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Epilepsy

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1. INTRODUCTION

In the early 1950s, Hayashai reported that clonic convulsions can be induced in dogs, monkeys and man by infusion of glutamate into the grey matter of the motor cortex *(43)*. Decades later, with the advent of brain slice recording, it was possible to show that the selective glutamate receptor agonist N-methyl-D-aspartate (NMDA) induces a pattern of burst firing in neurons reminiscent of the paroxysmal depolarization shift recorded in the epileptic brain *(99)*. Building on these pioneering studies, there has been a steady accumulation of evidence that the neurotransmitter glutamate plays a key role in the pathophysiology of seizures. At the same time, empirical evidence has mounted demonstrating the effectiveness of ionotropic glutamate receptor antagonists in protecting against various types of seizures in animal models. As a group, glutamate receptor antagonists have come to be recognized as powerful and broadly acting anticonvulsants, rivaling GABA modulators and sodium channel blockers in their ability to protect against seizures *(110)*. This has engendered optimism that glutamate receptor antagonists would have a role in epilepsy therapy. However, the development of glutamate receptor antagonists as clinically useful antiepileptic drugs has been more challenging than anticipated. No drug designed specifically as a glutamate receptor antagonist has, as yet, been approved for marketing. Nevertheless, there is reason for continued optimism. Understanding of the molecular physiology and pharmacology of glutamate receptors is increasing at an unprecedented rate as a result of the application of powerful new approaches in molecular biology and proteomics. Equally important, medicinal chemists continue to supply a steady stream of chemical compounds that allow more selective targeting of receptor subtypes

and provide novel approaches to modulating receptor function. This chapter provides an overview of preclinical research on ionotropic glutamate receptor antagonists and modulators in animal models of epilepsy. Where available, information is also provided on the clinical efficacy and side effect profiles of those agents that have advanced to human clinical trials.

1.1. Overview of Epilepsy

Epilepsy is a chronic brain disorder characterized by recurrent spontaneous seizures. Approximately 0.5 to 0.7% of the population is affected worldwide, making epilepsy one of the most common neurological disorders and a major international health problem *(14)*. Epileptic seizures are paroxysmal disturbances in the functioning of cortical systems caused by the abnormal synchronous firing of neurons. Seizures may be generalized, originating in both hemispheres simultaneously, or partial, originating in a part of one hemisphere, most commonly the temporal lobe. Partial seizures (sometimes also referred to as focal or localization-related seizures) are further subdivided into simple partial, complex partial, and partial seizures with secondary generalization, while generalized seizures are categorized into absence, myoclonic, clonic, tonic, tonic-clonic, and atonic seizures. Roughly 60% of all patients with epilepsy have partial seizures, while the remaining 40% have generalized seizures. In addition to characterizing patients with epilepsy according to the seizure types they experience, in some cases the specific disorder in an individual patient with epilepsy can be classified into one of more than 40 distinct syndromes *(14)*. This syndromic classification takes into account not only the seizure types but also the age of onset, response to treatment, EEG features, prognosis, and in some cases the underlying etiology. An epilepsy syndrome is either idiopathic, which invariably indicates a genetic basis, or symptomatic, which by definition is due to a structural lesion or an identifiable metabolic derangement. For many of the seizure types and epilepsy syndromes we have little information about their underlying cause. However, in recent years several rare epilepsy syndromes have been linked to mutations in genes encoding voltage- or ligand-gated ion channels, including potassium, sodium and calcium channels and $GABA_A$ receptors *(6,108)*. Drug treatments for epilepsy are invariably developed in clinical studies with patients who experience the most common types of seizures that are intractable to medications; these are largely complex and simple partial seizures. Although it would be desirable to have information on the utility of new anticonvulsant drugs in other seizure types (and also on the ability of the drugs to prevent the development or progression of epilepsy), it is generally not practical to obtain these data in the pharmaceutical company-sponsored clinical trials required by regulatory authorities for new drug registration.

1.2. Epilepsy Therapy

In the absence of a specific etiological understanding in most forms of epilepsy, approaches to drug therapy must necessarily be directed at the control of symptoms, i.e., the suppression of seizures. Chronic administration of antiepileptic drugs is the treatment modality of first choice. The selection of an antiepileptic drug is based primarily on its efficacy for the specific types of seizures exhibited by the patient. Table 1 gives the efficacies of many of the commonly used antiepileptic drugs. The goal of therapy is to keep the patient free of seizures without interfering with normal brain function or producing other untoward effects and adversely affecting the patient's quality of life. In most patients with epilepsy the prognosis for seizure control is very good. However, a significant proportion (about 20-30%) of individuals with epilepsy suffer from intractable seizures that are resistant to currently available antiepileptic drugs. Thus, there is a clear need for new drugs or other treatment approaches. Furthermore, there is increasing evidence that none of the currently available anticonvulsant medications is capable of preventing epilepsy, for example after brain injury, or affecting its often progressive course *(58)*. Thus, another important goal for the future will be to develop drugs that not only provide symptomatic relief but also prevent or cure the disorder.

1.3. Rationale for Use of Ionotropic Glutamate Receptor Antagonists and Modulators in Epilepsy Therapy

The excitatory amino acid glutamate participates in normal synaptic transmission throughout the central nervous system (CNS), and there is ample evidence that exaggerated activity of glutamatergic neurotransmission may contribute to epileptic phenomena *(12,97,106,107)*. As a general rule, blocking glutamate-mediated excitatory neurotransmission effectively protects against seizures in both *in vitro* and *in vivo* models of epilepsy. Consequently, over the last two decades there has been intense interest in the potential role of gluta-

mate receptor antagonists in epilepsy therapy *(58,70,97,106, 107)*. Initially, most attention was focused on NMDA receptors, largely because of the availability of selective antagonists for these receptors. As agents specifically targeting AMPA and kainate receptors have become available, there has been a shift in interest to these non-NMDA receptors. However, to date, no specific glutamate receptor antagonist has been introduced into clinical practice. Nevertheless, certain approved anticonvulsant drugs (most notably felbamate) do seem to interact with glutamate receptors and this action could contribute to their ability to protect against seizures.

2. ANTICONVULSANT AND ANTIEPILEPTOGENIC EFFECTS OF IONOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS AND MODULATORS IN ANIMAL MODELS

A great variety of animal models are used in epilepsy research, but only some of these play a practical role in the development of new antiepileptic drugs *(69,70)*. The most commonly employed animal models in the search for new anticonvulsant drugs are the maximal electroshock seizure (MES) test and the pentylenetetrazole (PTZ) seizure test *(69)*. The MES test assesses the ability of a drug to inhibit tonic hindlimb extension induced by bilateral corneal or transauricular electrical stimulation in mice or rats and is thought to be predictive of drug efficacy in preventing generalized tonic-clonic and partial seizures. In contrast, in the PTZ test, drugs are examined for their protective actitivity against generalized myoclonic and clonic seizures induced by systemic (usually s.c.) administration of convulsant doses of PTZ. The PTZ test was formerly thought to represent a model of generalized absence and/or myoclonic seizures in humans *(69)*, but it is now recognized that lack of activity in the PTZ test does not necessarily predict clinical ineffectiveness in these seizure types (Table 1). Nevertheless, the PTZ test still represents an important screen, providing additional information that complements the MES test and can highlight a drug's unique profile. Kindling models are gaining greater acceptance in the identification of antiepileptic drugs and may allow for the recognition of agents that are not detected in the classical screens. For instance, while the new antiepileptic drugs vigabatrin, tiagabine, and levetiracetam are not active in the MES test, they block fully kindled seizures in the amygdala-kindling model, substantiating that this model correctly predicts drug efficacy against partial seizures (Table 1). Whereas the MES and

Table 1. Comparison of the effects of iontropic glumate receptor antagonists with clincally established antiepileptic drugs in different animals seizure models and in human epilepsy. += effective; ± = weak or variable effect; NE = not effective; ? = possible activity. Blanks indicate no data available. MES, maximum electroshock seizure test; PTZ, pentylentetrazol test. For references, see Loscher (58) and text.

