Audiogenic seizure protection by elevated brain GABA concentrations in mice: effects of γ-acetylenic GABA and γ-vinyl GABA, two irreversible GABA-T inhibitors. Eur. J. Pharmacol. 45: 319–328, 1977.
SCHLICKER, E., REIMANN, W., AND GÖTHERT, M.: Gabapentin decreases monoamine release without affecting acetylcholine release in the brain. Arzneim. Forsch. Drug Res. 35: 1347–1349, 1985.
SCHMIDT, B.: Potential antiepileptic drugs. Gabapentin. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 925–935, Raven Press, New York, 1989a.
SCHMIDT, D.: Benzodiazepines. Diazepam. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreyfus, pp. 735–764, Raven Press, New York, 1989b.
SCHMIDT, D., AND UTECH, K.: Progabide for refractory partial epilepsy: A controlled add-on trial. Neurology 36: 217–221, 1986.
SCHMIDT, W. J., AND BUBSER, M: Anticataleptic effects of the N-methyl-D-aspartate antagonist MK-801 in rats. Pharmacol. Biochem. Behav. 32: 621–623, 1989.
SCHMUTZ, M., KLEBS, K., AND BALTZER, V.: Inhibition or enhancement of kindling evolution by antiepileptics. J. Neural Transm. 72: 245–257, 1988.
SCHMUTZ, M., OLPE, H.-R., AND KOELLA, W. P: Central actions of valproate sodium. J. Pharm. Pharmacol. 31: 413–414, 1979.
SCHOLFIELD, C. N.: A barbiturate induced intensification of the inhibitory potential in slices of guinea pig olfactory cortex. J. Physiol. (Lond.) 275: 559–566, 1978.
SCHOFIELD, P. R., DARLISON, M. G., FUJITA, N., BURT, D. R., STEPHENSON, F. A., RODRIGUEZ, H., RHEE, L. M., RAMACHANDRAN, J., REALE, V., GLENCOURSE, T. A., SEEBURG, P. G., AND BARNARD, E. A.: Sequence and functional expression of the $GABA_A$ receptors shows a ligand-gated receptor super-family. Nature (Lond.) 328: 221–227, 1987.
SCHOUSBOE, A., LARSSON, O. M., AND SEILER, N.: Stereoselective uptake of the GABA-transaminase inhibitors γ-vinyl GABA and γ-acetylenic GABA in neurons and astrocytes. Neurochem. Res. 11: 1497–1505, 1986.
SCHULZ, D. W., AND MACDONALD, R. L.: Barbiturate enhancement of GABA-mediated inhibition and activation of chloride ion conductance: correlation with anticonvulsant and anesthetic actions. Brain Res. 209: 177–188, 1981.
SCHTZ, H., FELDMANN, K. F., FAIGLE, J. W., KRIEMLER, H.-P., AND WINKLER, T.: The metabolism of ^{14}C-oxcarbazepine in man. Xenobiotica 16: 769–778, 1986.
SCHWARZ, J. R., AND GRIGAT, G.: Phenytoin and carbamazepine: potential- and frequency-dependent block of Na currents in mammalian myelinated nerve fibers. Epilepsia 30: 286–294, 1989.
SCHWARZ, J. R., AND VOGEL, W.: Diphenylhydantoin: excitability reducing action in single myelineated nerve fibres. Eur. J. Pharmacol. 44: 241–249, 1977.
SCHWARTZ, R. D., JACKSON, J. A., WEIGERT, D., SKOLNICK, P., AND PAUL, S. M.: Characterization of barbiturate-stimulated chloride efflux from rat brain synaptoneurosomes. J. Neurosci. 5: 2963–2970, 1985.
SCOLLO-LAVIZZARI, G.: The anticonvulsant effect of the benzodiazepine antagonist Ro 15–1788: an EEG study in 4 cases. Eur. Neurol. 23: 1–6, 1984.
SCOLLO-LAVIZZARI, G.: The clinical anti-convulsant effects of flumazenil, a benzodiazepine antagonist. Eur. J. Anesthesiol. 2 (suppl.): 129–138, 1988.
SCOTTI DE CAROLIS, A., LIPPARINI, F., AND LONGO, V. G.: Neuropharmacological investigations on muscimol, a psychotropic drug extracted from *Amanita muscaria*. Psychopharmacologia 15: 186–195, 1969.
SEALE, T. W., RODERICK, T. H., AND SKOLNICK, P.: Ontogeny of susceptibility to the convulsant, RO 5–4864, and its relationship to audiogenic seizure susceptibility in inbred mice. Life Sci. 40: 1267–1276, 1987.
SEDMAN, A. J., GILMET, G. P., SAYED, A. J., AND POSVAR, E. L.: Initial human safety and tolerance study of a GABA uptake inhibitor, CI-966: potential role of GABA as a mediator in the pathogenesis of schizophrenia and mania. Drug Dev. Res., in press, 1990.
SELZER, M. E., ADLER, E. M., DAVID, G., AND YAARI, Y.: Mechanisms of anticonvulsant action. *In* Mechanisms of Epileptogenesis: The Transition to Seizure, ed. by M. A. Dichter, pp. 221–238, Plenum Press, New York, 1988.
SELZER, M. E., DAVID, G., AND YAARI, Y.: On the mechanism by which phenytoin blocks post-tetanic potentiation at the frog neuromuscular junction. J. Neurosci. 5: 2894–2899, 1985.
SERNAGOR, E., KUHN, D., AND VYKLICKY, L., JR.: Open channel block of NMDA receptor responses evoked by tricyclic antidepressants. Neuron 2: 1221–1227, 1989.
SHENOY, A. K., MIYAHARA, J. T., SWINYARD, E. A., AND KUPFERBERG, H. J.: Comparative anticonvulsant activity and neurotoxicity of clobazam,

diazepam, phenobarbital, and valproate in mice and rats. Epilepsia **23:** 399–408, 1982.

SHERWIN, A. L.: Ethosuximide. Clinical use. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 685–698, Raven Press, New York, 1989.

SHERWIN, A. L., ROBB, J. P., AND LECHTER, M.: Improved control of epilepsy by monitoring plasma ethosuximide. Arch. Neurol. **28:** 178–181, 1973.

SHIMIZU, A., YAMAMOTO, J., YAMADA, Y., TANAKA, M., AND KAWASAKI, T.: The antiepileptic effect of zonisamide in patients with refractory seizures. Curr. Ther. Res. **42:** 147–155, 1987.

SHIN, C., RIGSBEE, L. C., AND MCNAMARA, J. O.: Anti-seizure and anti-epileptogenic effect of γ-vinyl γ-aminobutyric acid in amgdaloid kindling. Brain Res. **398:** 370–374, 1986.

SHORVON, S. D.: Benzodiazepines. Clobazam. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 821–840, Raven Press, New York, 1989.

SHUTO, H., SUGIMOTO, T., YASUHARA, A., HATANAKA, T., WOO, M., MURAKAMI, K., ARAKI, A., AND KOBAYASHI, Y.: Efficacy of zonisamide in children with refractory partial seizures. Curr. Ther. Res. Clin. Exp. **45:** 1031–1036, 1989.

SIMMONDS, M. A.: Antagonism of flurazepam and other effects of Ro 15–1788, Pk 8165 and Ro 5–4864 on the $GABA_A$ receptor complex in rat cuneate nucleus. Eur. J. Pharmacol. **117:** 51–60, 1985.

SIMMONDS, M. A., AND HORNE, A. L.: Barbiturates and excitatory amino acid interactions. *In* Excitatory Amino Acids in Health and Disease, ed. by D. Lodge, pp. 219–236, John Wiley & Sons, Chichester, 1988.

SIMON, D., AND PENRY, J. K.: Sodium di-N-propylacetate (DPA) in the treatment of epilepsy: a review. Epilepsia **16:** 549–573, 1975.

SINGH, L., DONALD, A. E., FOSTER, A. C., HUTSON, P. H., IVERSEN, L. L., IVERSEN, S. D., KEMP, J. A., LEESON, P. D., MARSHALL, G. R., OLES, R. J., PRIESTLEY, T., THORN, L., TRICKLEBANK, M. D., VASS, C. A., AND WILLIAMS, B. J.: Enantiomers of HA-966 (3-amino-1-hydroxypyrrolid-2-one) exhibit distinct central nervous system effects: (+)-HA-966 is a selective glycine/N-methyl-D-aspartate receptor antagonist, but (−)-HA-966 is a potent γ-butyrolactone-like sedative. Proc. Natl. Acad. Sci. USA **87:** 347–351, 1990.

SIVENIUS, J., KALVIAINEN, R., YLINEN, A., AND RIEKKINEN, P. J.: A double-blind study of gabapentin in the treatment of partial seizures. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 91, New Delhi, India, 1989.

SIVENIUS, J., MATILAINEN, R., RIEKKINEN, P., AND MURROS, K.: Efficacy of gamma-vinyl GABA (vigabatrin) in long-term therapy in patients with partial epilepsy. Neurology **40** (suppl. 1): 157, 1990.

SIVILOTTI, L., AND NISTRI, A.: Antagonism of the actions of glutamate by pentobarbitone or midazolam in the frog optic tectum *in vitro*. Neuropharmacology **28:** 1107–1112, 1989.

SKERRITT, J. H., DAVIES, L. P., AND JOHNSTON, G. A. R.: A purinergic component in the anticonvulsant action of carbamazepine? Eur. J. Pharmacol. **82:** 195–197, 1982.

SKERRITT, J. H., DAVIES, L. P., AND JOHNSTON, G. A. R.: Interaction of the anticonvulsant carbamazepine with adenosine receptors. 1. Neurochemical studies. Epilepsia **24:** 634–642, 1983.

SKERRITT, J. H., AND MACDONALD, R. L.: Multiple actions of convulsant barbiturates on mouse neurons in cell culture. J. Pharmacol. Exp. Ther. **230:** 82–88, 1984.

SKERRITT, J. H., WERZ, M. A., MCLEAN, M. J., AND MACDONALD, R. L.: Diazepam and its anomalous p-chloro derivative Ro 5–4864: comparative effects on mouse neurons in cell culture. Brain Res. **310:** 99–105, 1984.

SMITH, D. B., GOLDSTEIN, S. G., AND ROOMET, A.: A comparison of the toxicity effects of the anticonvulsant eterobarb (Antilon, DMMP) and phenobarbital in normal human volunteers. Epilepsia **27:** 149–155, 1986.

SMITH, D. B., MATTSON, R. H., CRAMER, J. A., COLLINS, J. F., NOVELLY, R. A., AND CRAFT, B.: Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. Epilepsia **28** (suppl. 3): S50–S58, 1987.

SNEAD, O. C., 3RD: Gamma-hydroxybutyrate in the monkey. II. Effect of chronic oral anticonvulsant drugs. Neurology **28:** 643–648, 1978.

SNEAD, O. C., 3RD: γ-Hydroxybutyrate model of generalized absence seizures: further characterization and comparison with other absence models. Epilepsia **29:** 361–368, 1988.

SNELL, L. D., AND JOHNSON, K. M.: Characterization of the inhibition of excitatory amino acid-induced neurotransmitter release in the rat striatum by phencyclidine-like drugs. J. Pharmacol. Exp. Ther. **238:** 938–946, 1986.

SNELL, L. D., AND JOHNSON, K. M.: Cycloleucine competitively antagonizes the strychnine-insensitive glycine receptor. Eur. J. Pharmacol. **151:** 165–166, 1988.

SNELL, L. D., YI, S.-J., AND JOHNSON, K. M.: Comparison of the effects of MK-801 and phencyclidine on catecholamine uptake and NMDA-induced norepinephrine release. Eur. J. Pharmacol. **145:** 223–226, 1988.