Drug	Anticonvulsant activity in experimental models			Clinical efficacy			
	MES test (mice or rats, generalized tonic seizures)	PTZ test (mice or rats, generalized clonic seizures)	Amygdala-kindling (rats, partial seizures)	Partial Seizures	Generalized seizures		
					Tonic-clonic	Absence	Myoclonic
Clinically Established Antiepileptic Drugs							
Carbamazepine	+	NE	+	+	+	NE	NE
Phenytoin	+	NE	±	+	+	NE	NE
Phenobarbital	+	+	+	+	+	NE	±
Primidone	+	+	+	+	+	NE	±
Valproate	+	+	+	+	+	+	+
Benzodiazepines	±	+	+	+	+	+	+
Ethosuximide	NE	+	NE	NE	NE	+	±
Lamotrigine	+	NE	+	+	+	+	+
Topiramate	+	NE	+	+	+	+	+
Oxcarbazepine	+	±	+	+	+	NE	NE
Felbamate	NE	+	±	+	+	±	+
Vigabatrin	NE	+	+	+	±	NE	NE
Tiagabine	±	+	+	+	?	?	NE
Gabapentin	±	+	+	+	+	NE	NE
Levetiracetam	NE	NE	+	+	+	±	±
Zonisamide	+	±	+	+	+	+	+
Ionotropic Glutamate Receptor Antagonists							
NMDA	+	±	NE	NE	NE		NE
AMPA	+	+	+	?			NE
Kainate	+		+				+

dicts drug efficacy against partial seizures (Table 1). Whereas the MES and

PTZ tests are performed in normal, nonepileptic mice or rats, so that these tests are models for acute seizures rather than for chronic epilepsy, in the kindling model there are chronic alterations in brain function that are thought to be similar to the processes involved in human temporal lobe epilepsy, the most common form of drug refractory epilepsy *(60,114)*. Apart from using fully kindled rats for testing of anticonvulsant drug effects, this model can be used to evaluate antiepileptogenic drug effects by treating the animals during kindling development *(114)*. In addition to the kindling model of temporal lobe epilepsy, there is increasing use of models in epilepsy research in which rats are made epileptic by inducing status epilepticus through chemical (e.g., kainate, pilocarpine) or electrical means *(60)*. In such models, the status epilepticus is followed by a latent ("silent") period, after which the animals develop spontaneous recurrent seizures. However, because monitoring spontaneous seizures is laborious and time-consuming, such models are only rarely used in the preclinical evaluation of new antiepileptic drugs.

In the following, we review the effects of different categories of ionotropic glutamate receptor antagonists and modulators in animal seizure and epilepsy models with emphasis on the MES, PTZ, and kindling models. Available information for drugs acting on NMDA, AMPA and kainate receptors is provided. Table 1 summarizes the actions of these various antagonists in the animal models and provides comparative information for presently marketed antiepileptic drugs along with their efficacies in different clinical seizure types.

2.1. Drugs Acting on NMDA Receptors

The functional activity of NMDA receptors can be inhibited by drugs that act at a diversity of sites on the NMDA receptor-channel complex (Figure 1). NMDA receptor antagonists have a broad spectrum of anticonvulsant activity in animal seizure models. They are particularly potent in blocking tonic seizures, such those occurring in the MES test and after administration of chemical convulsants, and are also highly effective in protecting against reflex seizures in genetic epilepsy models *(106,107)*. NMDA antagonists have lower potency against clonic and myoclonic seizures, such as in the PTZ test, and against focal seizures in the kindling model *(59)*. A particularly interesting feature of NMDA antagonists is their powerful ability to retard kindling development. This has been interpreted as indicating that NMDA antagonists have antiepileptogenic activity; that is, they may prevent the development or pro-
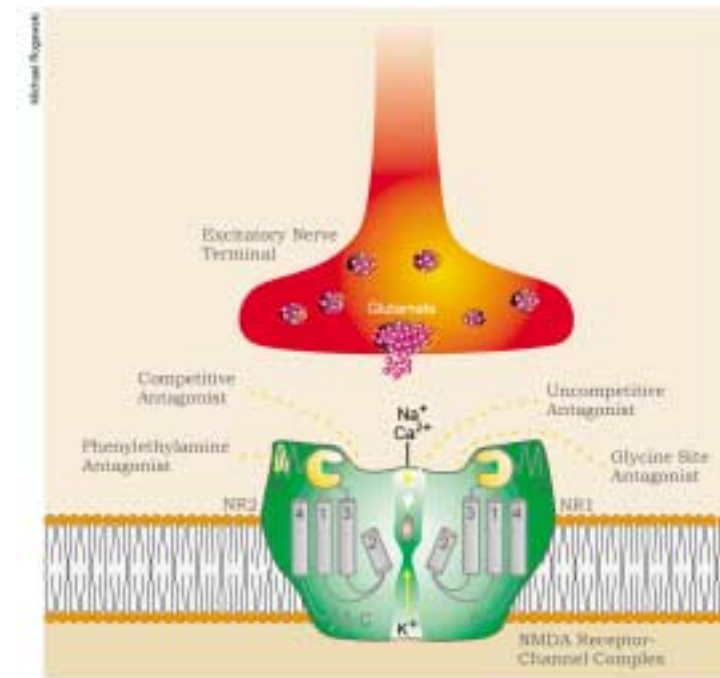
Fig. 1. Schematic illustration of an NMDA receptor at an excitatory synapse showing the various sites at which antagonists can inhibit the receptor's functional activity. NMDA receptors are heterotetrameric cation channels composed of various NR1 (8 splice variants) and NR2 (NR2A-D) subunits; only two subunits are illustrated here. Cylinders represent probable a-helical membrane segments. Glutamate released from excitatory nerve nerminals binds to a recognition site (*deep yellow, left*) on NR2 subunits formed by the subunit's extracellular N-terminal region (substrate binding domain S1) and loop between transmembrane segments 3 and 4 (substrate binding domain S2), causing gating of the channel that permits ion flux. Agonist occupation of the glycine site in a corresponding region of the NR1 subunit (*deep yellow, right*) is required for gating. Channel function is blocked in the presence of competitive glutamate recognition site or glycine site antagonists. Uncompetitive (channel blocking) antagonists such as Mg^{2+}, PCP, ketamine, MK-801 plug the pore (and ion selectivity filter) of the NMDA receptor which is formed by the second intramembrane loops from both the NR1 and NR2 subunits. Phenylethylamine antagonists (such as ifenprodil) have complex actions on NMDA receptors and interact with both NR1 and NR2 subunits although their block is selective for NMDA receptors containing the NR2B subunit. The subunit specific action may involve a LIVBP-like region (*light yellow*), homologous to the bacterial leucine/isoleucine/valine binding protein.

gression of a tendency toward recurrent focal or secondarily generalized seizures *(107)*. Although the initial enthusiasm from preclinical evaluation of NMDA antagonists in models of seizures or epilepsy has been dampened by increasing awareness of the various toxicities of these compounds and the failure of key clinical trials, the development of new types of NMDA receptor antagonists and modulators, such as low-affinity channel blocking (uncompetitive) NMDA antagonists, glycine-site ligands, and NMDA receptor subtype selective drugs, has maintained interest in the NMDA receptor as a target for anticonvulsant drug development *(106,107,109)*.