SNYDER, S. H.: Adenosine as a neuromodulator. Annu. Rev. Neurosci. **8:** 103–124, 1985.

SOHN, R. S., AND FERRENDELLI, J. A.: Anticonvulsant drug mechanisms: phenytoin, phenobarbital, and ethosuximide and calcium flux in isolated presynaptic endings. Arch. Neurol. **33:** 626–629, 1976.

SOMJEN, G. G.: Interstitial ion concentration and the role of neuroglia in seizures. *In* Electrophysiology of Epilepsy, ed. by P. A. Schwartzkroin and H. V. Wheal, pp. 305–341, Academic Press, London, 1984.

SPERBER, E. F., WURPEL, J. N., AHAO, D. Y., AND MOSHÉ, S. L.: Evidence for the involvement of nigral $GABA_A$ receptors in seizures of adult rats. Brain Res. **480:** 378–382, 1989.

SQUIRES, R. F., AND BRAESTRUP, C.: Benzodiazepine receptors in rat brain. Nature (Lond.) **266:** 732–734, 1977.

STAIMAN, A., AND SEEMAN, P.: The impulse-blocking concentrations of anesthetics, alcohols, anticonvulsants, barbiturates and narcotics on phrenic and sciatic nerves. Can. J. Physiol. Pharmacol. **52:** 535–557, 1974.

STASHEFF, S. F., ANDERSON, W. W., CLARK, S., AND WILSON, W. A.: NMDA antagonists differentiate epileptogenesis from seizure expression in an in vitro model. Science (Wash. DC) **245:** 648–651, 1989.

STEINFELS, G. F., TAM, S. W., AND COOK, L.: Electrophysiological effects of selective σ-receptor agonists, antagonists, and the selective phencyclidine receptor agonist MK-801 on midbrain dopamine neurons. Neuropsychopharmacology **2:** 201–208, 1989.

STERIADE, M., AND LLINÁS, R. R.: The functional states of the thalamus and the associated neuronal interplay. Physiol. Rev. **68:** 649–742, 1988.

STÉRU, L., CHERMAT, R., MILLET, B., MICO, J. A., AND SIMON, P.: Comparative study in mice of ten 1,4-benzodiazepines and of clobazam: anticonvulsant, anxiolytic, sedative and myorelaxant effects. Epilepsia **27** (suppl. 1): S14-S17, 1986.

STONE, T. W.: Comparison of kynurenic acid and 2-APV suppression of epileptiform activity in rat hippocampal slices. Neurosci. Lett. **84:** 234–238, 1988.

STRINGER, J. L., AND LOTHMAN, E. W.: Phenytoin does not block hippocampal long-term potentiation or frequency potentiation. Ann. Neurol. **23:** 281–286, 1988.

STUDY, R. E., AND BARKER, J. L.: Diazepam and (-)-pentobarbital: fluctuation analysis reveals different mechanisms for potentiation of γ-aminobutyric acid responses in cultured central neurons. Proc. Natl. Acad. Sci. USA **78:** 7180–7184, 1981.

SUZUKI, S., AND ROGAWSKI, M. A.: T-type calcium channels mediate the transition between tonic and phasic firing in thalamic neurons. Proc. Natl. Acad. Sci. USA **86:** 7228–7232, 1989.

SWINYARD, E. A., BROWN, W. C., AND GOODMAN, L. S.: Comparative assays of antiepileptic drugs in mice and rats. J. Pharmacol. Exp. Ther. **106:** 47–59, 1952.

SWINYARD, E. A., AND CASTELLION, A. W.: Anticonvulsant properties of some benzodiazepines. J. Pharmacol. Exp. Ther. **151:** 369–375, 1966.

SWINYARD, E. A., SOFIA, R. D., AND KUPFERBERG, H. J.: Comparative anticonvulsant activity and neurotoxicity of felbamate and four prototype antiepileptic drugs in mice and rats. Epilepsia **27:** 27–34, 1986.

SWINYARD, E. A., WOODHEAD, J. H., WHITE, H. S., AND FRANKLIN, M. R.: General principles. Experimental selection, quantification, and evaluation of anticonvulsants. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 85–102, Raven Press, New York, 1989.

TABERNER, P. V.: The anticonvulsant activity of ketamine against seizures induced by pentylenetetrazol and mercaptoproprionic acid. Eur. J. Pharmacol. **39:** 305–311, 1976.

TAKAHASHI, I., YAMAMOTO, N., FURUNE, S., ASO, K., TAKAESU, E., NEGORO, T., WATANABE, K., MATSUMOTO, A., TAKEUCHI, T., HAKAMADA, S., HAYAKAWA, F., AND MAEHARA, M.: Efficacy of zonisamide for intractable epilepsy in childhood. J. Jpn. Epilepsy Soc. **5:** 100–105, 1987.

TAKEDA, A., INAGUMA, J., AND SHIMIZU, A.: Treatment of intractable epilepsy with a new antiepileptic drug, zonisamide. Jpn. Pharmacol. Ther. **15:** 397–405, 1987.

TANG, A. H., AND HO, P. M.: Both competitive and non-competitive antagonists of N-methyl-D-aspartic acid disrupt brightness discrimination in rats. Eur. J. Pharmacol. **151:** 143–146, 1988.

TARTARA, A., MANNI, R., GALIMBERTI, C. A., HARDENBERG, J., ORWIN, J., AND PERRUCA, E.: Vigabatrin in the treatment of epilepsy: a double-blind, placebo-controlled study. Epilepsia **27:** 717–723, 1986.

TARTARA, A., MANNI, R., GALIMBERTI, C. A., MUMFORD, J. P., IUDICE, A., AND PERUCCA, E.: Vigabatrin in the treatment of epilepsy: a long-term follow-up study. J. Neurol. Neurosurg. Psychiatry **52:** 467–471, 1989.

TASSINARI, C. A., MICHELUCCI, R., AMBROSETTO, G., AND SALVI, F.: Double-blind study of vigabatrin in the treatment of drug-resistant epilepsy. Arch. Neurol. **44:** 907–910, 1987.