Activation of NMDA receptors requires the presence of agonist at both the glutamate and glycine coagonist recognition sites. The natural agonist at the glutamate site is presumed to be the neurotransmitter glutamate whereas either glycine or D-serine can serve as agonists for the higher affinity glycine recognition site *(85)*. Drugs acting at either of these recognition sites can antagonize the functional activity of NMDA receptors. In addition to the glutamate and glycine agonist recognition sites, the NMDA receptor complex has several modulatory sites that can serve as potential drug targets *(97,104,106)*. Furthermore, NMDA receptors exist in multiple forms with distinct physiological and pharmacological properties that are differentially distributed in the CNS *(97)*. The existence of these various forms provide opportunities for selective targeting which may theoretically allow the desired anticonvulsant or antiepileptogenic effects to be achieved while avoiding side effects. Two major NMDA receptor subunit families, designated NR1 and NR2 (or, more recently, GLU_{N1} and GLU_{N2}), have been cloned. Functional receptors are thought to be tetrameric complexes formed by combinations of an obligatory NR1 subunit, which exists in 8 alternatively spliced forms, and one of four NR2 subunits designated NR2A, NR2B, NR2C and NR2D. The glycine and glutamate recognition sites are present on the NR1 and NR2 subunits, respectively *(97)*. In the following, the different categories of NMDA receptor antagonists and modulators will be critically discussed with respect to their potential as anticonvulsant drug targets.

2.1.1. Competitive NMDA Recognition Site Antagonists

In 1982, Brian Meldrum's group reported that selective competitive NMDA recognition site antagonists such as 2-amino-5-phosphonopentanoic acid (AP-5) or 2-amino-7-phosphonoheptanoic acid (AP-7) suppress sound-induced clonic and tonic seizures in DBA/2 mice and PTZ-induced clonic seizures in Swiss mice, thus defining NMDA receptor antagonists as a new class of anticonvulsant agent *(22)*. This important observation stimulated an intensive research effort into the medicinal chemistry of competitive NMDA receptor antagonists *(106)*. The original compounds tested by Croucher et al. *(22)* are very polar and as a consequence have poor brain penetration and lack oral bioavailability. These disadvantages were overcome by the subsequent identification of several orally active competitive NMDA antagonists, including CGS 19755 (Selfotel), CPP, the unsaturated CPP analogue D-CPPene, the unsaturated AP-5 analogue CGP 37849 and its carboxyethylester analog CGP 39551, and CGP 40116, the biologically active (R)-enantiomer of CGP 37849. These compounds were shown to exhibit a broad spectrum of anticonvulsant activity in chemical, electrical and genetic animal models of generalized seizures *(70,107)*. While most authors observed a separation between anticonvulsant and motor impairing effects, this was not invariably the case *(71)*. Typically, the effect against tonic seizures in the MES test was more marked than against clonic seizures in the PTZ test. However, one AP-7-related competitive NMDA antagonist GPI-3000 (NPC 17742) has been reported to have relatively greater activity in the PTZ model than in the MES test *(31)*. In contrast to the anticonvulsant efficacy of competitive NMDA antagonists in rodent models of generalized seizures, experiments in amygdala-kindled rats showed that these drugs were relatively ineffective at protecting against focal seizures in this model of complex partial seizures, particularly when compared with clinically established antiepileptic drugs *(59, 63,64,71,73,136)*. Löscher and Hönack *(63,64)* therefore predicted in 1991 that competitive NMDA antagonists would not be clinically useful in the treatment of partial seizures. Furthermore, some of the competitive NMDA antagonists, including CGP 37849 and D-CPPene, exhibited phencyclidine (PCP)-like neurobehavioral effects (hyperactivity, stereotypies) in kindled rats at lower doses than in nonkindled rats *(59,62,135)*. With several competitive NMDA antagonists motor impairment in kindled rats was much more severe than in nonkindled animals. In fact, in the kindled animals, the competitive antagonists exhibited a spectrum of side effects like the more behaviorally toxic uncompetitive NMDA receptor antagonists such as PCP *(59; see section 2.1.2.)*. These observations suggested that limbic epileptogenesis might render the brain more susceptible to PCP-like adverse effects of competitive NMDA antagonists. Because PCP-like behavioral effects in rodents are thought to

model the psychotomimetic and reinforcing effects of PCP (an uncompetitive NMDA antagonist discussed in section 2.1.2.) and related dissociative anesthetic-like drugs in humans, Löscher and Hönack *(64)* predicted that competitive NMDA antagonists had a risk of producing significant adverse neurobehavioral effects, particularly if these drugs are used in patients with complex partial seizures. This prediction was subsequently confirmed by clinical trials (see section 3). Competitive NMDA antagonists have been reported to enhance dopamine release and turnover in some but not all studies *(74,103)*. Therefore, one possible explanation for the more marked PCP-like adverse effects of competitive NMDA antagonists in kindled rats is that these drugs may further augment the hyperdopaminergic state present in kindled animals *(1)*.

In contrast to the lack of anticonvulsant efficacy of competitive NMDA antagonists against focal seizures in the kindling model, some groups reported that these drugs reduce the severity of secondarily generalized (motor) seizures in this model *(59)*. However, motor impairment was seen at doses similar to those that affected motor seizures, suggesting that the effect on motor seizures could be due to muscle relaxation *(17)*. The ability of different categories of centrally active antagonists of the NMDA receptor-channel complex to cause disturbances of motor coordination correlate directly with their ability to antagonize the receptor complex *in vivo*, irrespective of the blocking mechanism (competitive, uncompetitive or glycine site antagonist) *(16)*.

Since the first clinical trials of newly developed anticonvulsants are usually add-on studies in patients with difficult-to-treat partial seizures, the anticonvulsant and adverse effect profiles of combination therapy with NMDA antagonists and commonly used antiepileptic drugs were evaluated in kindled rats. The competitive antagonist CGP 37849 synergistically increased the anticonvulsant effect of valproate on focal seizures but at the same time induced a marked increase in adverse effects so that the therapeutic index of the combination was lower than that of equieffective doses of valproate alone *(66)*. Interestingly, nonkindled rats were much less sensitive to potentiation of adverse effects by combined treatment with valproate and NMDA antagonists than kindled rats, again demonstrating the altered susceptibility to NMDA antagonists induced by kindling *(59)*. These data indicated that add-on treatment of epileptic patients with a competitive NMDA antagonist might decrease the tolerability of the standard medication.

Until recently, it was not appreciated that competitive NMDA recognition

site antagonists may exhibit differing activities at NMDA receptors composed of different subunit combinations, but the information now available indicates that this is the case *(107)*. Therefore, it may be possible to more selectively target specific NMDA receptor subunit combinations, thus potentially providing for the development of less toxic anticonvulsants (see section 2.1.4. below).

2.1.2. Channel-blocking (Uncompetitive) NMDA Receptor Antagonists

NMDA receptor channel blockers interfere with the functional activity of NMDA receptors (i.e., their ability to cause neuronal excitation) by occupying a site within the ionophore of the NMDA receptor-channel complex, thereby preventing cation flux through the channel. NMDA receptor channel blockers are often referred to as "uncompetitive" antagonists, because their binding and blocking action requires the receptor-channel to be gated in the open state. Unlike competitive NMDA recognition site antagonists, uncompetitive antagonists share with other noncompetitive antagonists of the NMDA receptor the theoretical advantage that their blocking action would not be overcome by high synaptic levels of glutamate as may occur during seizures. In addition, uncompetitive antagonists have the additional theoretical advantage of use-dependence, implying that their inhibitory action may specifically be potentiated at sites of excessive receptor activation *(105,107)*.

Channel-blocking NMDA receptor antagonists fall into two broad categories: dissociative anesthetic-like agents (e.g., PCP, ketamine, tiletamine, and MK-801 [dizocilpine]) and low-affinity antagonists *(104,105)*. In animals, dissociative anesthetics at low doses cause hyperlocomotion, stereotypies and ataxia; at higher anesthetic doses they induce a state of immobility, analgesia, and amnesia. In humans, these agents produce a variety of psychotropic effects at subanesthetic doses, including hallucinations and "dissociation" which refers to a perception of being separated from one's body. Thus, while PCP was originally developed as an anesthetic in the 1950s, it was later abandoned because it frequently induced a state of postoperative delirium. These effects are much less frequent with ketamine, which was introduced in the 1960s and is still in limited use, mainly in children. Nevertheless, ketamine is well recognized to produce a psychosis-like state with some features of schizophrenia. Shortly after their development, PCP and ketamine were shown to exert anticonvulsant effects at doses much below those used in anesthesia, but the glutamate antagonistic action of these drugs was not recognized until the

early 1980s *(104,107)*. Because of their powerful psychotomimetic effects, these drugs were never seriously considered as candidates for clinical trials in the chronic treatment of epilepsy. However, in contrast to PCP and ketamine, MK-801 – which acts in a similar fashion as a channel blocking NMDA receptor antagonist but is far more potent – did undergo clinical evaluation *(125)* (see below). Like competitive NMDA antagonists, MK-801 has a broad spectrum of anticonvulsant activity in animal models of generalized seizures, but no significant effects on focal seizures in the kindling model *(59)*. In animals MK-801 has substantial behavioral toxicity and at high doses induces dissociative anesthesia similar to that seen with ketamine *(70,72)*. Also, as with competitive antagonists, the therapeutic index of valproate was considerably reduced by coadministration with MK-801 in kindled rats *(28)*. In human volunteers, low i.v. doses of MK-801 (0.5–2.5 mg/kg) were well tolerated, but a high proportion of subjects receiving a 5 mg/kg dose reported perioral numbness, lightheadedness and headache, and some experienced abnormal sensations and gait disturbance (Merck, unpublished). The mean peak serum concentration associated with the 5 mg/kg dose was 520 pg/ml (=1.5 nM), which is near the K_i for binding to NMDA receptors (e.g., 2.6 nM) *(95)*. There was also a significant increase in blood pressure associated with serum concentrations >0.875 ng/ml; a similar hypertensive effect occurs in animals *(56)*. Results in a clinical efficacy trial of MK-801 are discussed in section 3.1.

An interesting feature of NMDA antagonists, including channel blockers such as MK-801, is their powerful inhibitory effect on kindling development, indicating that NMDA receptors are critically involved in the processes leading to kindling *(106,107)*. Furthermore, these drugs inhibit seizure-induced brain damage in several animal models. However, it is an open question whether such "excitotoxic" brain damage is the cause of spontaneous recurrent seizures (i.e., whether it represents a basis of epileptogeneis). To address this important issue, MK-801 was administered to rats after kainate-induced status epilepticus, but before the development of spontaneous recurrent seizures (i.e., within the latent period) *(29)*. Remarkably, the massive sclerosis in the hippocampus and piriform cortex that occurs following such seizures could be prevented by MK-801, probably because the sclerosis is due to delayed cell death resulting from activation of NMDA receptors by glutamate released during the seizures. However, despite this neuroprotective effect of MK-801, all rats developed spontaneous recurrent seizures, indicating that damage in limbic brain regions is not the main reason for limbic epileptogenesis.

Dissociative anesthetic-like agents such as PCP or MK-801 with high neurobehavioral toxicity typically have high affinity for NMDA receptors (<100 nM) *(105)*. In recent years, a variety of structurally diverse channel-blocking (uncompetitive) NMDA receptor antagonists have been identified with substantially lower behavioral toxicity. These better tolerated antagonists, which include memantine, dextrorphan, dextromethorphan, remacemide, and ADCI the carboxamide analog of MK-801 protect against seizures in animals at doses below those inducing motor impairment *(59,105-107,109)*. All of these compounds exhibit lower affinity (>500 nM) for NMDA receptors than do PCP and MK-801. For certain of these low-affinity antagonists (e.g., dextromethorphan, remacemide, memantine), the low animal behavioral toxicity is confirmed by human clinical experience documenting an acceptable level of safety. The basis for the reduced toxicity of the low-affinity antagonists is not known with certainty. However, it has been proposed that channel-level kinetic factors (i.e., the speed at which block develops and recovers) are important *(105,109)*. For drug concentrations producing equivalent levels of channel block, lower affinity antagonists exhibit faster rates of block and unblock, which may allow the level of block to adjust in a more dynamic fashion (since block can be relieved in a voltage-dependent fashion by synaptic depolarization). However, reduced binding affinity at NMDA receptors alone cannot completely explain the lower toxicity since there is an imperfect correlation between binding affinity and margin of safety *(109)*. Moreover, the dissociative anesthetic ketamine has a binding affinity comparable to many of the less toxic channel-blocking agents. Thus, factors in addition to binding affinity account for the improved tolerability of some of the low-affinity uncompetitive NMDA receptor antagonists *(109)*. One potentially important factor is the extent to which the rates of block and unblock and the magnitude of steady-state block are influenced by the degree of agonist (glutamate) activation of the receptor. This factor is critical since the extent of receptor activation may be dramatically different during normal behavior and during seizures where synaptic glutamate levels are likely to be much higher. The simple relationship between binding affinity and rate of block discussed above applies only if the blocking drug does not affect channel gating. However, it has recently been shown that channel blocking NMDA antagonists can affect the gating properties of the receptor-channel complex *(24)*. In fact, the extent of block of some low affinity antagonists, including memantine, may be

strongly dependent upon the glutamate concentration, which determines the degree of channel gating *(19)*. Additional factors that may be important in determining the behavioral toxicity of a particular channel blocking NMDA antagonist include subunit selectivity (antagonists that exhibit high affinity for NMDA receptors containing the NR2A subunit seem to exhibit higher toxicity) and synergistic effects produced by additional actions at receptor targets apart from NMDA receptors (inhibitory actions on voltage-dependent sodium channels, for example, may enhance efficacy without substantially increasing toxicity) *(109)*. The recognition that there can be large differences in the neurobehavioral toxicity of channel blocking NMDA receptor antagonists should provide an impetus for further investigation of this class of drug as an epilepsy treatment approach.

In addition to neurobehavioral toxicity, an important factor that may limit the clinical utility of both high- and low-affinity uncompetitive NMDA antagonists is "paradoxical" proconvulsant activity. Thus, PCP, ketamine, tiletamine, memantine, dextromethorphan, and dextrorphan have all been reported to have convulsant actions in various species including man *(49,50,53,54,61,65,81,88,123,124)*. Moreover, a pre-existing susceptibility to seizures can potentiate the convulsant activity of these agents. Thus, kindling enhances the convulsant activities of memantine *(61)* and dextrorphan *(65)*, and MK-801 sensitizes rodents to pilocarpine-induced limbic seizures *(46,118)*. In epileptic patients, ketamine has been used for activation of epileptic discharges as a means for localization of epileptic foci during surgical treatment of epilepsy *(7)*. These proconvulsant effects of uncompetitive NMDA antagonists are not non-specific high-dose effects of these drugs but, at least in part, were observed at the relatively low doses commonly used for NMDA receptor blockade *in vivo*. Therefore, while the proconvulsant activity of PCP and other similar drugs may be related to the blockade of ion channels other than NMDA receptors, including potassium channels *(35)*, cerebral activating effects caused specifically by actions on NMDA receptors also probably play a role. This conclusion is supported by the observation that the competitive NMDA antagonist AP-7 markedly increases the convulsant potency of tiletamine in rodents *(49)*.