TAYLOR, C. P., VARTANIAN, M. G., SCHWARZ, R. D., ROCK, D. M., CALLAHAN, M. J., AND DAVIS, M. D.: The pharmacology of CI-966, a potent GABA uptake inhibitor in vivo and in experimental animals. Drug Dev. Res., in press, 1990.

TAYLOR, J. (ED.): Selected Writings of John Hughlings Jackson, vol. 1: On Epilepsy and Epileptiform Convulsions, Hodder and Stoughton, London (Reprint Basic Books, New York), 1931.

TEICHBERG, V. I., TAL, N., GOLDBERG, O., AND LUINI, A.: Barbiturates, alcohols, and the CNS excitatory neurotransmission: specific effects on the kainate and quisqualate receptors. Brain Res. **291:** 285–292, 1984.

TESTA, R., AND BERTIN, D.: Denzimol. *In* New Anticonvulsant Drugs, ed by B. S. Meldrum and R. J. Porter, p. 85, John Libbey, London, 1986.

THEODORE, W. H., BAIRAMIAN, D., NEWMARK, M. E., DICHIRO, G., PORTER,

R. J., LARSON, S., AND FISHBEIN, D.: Effect of phenytoin on human cerebral glucose metabolism. J. Cereb. Blood Flow Metab. **6:** 315–320, 1986a.

THEODORE, W. H., DICHIRO, G., MARGOLIN, R., FISHBEIN, D., PORTER, R. J., AND BROOKS, R. A: Barbiturates reduce human cerebral glucose metabolism. Neurology **36:** 60–64, 1986b.

THEODORE, W. H., AND PORTER, R. J.: Removal of sedative-hypnotic antiepileptic drugs from the regimens of patients with intractable epilepsy. Ann. Neurol. **13:** 320–324, 1983.

THEODORE, W. H., RAUBERTAS, R., PORTER, R. J., NICE, F., DEVINSKY, O., REEVES, P., BROMFIELD, E., ITO, B., AND BALISH, M.: Felbamate: a double-blind placebo-controlled three-period crossover trial. Epilepsia **30:** 661, 1989.

THURKAUF, A., DE COSTA, B., YAMAGUCHI, S., MATTSON, M. V., JACOBSON, A. E., RICE, K. C., AND ROGAWSKI, M. A.: Synthesis and anticonvulsant activity of 1-phenylcyclohexylamine analogues. J. Med. Chem. **33:** 1452–1458, 1990.

TICKU, M. K., AND DAVIS, W. C.: Effect of valproic acid on [^{3}H]diazepam and [^{3}H]dihydropicrotoxinin binding sites at the benzodiazepine-GABA receptor-ionophore complex. Brain Res. **223:** 218–222, 1981.

TICKU, M. R., AND RAMANJANEYULU, R.: Ro 5–4864 inhibits the binding of [^{35}S]t-butylbicyclophosphorothionate to rat brain membranes. Life Sci. **34:** 631–638, 1984.

TIETZ, E. I., ROSENBERG, H. C., AND CHIU, T. H.: A comparison of the anticonvulsant effects of 1,4- and 1,5-benzodiazepines in the amygdala-kindled rat and their effects on motor function. Epilepsy Res. **3:** 31–40, 1989.

TODD, P. A., AND BENFIELD, P.: Flunarazine. A reappraisal of its pharmacological properties and therapeutic uses in neurological disorders. Drugs **38:** 481–499, 1989.

TOMAN, J. E. P.: The neuropharmacology of antiepileptics. EEG Clin. Neurophysiol. **1:** 33–44, 1949.

TOMAN, J. E. P., SWINYARD, E. A., AND GOODMAN, L. S: Properties of maximal seizures, and their alteration by anticonvulsant drugs and other agents. J. Neurophysiol. **9:** 231–240, 1946.

TOMASELLI, G. F., MARBAN, E., AND YELLEN, G.: Sodium channels from human brain RNA expressed in *Xenopus* oocytes. Basic electrophysiologic characteristics and their modification by diphenylhydantoin. J. Clin. Invest. **83:** 1724–1732, 1989.

TORTELLA, F. C., FERKANY, J. W., AND PONTECORVO, M. J.: Anticonvulsant effects of dextrorphan in rats: possible involvement in dextromethorphan-induced seizure protection. Life Sci. **42:** 2509–2514, 1988a.

TORTELLA, F. C., AND MUSACCHIO, J. M.: Dextromethorphan and carbetapentane: centrally acting non-opioid antitussive agents with novel anticonvulsant properties. Brain Res. **383:** 314–318, 1986.

TORTELLA, F. C., PELLICANO, M., AND BOWERY, N. G.: Dextromethorphan and neuromodulation: old drug coughs up new activities. Trends Pharmacol. Sci. **10:** 501–507, 1989.

TORTELLA, F. C., WITKIN, J. M., AND MUSACCHIO, J. M.: Caramiphen: a non-opioid antitussive with potent anticonvulsant activity in rats. Eur. J. Pharmacol. **155:** 69–75, 1988b.

TOTH, E., LAJTHA, A., SARHAN, S., AND SEILER, N.: Anticonvulsant effects of some inhibitory neurotransmitter amino acids. Neurochem. Res. **8:** 293–302, 1983.

TREIMAN, D. M., WILENSKY, A. J., BEN-MENACHEM, E., OJEMANN, L., YERBY, M., BARBER, K. O., MCCORMICK, K. B., CEREGHINO, J. J., WHITE, B. G., AND SWISHER, K.: Efficacy of nafimidone in the treatment of intractable partial seizures: report of a two-center pilot study. Epilepsia **26:** 607–611, 1985.

TREVISOL-BITTENCOURT, P. C., SANDER, J. W. A. S., AND SHORVON, S. D.: Long term evaluation of vigabatrin as an add-on drug in the management of severe epilepsy. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 15, New Delhi, India, 1989.

TRICKLEBANK, M. D., SINGH, L., OLES, R. J., PRESTON, C., AND IVERSEN, S. D.: The behavioural effects of MK-801: a comparison with antagonists acting non-competitively and competitively at the NMDA receptor. Eur. J. Pharmacol. **167:** 127–135, 1989.

TRICKLEBANK, M. D., SINGH, L., OLES, R. J., WONG, E. H. F., AND IVERSEN, S. D.: A role for receptors of N-methyl-D-aspartic acid in the discriminitive stimulus properties of phencyclidine. Eur. J. Pharmacol. **141:** 497–501, 1987.

TRIMBLE, M. R., AND ROBERTSON, M. M.: Clobazam. *In* New Anticonvulsant Drugs, ed. by B. S. Meldrum and R. J. Porter, pp. 65–84, John Libbey, London, 1986.

TROTTIER, S., SAZDOVITCH, V., CHAUVEL, P., BEAUMONT, D., AND HAUW, J. J.: Neuropathological study of brain tissue in six patients treated with long term vigabatrin. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 141, New Delhi, India, 1989.

TROUPIN, A. S., MENDIUS, J. R., CHENG, F., AND RISINGER, M. W.: MK-801. *In* New Anticonvulsant Drugs, ed. by B. S. Meldrum and R. J. Porter, pp. 191–201, John Libbey, London, 1986.

TROUPIN, A. S., OJEMANN, L. M., AND DODRILL, C. B.: Mephenytoin: a reappraisal. Epilepsia **17:** 403–414, 1976.

TRUONG, D. D., DIAMOND, B., PEZZOLI, G., MENA, M. A., AND FAHN, S.: Monoamine oxidase inhibitory properties of milacemide in rats. Life Sci. **44:** 1059–1066, 1989.

TRUSSELL, L. O., AND JACKSON, M. B.: Adenosine-activated potassium conductance in cultured striatal neurons. Proc. Natl. Acad Sci. USA **82:** 4857–4861, 1985.

TRUSSELL, L. O., AND JACKSON, M. B.: Dependence of an adenosine-activated potassium current on a GTP-binding protein in mammalian central neurons. J. Neurosci. **7:** 3306–3416, 1987.

TSIEN, R. W., FOX, A. P., HESS, P., MCCLESKEY, E. W., NILIUS, B., NOWYCKY, M. C., AND ROSENBERG, R. L.: Multiple types of calcium channel in excitable cells. *In* Proteins of Excitable Membranes, Society of General Physiologists Series, ed. by B. Hille and D. M. Fambrough, pp. 167–188, John Wiley & Sons, New York, 1987.

TSUCHIYA, T., AND FUKUSHIMA, H.: Effects of benzodiazepines and pentobarbitone on the GABA-ergic recurrent inhibition of hippocampal neurons. Eur. J. Pharmacol. **48:** 421–424, 1978.

TURNBULL, D. M., HOWEL, D., RAWLINS, M. D., AND CHADWICK, D. W.: Which drug for the adult epileptic patient: Phenytoin or valproate? Br. Med. J. **290:** 815–819, 1985.

TWOMBLY, D. A., YOSHII, M., AND NARAHASHI, T.: Mechanisms of calcium channel block by phenytoin. J. Pharmacol. Exp. Ther. **246:** 189–195, 1988.

TWYMAN, R. E., ROGERS, C. J., AND MACDONALD, R. L.: Differential regulation of γ-aminobutyric acid receptor channels by diazepam and phenobarbital. Ann. Neurol. **25:** 213–220, 1989.

TYTGAT, J., VEREECKE, J., AND CARMELIET, E.: Differential effects of verapamil and flunarizine on cardiac L-type and T-type Ca channels. Naunyn-Schmiedebergs Arch. Pharmacol. **337:** 690–692, 1988.

VAN DER LAAN, J. W., DE BOER, T., AND BRUINVELS, J.: Di-n-propylacetate and GABA degradation. Preferential inhibition of succinic semialdehyde dehydrogenase and indirect inhibition of GABA transaminase. J. Neurochem. **32:** 1769–1780, 1979.

VAN DER LINDEN, G. J., MEINARDI, H., MEIJER, J. W. A., BOSSI, L., AND GOMENI, C.: A double-blind cross-over trial with progabide (SL 76002) against placebo in patients with secondary generalized epilepsy. *In* Advances in Epileptology: XIIth Epilepsy International Symposium, ed. by M. Dam, L. Gram, and J. K. Penry, pp. 141–144, Raven Press, New York, 1981.

VANDONGEN, A. M. J., VANERP, M. G., AND VOSKUYL, R. A.: Valproate reduces excitability by blockage of sodium and potassium channels. Epilepsia **27:** 177–182, 1986.

VAN DORSSER, W., BARRIS, D., CORDI, A., AND ROBA, J: Anticonvulsant activity of milacemide. Arch. Int. Pharmacodyn. Ther. **266:** 239–249, 1983.

VAUGHT, J. L., MARGUL, B. L., MARRIOTT, T. B., MARYANOFF, B. E., SHANK, R. P., AND SETLER, P. E.: Preclinical and clinical profile of topiramate: a structurally novel anticonvulsant. *In* Abstracts of The First Princeton Drug Research Symposium, Princeton, NJ, May 21–23, 1989. ed. by M. Williams, p. 43, 1989.

VAZQUEZ, A. J., DIAMOND, B. I., AND SABELLI, H. C.: Differential effects of phenobarbital and pentobarbital on isolated nervous tissues. Epilepsia **16:** 601–608, 1975.

VERGNES, M., MARESCAUX, C., DEPAULIS, A., MICHELETTI, G., AND WARTER, J. M.: Spontaneous spike and wave discharges in thalamus and cortex in a rat model of genetic petit mal-like seizures. Exp. Neurol. **96:** 127–136, 1987.

VERMA, A., AND SNYDER, S. H.: Peripheral type benzodiazepine receptors. Annu. Rev. Pharmacol. Toxicol. **29:** 307–322, 1989.