Some low-affinity uncompetitive NMDA receptor antagonists are in clinical use for indications other than epilepsy. Dextromethorphan is marketed as an antitussive agent. Memantine is used for the symptomatic treatment of neurodegenerative dementia and spasticity, and is under investigation as a treatment for neuropathic pain and AIDS dementia. Whereas both drugs exert anticonvulsant effects in models of generalized seizures, they differ in their anticonvulsant effects against focal seizures in the kindling model *(59)*. Dextromethorphan exerted significant anticonvulsant activity at doses below those inducing motor impairment or PCP-like behavioral effects *(65)*. In contrast, dextrorphan, the major active metabolite of dextromethorphan that is also low-affinity channel blocker of the NMDA receptor *(95)*, only protects against kindled seizures at doses that are associated with toxic neurobehavioral side effects *(65)*. Dextromethorphan may interact with ion channels other than NMDA receptors that could serve as anticonvulsant targets including voltage-gated calcium and sodium channels *(89)* and this could explain its relatively high potency in the kindling model *(59)*. Indeed, it has been proposed that synergism between effects on NMDA receptors and other anticonvulsant targets could be critical to the powerful anticonvulsant activity and low toxicity of other low-affinity NMDA channel blockers such as ADCI *(109)*. In contrast to detromethorphan, memantine, like other more selective NMDA receptor antagonists, is ineffective against kindled seizures and may even induce seizures in kindled rats (but not in nonkindled rats) at higher doses *(61)*.

2.1.3. Glycine Site Antagonists

Activation of the NMDA receptor by the neurotransmitter glutamate requires the presence of a coagonist at the receptor's strychnine-insensitive glycine site (also termed glycine_B site). While glycine was the first endogenous substance to be identified that is capable of serving as a coagonist, there is evidence that D-serine, which is at least as potent an agonist as glycine, may be the endogenous coagonist under some circumstances *(85,117)*. Agents that competitively antagonize the action of endogenous coagonists at the glycine_B site produce a functional block of NMDA receptors, so that this site represents an additional antiepileptic drug target *(23)*. As is the case for other NMDA receptor antagonists, glycine_B antagonists inhibit generalized convulsions induced by electroshock, PTZ and other means *(23)*. Known glycine_B antagonists include quinoline derivatives, such as kynurenic acid (which also acts at the NMDA recognition site), 7-chlorokynurenic acid and L689,560; quinoxaline derivatives, such as MNQX and ACEA1021; cyclic analogs of amino acids, such as cycloleucine, ACPC, ACBC, D-cycloserine; pyrrolidine derivatives, such as

(+)-HA-966 and L-701,324; phthalazine-diones such as MRZ 2/570, MRZ 2/571, and MRZ 2/576; and indole-2-carboxylates such as GV150,526 and GV196,771 *(15,23, 44)*.

Only some of these compounds (e.g., 7-chlorokynurenic acid) are full antagonists (lacking intrinsic agonist activity at the glycine site), while other act as partial agonists with degrees of intrinsic activity ranging from low [e.g., (+)-HA-966] to high (e.g., D-cycloserine or ACPC). Many glycine$_B$ antagonists and partial agonists have been shown to exert anticonvulsant activity after either central (e.g., i.c.v.) or systemic administration *(15,23,107)*. In general, the behavioral effects of glycine$_B$ site partial agonists are poorly predicted by the degree of NMDA receptor inhibition, but several studies have indicated that partial agonists with relatively high intrinsic (agonist) activity such as ACPC or D-cycloserine are more efficacious as anticonvulsants than compounds with low intrinsic activity *(23,59)*. In the kindling model, in which competitive or uncompetitive NMDA antagonists are generally ineffective, glycine$_B$ antagonists or partial agonists have paradoxically been shown to exert anticonvulsant effects at doses below those inducing motor impairment or other adverse effects *(23,59)*. For example, Löscher's group found that i.c.v. injection of the full antagonist 7-chlorokynurenic acid; the partial agonists (+)-HA-966 (about 10% intrinsic activity) and D-cycloserine (about 60% intrinsic activity); and, surprisingly, the full agonist D-serine significantly increased the threshold for kindled seizures *(113)*. D-cycloserine and the glycine site antagonist L-701,324, but not (+)-HA-966, also increased the threshold for kindled seizures after i.p. administration, but the anticonvulsant effect of L-701,324 was associated with marked motor impairment *(76, 133)*. One explanation for the anticonvulsant effects of glycine$_B$ agonists or high efficacy partial agonists could be that these compounds induce desensitization of the receptor *(116)*, but this has been disputed *(97)*. In contrast to the results with other glycine$_B$ antagonists, the tricyclic pyrido-phthalazine-dione glycine$_B$ antagonist MRZ 2/576 failed to protect against kindled seizures even when administered at doses producing motor impairment *(133)*, despite the fact that it is active in various chemoconvulsant models *(96)*. The marked variability in the *in vivo* anticonvulsant activity of different glycine$_B$ antagonists is not well understood, but could be related to differences in receptor subtype selectivity or to actions of the drugs on other targets.

An important feature of glycine$_B$ antagonists is that they do not produce PCP-like behavioral effects (hyperactivity, stereotypies) that are characteristic of uncompetitive and competitive NMDA receptor antagonists. However, systemic administration of (+)-HA-966 has been reported to induce paroxysmal electrographic activity in limbic brain regions of kindled (but not nonkindled) rats, although the effect did not occur with cycloserine *(134)*. Moreover, as is the case for some uncompetitive NMDA receptor antagonists (see above), proconvulsant effects have been observed with (+)-HA-966 and 7-chlorokynurenic acid *(50,52)*. Whether these proconvulsant actions are related to effects on NMDA receptors or to other actions of the drugs remains to be determined.

In sum, although a variety of glycine site antagonists are now available, some of which have high systemic potency and excellent oral bioavailability, the results of animal studies have been insufficiently compelling to lead to the clinical development of any of these compounds. Nevertheless, glycine$_B$ antagonists, particularly those with relatively high intrinsic activity such as D-cycloserine or ACPC, continue to have potential *(59,107)*. Moreover, it has been proposed that glycine$_B$ site antagonists could be used in combination with agents acting at other recognition sites of the NMDA receptor *(30, 135)*, or that molecules with combined activities at the glycine$_B$ site and other anticonvulsant targets (including the NMDA recognition site or AMPA receptors) might be particularly advantageous *(107)*.

2.1.4. Polyamine Site and NR2B-Selective Antagonists

In the late 1980s, the endogenous polyamines spermidine and spermine were found to have multiple effects on the activity of NMDA receptors, including the induction of an increase in channel opening frequency and affinity for glycine *(132)*. This led to the notion that polyamines facilitate the gating of NMDA receptors by interacting with a distinct recognition site on the receptor-channel complex. More recently the polyamine stimulation has been found to be subunit specific and to exist in two forms. One form (the so-called glycine-independent form seen only with NMDA receptors containing the NR2B subunit) has been linked to the relief of tonic inhibition by protons, which act as endogenous negative modulators of NMDA receptors *(36)*.