VEZZANI, A., WU, H.-Q., MONETA, E., AND SAMANIN, R.: Role of the *N*-methyl-D-aspartate-type receptors in the development and maintenance of hippocampal kinding in rats. Neurosci. Lett. **87:** 63–68, 1988a.

VEZZANI, A., WU, H.-Q., STASI, M. A., ANGELICO, P., AND SAMANIN, R.: Effect of various calcium channel blockers on three different models of limbic seizures in rats. Neuropharmacology **27:** 451–458, 1988b.

VINCENT, J. C.: Stiripentol. *In* New Anticonvulsant Drugs, ed. by B. S. Meldrum and R. J. Porter, pp. 255–263, John Libbey, London, 1986.

VINING, E. P. G., MELLITIS, E. D., DORSEN, M. M., CATALDO, M. F., QUASKEY, S. A., SPIELBERG, S. P., AND FREEMAN, J. M.: Psychologic and behavioral effects of antiepileptic drugs in children: a double-blind comparison between phenobarbital and valproic acid. Pediatrics **80:** 165–174, 1987.

VONVOIGTLANDER, P. F., ALTHAUS, J. S., LEWIS, R. A., AND GREEN, D. S.: Relationship of anticonvulsant activity to brain concentrations of the chiral anticonvulsant U-54494A. Drug Dev. Res. **18:** 205–216, 1989.

VONVOIGTLANDER, P. F., HALL, E. D., OCHOA, M. C., LEWIS, R. A., AND TRIEZENBERG, H. J.: U-54494A: a unique anticonvulsant related to kappa opioid agonists. J. Pharmacol. Exp. Ther. **243:** 542–547, 1987.

WADA, J. A.: Pharmacological prophylaxis in the kindling model of epilepsy. Arch. Neurol. **34:** 389–395, 1977.

WADA, T., NAKAJIMA, R., KURIHARA, E., NARUMI, S., MASUOKA, Y., GOTO, G., SAJI, Y., AND FUKUDA, N.: Pharmacologic characterization of a novel non-benzodiazepine selective anxiolytic, DN-2327. Jpn. J. Pharmacol. **49:** 337–349, 1989.

WAGNER, B., STRUMPF, G., AND BARTOSZYK, G. D.: Similar effects of ralitoline and phenytoin on papillary muscle action potentials: evidence for sodium antagonistic activity. Pharmacol. Res. Commun. **19:** 591–596, 1987.

WAGNER, J., AND SCHMIDT, K.: Induction of microsomal enzymes in rat liver by oxcarbazepine, 10,11-dihydro-10-hydroxy-carbamazepine and carbamazepine. Xenobiotica **17:** 951–956, 1987.

WAKAMORI, M., KANEDA, M., OYAMA, Y., AND AKAIKE, N.: Effects of chlordiazepoxide, chloropromazine, diazepam, diphenylhydantoin, flunitrazepam and haloperidol on the voltage-dependent sodium current of isolated mammalian brain neurons. Brain Res. **494:** 374–378, 1989.

WALKER, K. A., WALLACH, M. B., AND HIRSCHFELD, D. R.: 1-(Naphthylalkyl)-1H-imidazole derivatives, a new class of anticonvulsant agents. J. Med. Chem. **24:** 67–74, 1981.

WALLACE, S. J.: Lamotrigine (Lamictal®) in resistant childhood epilepsy. *In* Book of Abstracts, 18th International Epilepsy Congress, p. 143, New Delhi, India, 1989.

WATKINS, J. C.: The NMDA receptor concept: origins and development. *In* The NMDA Receptor, ed. by J. C. Watkins and G. L. Collingridge, pp. 1–17, IRL Press, Oxford, 1989.

WAUQUIER, A., ASHTON, D., CLINCKE, G., FRANSEN, J., GILLARDIN, J. M., AND JANSSEN, P. A. J.: Anticonvulsant profile of flunarizine. Drug Dev. Res. **7:** 49–60, 1986.

WAUQUIER, A., ASHTON, D., AND MELIS, W.: Behavioural analysis of amygdaloid kindling in beagle dogs and the effects of clonazepam, diazepam, phenobarbital, diphenylhydantoin and flunarizine on seizure manifestation. Exp. Neurol. **64:** 579–586, 1979.

WEBER, M., VERSPIGNANI, H., REMY, M. C., REGNIER, F., AND BOSSI, L.: Controlled trial of progabide versus placebo in severe therapy resistant epilepsies. *In* Epilepsy and GABA Receptor Agonists—Basic and Therapeutic Research, L.E.R.S. vol. 3, ed. by G. Bartholini, L. Bossi, K. G. Lloyd, and P. L. Morselli, pp. 353–361, Raven Press, New York, 1985.

WEGMANN, R., ILIES, A., AND AUROUSSEAU, M.: Pharmaco-cellular enzymology of the mode of action of the stiripentol during the cardiazolic epilepsy. III. The metabolism of lipids, proteins, nucleoproteins and proteoglycans. Cell. Mol. Biol. **23:** 455–480, 1978.

WEIR, R. L., ANDERSON, S. M., AND DALY, J. W.: Inhibition of N^6-[^{3}H] cyclohexyladenosine binding by carbamazepine. Epilepsia, in press, 1990.

WEIR, R. L., PADGETT, W., DALY, J. W., AND ANDERSON, S. M.: Interaction of anticonvulsant drugs with adenosine receptors in the central nervous system. Epilepsia **25:** 492–498, 1984.

WEISS, D. S., AND HABLITZ, J. J.: Interaction of penicillin and pentobarbital with inhibitory synaptic mechanisms in neocortex. Cell. Mol. Neurobiol. **4:** 310–317, 1984.

WEISS, S. R. B., POST, R. M., PATEL, J., AND MARANGOS, P. J.: Differential mediation of the anticonvulsant effects of carbamazepine and diazepam. Life Sci. **36:** 2413–2419, 1985.

WEISSMAN, B. A., COTT, J., HOMMER, D., PAUL, S., AND SKOLNICK, P.: Electrophysiological and pharmacological actions of the convulsant benzodiazepine Ro 5–4864. Eur. J. Pharmacol. **97:** 257–263, 1984.

WEISSMAN, B. A., COTT, J., JACKSON, J. A., BOLGER, G. T., WEBER, K. H., HORST, W. D., PAUL, S. M., AND SKOLNICK, P.: "Peripheral-type" binding sites for benzodiazepines in brain: relationship to the convulsant actions of Ro 5–4864. J. Neurochem. **44:** 1494–1499, 1985a.

WEISSMAN, B. A., COTT, J., PAUL, S. M., AND SKOLNICK, P.: Ro 5–4864: a potent benzodiazepine convulsant. Eur. J. Pharmacol. **90:** 149–150, 1983.

WEISSMAN, B. A., COTT, J., WEBER, K. H., AND SKOLNICK, P.: Are "peripheral-type" binding sites for benzodiazepines in brain related to the convulsant actions of Ro 5–4864? Prog. Clin. Biol. Res. **192:** 197–203, 1985b.

WEIZMAN, A., TANNE, Z., KARP, L., MARTFELD, Y., TYANO, S., AND GAVISH, M.: Carbamazepine up-regulates the binding of [^{3}H]PK 11195 to plateletes of epileptic patients. Eur. J. Pharmacol. **141:** 471–474, 1987.

WERZ, M. A., AND MACDONALD, R. L.: Barbiturates decrease voltage-dependent calcium conductance of mouse neurons in dissociated cell culture. Mol. Pharmacol. **28:** 269–277, 1985.

WHEATLEY, P. L., AND MILLER, A. A.: Effects of lamotrigine on electrically induced afterdischarge duration in anaesthetised rat, dog and marmoset. Epilepsia **30:** 34–40, 1989.

WHITTLE, S. R., AND TURNER, A. J.: Effects of the anticonvulsant sodium valproate on γ-aminobutyrate and aldehyde metabolism in ox brain. J. Neurochem. **31:** 1453–1459, 1978.

WILDER, B. J., AND RANGEL, R. J.: Phenytoin. Clinical use. *In* Antiepileptic Drugs, 3rd ed., ed, by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 233–239, Raven Press, New York, 1989.

WILENSKY, A. J., AND FRIEL, P. N.: Benzodiazepines. Clorazepate. *In* Antiepileptic Drugs, 3rd ed., R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 805–820, Raven Press, New York, 1989.

WILENSKY, A. J., FRIEL, P. N., OJEMANN, L. M., DODRILL, C. B., MCCORMICK, K. B., AND LEVY, R. H.: Zonisamide in epilepsy: a pilot study. Epilepsia **26:** 212–220, 1985.

WILENSKY, A. J., FRIEL, P. N., OJEMANN, L. M., KUPFERBERG, H. K., AND LEVY, R. H.: Pharmacokinetics of W-554 (ADD 03055) in epileptic patients. Epilepsia **26:** 602–606, 1986.

WILENSKY, A. J., OJEMANN, L. M., CHMELIR, T., MARGUL, B. L., AND DOOSE, D. R.: Topiramate pharmacokinetics in epileptic patients receiving carbamazepine. Epilepsia **30:** 645, 1989.

WILLETTS, J., AND BALSTER, R. L.: The discriminitive stimulus effects of *N*-methyl-D-aspartate antagonists in phencyclidine-trained rats. Neuropharmacology **27:** 1249–1256, 1988.

WILLIAMS, K., ROMANO, C., AND MOLINOFF, P. B.: Effects of polyamines on the binding of [^{3}H]MK-801 to the *N*-methyl-D-aspartate receptor: pharmacological evidence for the existence of a polyamine recognition site. Mol. Pharmacol. **36:** 575–581, 1989a.

WILLIAMS, K., ROMANO, C., AND MOLINOFF, P. B.: Effects of polyamines on the binding of [^{3}H]MK-801 to the NMDA receptor: agonist and antagonist effects at a putative polyamine recognition site. Soc. Neurosci. Abst. **15:** 201, 1989b.

WILLIAMS, M.: Adenosine antagonists. Med. Res. Rev. **9:** 219–243, 1989.

WILLOW, M., AND CATTERALL, W. A.: Inhibition of binding of [^{3}H]batrachotoxinin A 20-α-benzoate to sodium channels by the anticonvulsant drugs diphenylhydantoin and carbamazepine. Mol. Pharmacol. **22:** 627–635, 1982.

WILLOW, M., GONOI, T., AND CATTERALL, W. A.: Voltage clamp analysis of the inhibitory actions of diphenylhydantoin and carbamazepine on voltage-sensitive sodium channels in neuroblastoma cells. Mol. Pharmacol. **27:** 549–558, 1985.

WILLOW, M., KUENZEL, E. A., AND CATTERALL, W. A.: Inhibition of voltage-sensitive sodium channels in neuroblastoma cells and synaptosomes by the anticonvulsant drugs diphenylhydantoin and carbamazepine. Mol. Pharmacol. **25:** 228–234, 1984.

WILSON, M. A., AND GALLAGER, D. W.: GABAergic subsensitivity of dorsal raphe neurons in vitro after chronic benzodiazepine treatment in vivo. Brain Res. **473:** 198–202, 1988.

WILSON, T. C. M., MACHULSKIS, G. E., GARSKE, G. E., AND HARRIS, E. W.: Anticonvulsant concentrations in CSF and serum of rats protected against MES by PR934–423A. Soc. Neurosci. Abst. **14:** 1034, 1988.

WOLF, P., AND HAAS, H. L.: Effects of diazepines and barbiturates on hippocampal recurrent inhibition. Naunyn-Schmiedeberg's Arch. Pharmacol. **229:** 211–218, 1977.

WONG, B. Y., COULTER, D. A., CHOI, D. W., AND PRINCE, D. A.: Dextrorphan and dextromethorphan, common antitussives, are antiepileptic and antagonize *N*-methyl-D-aspartate in brain slices. Neurosci. Lett. **85:** 261–266, 1988a.