The phenylethanolamine ifenprodil and its analog eliprodil were initially proposed as polyamine site antagonists because they block NMDA receptors in a spermine-sensitive manner. More recently, however, ifenprodil and

eliprodil have been found to selectively block NMDA receptors containing the NR2B subunit. This occurs through a unique activity-dependent blocking mechanism that may involve an increase in proton inhibition of NMDA receptors containing the NR2B subunit (86). As is the case for other NMDA antagonists, ifenprodil and eliprodil have a broad spectrum of anticonvulsant activity in animal models of generalized seizures (107). However, the therapeutic index of these compounds is not sufficiently high to have stimulated interest in their development as anticonvulsants. Moreover, neither drug exhibited any consistent anticonvulsant effect in the kindling model at doses that exerted marked motor impairment (30,136). Ifenprodil and eliprodil have multiple actions on other receptors and ion channels, including most prominently a-adrenergic receptors as well as serotonin receptors and sodium and calcium channels, that likely contribute to their toxicity. Nevertheless, there is emerging evidence from studies with other NR2B selective agents that supports the concept that NR2B selectivity may confer lower toxicity than nonselective NMDA receptor blockade, although such selectivity is not necessary for low toxicity (109). For example, the well tolerated channel blocking NMDA receptor antagonist ADCI has a modestly greater blocking potency for NMDA receptors composed of the NR2B subunits than those containing NR2A or NR2C subunits (T. P. Harty and M. A. Rogawski, unpublished). Similarly, the anticonvulsant felbamate, an NMDA receptor antagonist with low behavioral toxicity, blocks NMDA receptors composed of the NR2B subunits 3- to 4-fold more potently than those containing the NR2A or NR2C subunits (42). This contrasts with the highly toxic channel blocker ketamine, which has similar potency as an antagonist of NR2A and NR2B containing receptors and is modestly less potent at those containing NR2C. PCP and MK-801 are also equieffective as antagonists of NR2A and NR2B containing receptors (84). However, the moderately toxic uncompetitive NMDA antagonist memantine (38) has roughly equal potency at NR2A and NR2B containing receptors and dextromethorphan is four-fold more potent at NR2A than NR2B receptors (5), demonstrating that NR2B selectivity is not required for reduced toxicity. In contrast to the dissociative anesthetic-like agents that are most potent on NR2A and NR2B, memantine preferentially blocks NMDA receptors containing the NR2C and NR2D subunits (13,98), and dextromethorphan selectively blocks NR2C (84). Overall, tolerability is enhanced for antagonists that preferentially affect NMDA receptors other than those containing the NR2A subunit and the bulk of evidence suggests that NR2B selectivity is particularly desirable. To this end there has been intense interest in the medicinal chemistry of NR2B selective agents. Several selective NR2B antagonists have been described with far less propensity than ifenprodil and eliprodil for interacting with α-adrenergic receptors. Among these, Ro 25-6981 (32) and its analog (R)-1-[2-hydroxy-3-(4-hydroxy-phenyl)-propyl]-4-(4-methyl-benzyl)-piperidin-4-ol have been demonstrated to exhibit systemic anticonvulsant activity (101), as have Co 101244 (PD174494) (139) and related piperidines and pyrrolidines (40), and the cone snail peptide toxin conantokin G (26). Additional NR2B-selective antagonists include GV150526, which was well tolerated in clinical trials but failed to show activity in acute stroke and will therefore not likely be developed further; and the phenylpyridine NR2B-selective antagonist CP-101,606 (18), which was in clinical development, but whose development was halted because of electrocardiographic abnormalities (QT prolongation) related to potassium channel blockade.

2.1.5. Neurotoxicity of NMDA Receptor Antagonists

In rats, low to moderate doses of some types of NMDA receptor antagonists trigger reversible injury of neurons in the posterior cingulate and retrosplenial cortices manifested as transient intracytoplasmic vacuolization (93). At higher doses that induce a prolonged blockade of NMDA receptors, there may be irreversible degeneration of neurons in these regions (34). This worrisome phenomenon is seen with many uncompetitive and competitive antagonists, but has not been reported for glycine$_B$ antagonists and some low affinity channel blockers, including ADCI. Whether glycine$_B$ antagonists as a class are fundamentally different from other types of NMDA receptor antagonists in terms of their potential to induce this type of neurotoxicity is not known (97). NR2B-selective antagonists may also have reduced liability for neurotoxicity, at least as predicted by effects on heat shock protein (HSP), a putative marker of cell injury. Thus, eliprodil at high doses did not induce HSP70 in posterior cingulate and retrosplenial cortical neurons and even blocked the ability of MK-801 to induce HSP70 in these regions (127). In addition, the vacuolization and neuronal degeneration produced by NMDA antagonists can be prevented by coadministration of drugs that facilitate GABAergic neurotransmission (47). In sum, it may be possible to avoid the reversible and irreversible pathological effects of NMDA receptor antagonists through the selection of

agents with reduced propensity for these neurotoxic effects or through other strategies. Moreover, in assessing the clinical relevance of these phenomena, it should be kept in mind that neurotoxic effects of NMDA receptor antagonists might be unique in rodents, having never been reproduced in primates *(97)*.

2.2. Drugs Acting on Non-NMDA Ionotropic Glutamate Receptors

The non-NMDA ionotropic glutamate receptors are composed of two pharmacologically distinct families of receptors referred to as the 'AMPA' and 'kainate' receptors; each family consists of a unique set of subunits that coassemble to form a diverse group of tetrameric receptors *(11)*. Four AMPA receptor subunits (designated GluR1–GluR4 or, more recently, GLU_{A1}–GLU_{A4}) and five kainate receptor subunits (designated KA1, KA2, GluR5–GluR7, or, more recently, GLU_{K1}–GLU_{K5}) have been cloned. Over the last five years, there has been remarkable progress in the development of selective ligands for AMPA and kainate receptors, which has allowed enhanced understanding of the role of these receptors in synaptic function. AMPA receptors are probably involved in mediating most forms of fast glutamatergic neurotransmission in the CNS. Kainate receptors were previously thought to be largely presynaptic at both excitatory and inhibitory synapses, but are now known to be situated postsynaptically where they mediate fast excitatory transmission in many brain regions, including the amygdala and hippocampus which are critical regions for epilepsy and epileptogenesis *(20,57)*. AMPA antagonists are well known to have powerful anticonvulsant effects; consequently, AMPA receptors represent potentially important anticonvulsant drug targets *(59,97, 137)*. There is emerging evidence that kainate receptors may also be suitable anticonvulsant targets *(8)*. Although AMPA and kainate receptors are potentially highly diverse given the large number of subunit combinations, the possibilities of selective targeting are only beginning to be explored.

2.2.1. AMPA Receptor Antagonists

AMPA receptors are key mediators of seizure spread and there is emerging evidence that these receptors may also play a role in seizure-induced brain damage, so that AMPA receptor antagonists could have broad utility in epilepsy therapy *(111)*. The first selective AMPA receptor antagonists were identified in the late 1980s. These quinoxalinedione derivatives, which include NBQX and CNQX, act as competitive antagonists at the glutamate recognition site on AMPA receptors *(107)*. Although such quinoxalinediones have become standard tools for the study of AMPA receptors, they also have significant affinity for kainate receptors (CNQX more so than NBQX), a factor that limits their utility in discriminating between the two classes of non-NMDA receptors *(11,78)*. Furthermore, NBQX has been shown to suppress inhibitory glycine currents *(138)*, which further complicates its pharmacology. Decahydroisoquinolines, including LY293558, represent another class of competitive AMPA receptor antagonist. In addition to their blocking activity at AMPA receptors, these compounds also have varying degrees of activity as antagonists of kainate receptors containing the GluR5 subunit *(11)*. More recently, a new pyrrolyl-quinoxalinedione series of non-NMDA ionotropic glutamate receptor antagonists has been described, including the most potent competitive AMPA receptor antagonists described to date *(78,79)*. From the clinical perspective, a problem with some quinoxalinedione competitive AMPA antagonists such as NBQX is that these compounds tend to precipitate in the kidney, leading to crystaluria and nephrotoxicity. However, this does not occur with the more recently developed quinoxalinedione *(78,79,126)* and non-quinoxalinedione agents *(90)*.