WONG, E. H. F., KEMP, J. A., PRIESTLEY, T., KNIGHT, A. R., WOODRUFF, G. N., AND IVERSEN, L. L.: The anticonvulsant MK-801 is a potent *N*-methyl-D-aspartate antagonist. Proc. Natl. Acad. Sci. USA **83:** 7104–7108, 1986.

WONG, E. H. F., KNIGHT, A. R., AND WOODRUFF, G. N.: [^{3}H]MK-801 labels a site on the *N*-methyl-D-aspartate receptor channel complex in rat brain membranes. J. Neurochem. **50:** 274–281, 1988b.

WONG, E. H. F., LEEB-LUNDBERG, L. M. F., TEICHBERG, V. I., AND OLSEN, R. W.: γ-Aminobutyric acid activation of $^{36}Cl^-$ flux in rat hippocampal slices and its potentiation by barbiturates. Brain Res. **303:** 267–275, 1984.

WONG, W.-S., AND RAHWAN, R. G.: Examination of the potential antiepileptic activity of calcium antagonists with different sites of action. Gen. Pharmacol. **20:** 309–312, 1989.

WOODBURY, D. M.: Phenytoin. Absorption, distribution, and excretion. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 177–195, Raven Press, New York, 1989.

WOODBURY, D. M., AND KEMP, J. W.: Other antiepileptic drugs. Sulfonamides and derivatives: acetazolamide. *In* Antiepileptic Drugs, 3rd ed., ed. by R. Levy, R. Mattson, B. Meldrum, J. K. Penry, and F. E. Dreifuss, pp. 855–875, Raven Press, New York, 1989.

WORLEY, P. F., AND BARABAN, J. M.: Site of anticonvulsant action on sodium channels: autoradiographic and electrophysiological studies in rat brain. Proc. Natl. Acad. Sci. USA **84:** 3051–3055, 1987.

WORMS, P., DEPOORTERE, H., DURAND, A., MORSELLI, P. L., LLOYD, K. G., AND BARTHOLINI, G.: γ-Aminobutyric acid (GABA) receptor stimulation. I. Neuropharmacological profiles of progabide (SL 76002) and SL 75102, with emphasis on their anticonvulsant spectrum. J. Pharmacol. Exp. Ther. **220:** 660–671, 1982.

YAARI, Y., AND CARBONE, E.: Phenytoin reduces the number of Na channel openings in outside-out patches of avian sensory neurons. Pfluegers Arch. Eur. J. Physiol. **405** (suppl. 2): R47, 1985.

YAARI, Y., HAMON, B., AND LUX, H. D.: Development of two types of calcium channels in cultured mammalian hippocampal neurons. Science (Wash. DC) **235:** 680–682, 1987.

YAARI, Y., PINCUS, J. H., AND ARGOV, Z.: Phenytoin and transmitter release at the neuromuscular junction of the frog. Brain Res. **160:** 479–487, 1979.

YAARI, Y., SELZER, M. E., AND PINCUS, J. H.: Phenytoin: mechanisms of its anticonvulsant action. Ann. Neurol. **20:** 171–184, 1986.

YANG, J., AND OLSEN, R. W.: γ-Aminobutyric acid receptor regulated $^{36}Cl^-$ flux in mouse cortical slices. J. Pharmacol. Exp. Ther. **241:** 677–685, 1987a.

YANG, J. S. J., AND OLSEN, R. W.: γ-Aminobutyric acid receptor binding in fresh mouse brain membranes at 22°C: ligand-induced changes in affinity. Mol. Pharmacol. **32:** 266–277, 1987b.

YATANI, A., HAMILTON, S. L., AND BROWN, A. M.: Diphenylhydantoin blocks cardiac calcium channels and binds to the dihydropyridine receptor. Circ. Res. **59:** 356–361, 1986.

YEUNG, S. M. H, AND GREEN, R. D.: Agonist and antagonist affinities for inhibitory adenosine receptors are reciprocally affected by 5′-guanylylimidodiphosphate or *N*-ethylmaleimide. J. Biol. Chem. **258:** 2334–2339, 1983.

YOUNG, N. A., LEWIS, S. J., HARRIS, Q. L., JARROTT, B., AND VAJDA, F. J.:

Differences in the development of tolerance to two anticonvulsant benzodiazepines in the amygdaloid kindled rat. J. Pharm. Pharmacol. **40:** 365–367, 1988.

YOUNG, N. A., LEWIS, S. J., VAJDA, F. J. E., AND BEART, P. M.: Effects of the NMDA receptor antagonist MK-801 against amygdaloid-kindled seizures in the rat. Exp. Neurol. **103:** 199–202, 1989.

YU, O., CHIU, T. H., AND ROSENBERG, H. C.: Modulation of GABA-gated chloride ion flux in rat brain by acute and chronic benzodiazepine administration. J. Pharmacol. Exp. Ther. **246:** 107–113, 1988.

ZBICZ, K. L, AND WILSON, W. A.: Barbiturate enhancement of spike frequency adaptation in *Aplysia* giant neurons. J. Pharmacol. Exp. Ther. **217:** 222–227, 1981.

ZIVKOVIC, B., PERRAULT, G., MOREL, E., AND SANGER, D. J.: Differential neuropsychopharmacological profiles of PCP-like and ifenprodil-like NMDA antagonists. Soc. Neurosci. Abst. **15:** 200, 1989.

ZONA, C., TANCREDI, V., PALMA, E., PIRRONE, G. C., AND AVOLI, M.: Potassium currents in rat cortical neurons in culture are enhanced by the antiepileptic drug carbamazepine. Can. J. Physiol. Pharmacol. **68:** 545–547, 1990.

ZWILLICH, C. W., SUTTON, F. D., NEFF, T. A., COH, W. M., MATTAY, R. A., AND WEINBERGER, M. M.: Theophylline-induced seizures in adults. Ann. Intern. Med. **82:** 784–787, 1975.