Competitive AMPA receptor antagonists are protective in the MES test and against seizures induced by various chemoconvulsants *(107)*. Furthermore, in contrast to NMDA antagonists, competitive AMPA antagonists are potent anticonvulsants in the kindling model, and the anticonvulsant effects occur at doses clearly below those inducing motor impairment *(73,78,112)*. In contrast to NMDA antagonists, kindling does not increase the adverse effect potential of competitive AMPA antagonists *(59)*. However, in mouse chemoconvulsant and electroshock models of generalized seizures, NBQX produces motor impairment at doses similar to those that are protective against seizures *(68,137)*. The significance of this narrow therapeutic window as a predictor of tolerability in the clinical setting is uncertain, particularly since there is little clinical experience with AMPA receptor antagonists. Indeed, it is well recognized that for anticonvulsants that act by novel mechanisms, the therapeutic index is a poor predictor of tolerability in man, as is the case for valproate, which has a low therapeutic index in generalized seizure models but an excellent record of acceptance by patients. Moreover, AMPA receptor antagonists have not been reported to cause PCP-like behavioral effects in animals or psy-

chotomimetic effects in man. The high efficacy of AMPA antagonists in kindling models suggests that these agents might be particularly effective against complex partial seizures.

Some years after the development of quinoxalinedione competitive AMPA receptor antagonists, a novel class of AMPA antagonists was identified that exert their blocking action in a mechanistically distinct fashion *(122)*. These 2,3-benzodiazepines, such as GYKI 52466, do not interact with the AMPA recognition site, nor do they act as channel blockers, but appear to block AMPA receptors in a noncompetitive fashion via an allosteric site on the AMPA receptor complex *(25)*. Noncompetitive AMPA receptor antagonists such as GYKI 52466 show a greater selectivity for AMPA receptors (vs. kainate receptors) than do competitive AMPA antagonists and they permit AMPA and kainate receptor-mediated events to be pharmacologically separated *(11)*. Like competitive AMPA antagonists, noncompetitive (allosteric) antagonists such as GYKI 52466 have anticonvulsant activity in a broad spectrum of animal seizure models, including the kindling model *(59,107,112)*. However, in the MES and PTZ models in mice, GYKI 52466 was reported to exert anticonvulsant effects only at doses that caused motor impairment *(68,137)*. The GYKI 52466 analog talampanel (GYKI 53773; LY 300164) has been selected for further development. Talampanel is the active (R)-enantiomer of GYKI 53405, the N-acetylated derivative of GYKI 52466. Both GYKI 53405 and talampanel are protective in the MES test in mice and also in various chemoconvulsant models, but only at doses near those that cause motor side effects *(4,10,27)*. The results of a promising clinical trial with talampanel in epilepsy are discussed in section 3.7. Other AMPA receptor antagonists that have advanced to human trials include the highly potent, water-soluble competitive AMPA receptor antagonist YM872 *(121)*. YM872 was well tolerated in Phase I studies in volunteers although elderly subjects experienced euphoria or sedation at high dose levels. Trials of the water-soluble phosphonate quinoxalinedione AMPA antagonist ZK200775 *(126)* were halted because of excessive sedation. The decahydroisoquinoline mixed AMPA and GluR5 kainate receptor antagonist LY293558 has also been evaluated in humans, mainly for the treatment of pain. When administered i.v., the drug exhibited modest efficacy but some test subjects experienced dose-related sedation, and there was a disturbing occurrence in some individuals of hazy vision that appeared to be due to a neural mechanism *(37,118)*. Since other AMPA receptor antagonists do not cause similar visual symptoms, the

possibility exists that the visual disturbance is related to the unique GluR5 kainate receptor blocking activity of LY293558. However, a definitive conclusion requires corroboration from trials with other kainate receptor antagonists.

Interestingly, in the kindling model, the anticonvulsant activity of NBQX can be synergistically enhanced by low doses of NMDA antagonists, without producing an increase in adverse effects *(67, 73,102)*. With MK-801, the maximum synergistic effect was obtained at 0.01 mg/kg, far below the doses that induce adverse effects. This observation led to the investigation of a series of quinoxalines combining NMDA and non-NMDA antagonistic properties, including LU 73068 which binds with high affinity to both the glycine site of NMDA receptors and to AMPA receptor (and also to some kainate receptors) *(102)*. However, one potential problem of combining antagonism at both NMDA and non-NMDA receptors seems to be respiratory depression *(59)*, although in the case of LU 73068 this occurred only at doses much greater than those that exhibited anticonvulsant effects.

In sum, the available evidence to date suggests that AMPA receptor antagonists may be more promising as antiepileptic agents than NMDA antagonists, but definitive conclusions await more extensive clinical evaluation.

2.2.2. Kainate Receptor Antagonists

The role of kainate receptors in the generation of seizures has not been fully explored although it does appear that kainate receptors mediate excitatory neurotransmission in areas relevant to epilepsy, including the amygdala and hippocampus *(9,55,57)*, and activation of GluR5 kainate receptors can lead to epileptiform activity and seizures *(8)*. This occurs as a result of the direct excitatory action of kainate receptors and, perhaps even more importantly, because of the ability of kainate receptors to suppress GABAergic inhibition. Selective antagonists for kainate receptors have only recently become available. These include the series of decahydroisoquinolines noted in section 2.2.1. that have variable degrees of activity at AMPA and GluR5 kainate receptors *(11,92)*. The full spectrum of effects of the highly GluR5 selective members of this drug family is yet to be determined. However, using the mixed AMPA/GluR5 kainate receptor blocking decahydroisoquinoline LY293558, it was demonstrated that GluR5 antagonism does not provide an increase in anticonvulsant activity in the amygdala kindling model beyond the effect produced by AMPA receptor antagonism alone, and moreover that

GluR5 kainate receptor blockade does not interfere with kindling development *(112)*. However, results with the pyrrolyl-quinoxalinedione LU 97175 do support the view that kainate receptor antagonism produces anticonvulsant effects in some circumstances and that this occurs with reduced toxicity compared with AMPA receptor blockade. LU 97175 is a member of a large series of related compounds with non-NMDA receptor blocking activity. Unlike the other members of the series, LU 97175 binds selectively to kainate receptors, possessing high affinity for GluR5, GluR6 and particularly GluR7 subunits, but has little activity at AMPA receptors *(78)*. Thus, in contrast to the members of the series with affinity for AMPA receptors, LU 97175 did not block AMPA-induced lethal convulsions in mice. However, it was effective in the MES test and the kindling model at doses below those inducing motor impairment, suggesting that kainate receptor antagonism may provide a novel approach to seizure therapy. Moreover, although the mixed AMPA/GluR5 kainate receptor antagonist LY293558 did not show superior activity in comparison with the selective AMPA receptor antagonist GYKI 52466 in the mouse kindling model *(112)*, data obtained with members of the pyrrolyl-quinoxalinedione series that have mixed activity at AMPA and kainate receptors suggest that combined AMPA/kainate receptor blockade may in some circumstances confer enhanced efficacy and tolerability *(78)*.

3. CLINICAL TRIALS WITH IONOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS AND MODULATORS

3.1. MK-801

As noted in section 2.1.2., the first selective glutamate receptor antagonist to undergo a clinical trial in epilepsy was the uncompetitive NMDA antagonist MK-801 which, even in Phase I studies in normal volunteers, induced a variety of troubling adverse effects. In a clinical epilepsy trial, some subjects also experienced neurobehavioral side effects, including restlessness, hyperactivity and agitated confusion *(125)*. However, they did not experience sedation, and often the drug had a positive effect on mood and alertness. In this open label trial, there were some indications of efficacy against partial seizures, but the effect was not sustained, even at doses up to 34 mg/kg/day. Further development of MK-801 was terminated when evidence emerged that it may induce neuronal damage (see section 2.1.5.).

3.2. D-CPPene

In some preclinical models used in the evaluation of antiepileptic drugs, competitive NMDA receptor antagonists were found to possess a more favorable therapeutic index than MK-801. These were judged to be less likely to produce PCP-like adverse effects *(83, 131)*, raising hopes that this class of antagonist would avoid the difficulties encountered with MK-801. However, as discussed in section 2.1.1., NMDA antagonists have poor activity in the kindling model, and kindling markedly enhances the adverse effect potential of these agents *(64)*. Nevertheless, the first clinical trials with newly developed antiepileptic drugs are typically performed as add-on studies in patients with localization related seizures (most often complex partial seizures) for which kindling may be an appropriate model. Therefore, it is not surprising that the first (and only) clinical trial with a competitive NMDA antagonist in patients with epilepsy was not encouraging *(120)*. Dose-ranging studies in healthy volunteers demonstrated that the competitive NMDA antagonist D-CPPene is well tolerated at doses up to 2000 mg/day. In contrast, in an add-on trial in 8 patients with refractory complex partial seizures, D-CPPene in daily doses of 500 to 1000 mg induced severe adverse effects in all patients, requiring hospitalization in six patients and premature termination of the trial. All 8 subjects had impaired concentration and sedation, six had gait ataxia, four reported confusion and disorientation, three experienced depression, and one had unilateral choreoathetosis. Seizure control was worsened in 3 patients and unchanged in the others; the patient with the highest plasma concentration of D-CPPene developed complex partial status epilepticus. Plasma D-CPPene levels were approximately twice those obtained in the normal volunteers, indicating that pharmacokinetic factors could have partially accounted for the disappointing outcome *(120)*. However, it also seems likely that the subjects with epilepsy were more sensitive to the adverse effects of the antagonist, as had been predicted in studies with kindled rats *(64)*. Interestingly, preliminary reports from clinical trials with another competitive NMDA antagonist CGS-19755 in patients with stroke have also revealed a high incidence of adverse neurobehavioral effects which had not been observed in healthy volunteers, including agitation and hallucinations *(39)*. In this respect, it is noteworthy that, in rats, focal ischemia also increases the adverse effects of NMDA antagonists in a similar fashion as kindling *(77)*.

3.3. Dextromethorphan

As noted in section 2.1.2, dextromethorphan is a low-affinity channel blocking NMDA receptor antagonist *(21)* that is marketed as an antitussive. At recommended doses (120 mg/day or below), dextromethorphan has acceptable tolerability; higher doses may cause a variety of adverse effects including sedation, hyperexcitability, ataxia, dystonia, and psychotic-like reactions *(94)*. Some of dextromethorphan's toxicity is attributed to its major metabolite dextrorphan, which has an approximately 10-fold higher affinity for NMDA receptors than the parent drug. In a double-blind, crossover, add-on study in 9 patients with complex partial seizures, seizure frequency increased by 25% during treatment with dextromethorphan at a dose of 120 mg/day *(33)*. In contrast, subsequent clinical studies using higher daily doses of the drug have suggested that dextromethorphan may be capable of improving medically refractory seizures *(75,115,130)*. For example, in an open-label study in 16 patients with intractable partial epilepsy, addition of dextromethorphan to existing antiepileptic medications at doses of up to 200 mg/day resulted in improved seizure control *(48)*. Although the drug was generally well tolerated, two patients experienced increased seizure frequency and were withdrawn from the trial. While encouraging, definite conclusions about the efficacy and tolerability of detromethorphan await more controlled therapeutic trials.

Dextromethorphan has also been tried in non-ketotic hyperglycinemia, a rare autosomal recessive disorder of glycine metabolism associated with increased cerebrospinal fluid glycine due to inborn errors in the glycine cleavage system. It has been proposed that excessive activity of NMDA receptors resulting from increased brain glycine leads to the intractable seizures characteristic of this condition *(51)*. In uncontrolled trials, dextromethorphan has been reported to decrease or eliminate seizures in children with non-ketotic hyperglycinemia *(41)*. Dose-related somnolence was the major side effect.

3.4. Remacemide

Remacemide is a weak NMDA receptor antagonist that is metabolically activated by desglycination to the more potent channel blocking NMDA antagonist 1,2-diphenylpropylamine (ARL 12495) *(2,84,119)*. Remacemide has undergone extensive clinical evaluation *(10,94)*. In general, the drug is relatively well tolerated, but it does produce dose-related CNS side effects including dizziness, fatigue, somnolence and diplopia and there is a high incidence of gastrointestinal complaints (nausea, vomiting, dyspepsia and abdominal pain). Importantly, some volunteers and subjects in clinical trials experienced PCP-like neurobehavioral symptoms including agitation, confusion and hallucinations as well as somnolence, ataxia, mood change and visual abnormalities. Phase II clinical trials in patients with complex partial seizures indicated that the drug has efficacy, particularly in those subjects with secondary generalized tonic-clonic seizures *(17a,47a)*. In addition, the drug exhibited substantial efficacy in a presurgical study *(3,10)*. However, in a major Phase III randomized trial (SEReNE), remacemide was shown to be inferior to carbamazepine *(45,129)*, thus diminishing enthusiasm for its further development in epilepsy treatment.

3.5. Felbamate

Among other actions, including effects on $GABA_A$ receptors and voltage-activated sodium channels, the marketed anticonvulsant felbamate is an NMDA antagonist with modest selectivity for the NR2B subunit (section 2.1.4.). Felbamate is the only approved anticonvulsant drug that blocks NMDA receptors at clinically relevant doses. In an extensive series of premarketing clinical trials, felbamate was demonstrated to be efficacious in the treatment of partial seizures with or without secondary generalization in adults and in the treatment of the Lennox-Gastaut syndrome in children *(94)*. It has been suggested that the unique activity of felbamate in the Lennox-Gastaut syndrome, a pediatric epilepsy syndrome that is notoriously difficult to treat, could be related to the high levels of expression of the NR2B subunit in the immature brain *(128)*. The most common adverse effects in clinical trials were insomnia, nervousness, anorexia, vomiting, nausea and headache. In this regard, it is interesting to note that NMDA receptor antagonists, particularly those with dissociative anesthetic-like effects, often have locomotor stimulatory effects in animals; the activating effects of felbamate in human subjects could be due to a similar mechanism. Nevertheless, the fact that felbamate has multiple pharmacological actions makes it difficult to link either the therapeutic activity or any of its side effects to a known pharmacological activity of the drug. Moreover, although it would be attractive to point to felbamate as evidence that the NMDA receptor is a promising target for anticonvulsant drug development, this may be overly optimistic since so many other NMDA

receptor antagonists have shown unimpressive activity in clinical trials. In any case, the recognition that felbamate can induce severe idiosyncratic side effects, (aplastic anemia and hepatotoxicity) has drastically curtailed its use *(100)*.

3.6. Magnesium Sulfate

Magnesium is a physiological antagonist of NMDA receptors by virtue of its ability to act as a rapid blocker of the ionophore of the receptor-channel complex *(82,91)*. The cation can be considered to be an endogenous anticonvulsant inasmuch as reducing extracellular magnesium concentrations in experimental systems (such as in the hippocampal brain slice) readily leads to epileptiform activity *(106)*. In animal models, magnesium does not exhibit anticonvulsant activity when administered acutely, probably because the cation fails to alter brain magnesium levels unless systemic levels are elevated for prolonged periods of time *(87)*. Nevertheless, magnesium sulfate has a venerable history and proven efficacy in the treatment of pre-eclampsia and eclamptic seizures *(80)*. The mechanisms underlying these actions are debated in the obstetrical literature.

3.7. Talampanel

Although several AMPA receptor antagonists have undergone clinical evaluation, only the 2,3-benzodiazepine noncompetitive AMPA receptor antagonist talampanel has been evaluated for epilepsy. In a Phase II add-on trial in 49 patients with refractory partial seizures, orally-administered talampanel appeared to show efficacy *(10)*. Dizziness (52%) and ataxia (26%) were the only significant adverse events, and there was no cognitive or psychomotor impairment. Discontinuation rates were similar in the active drug and placebo groups. However, because of pharmacokinetic interactions, the results were inconclusive. Additional trials will be required to confirm these initially promising results.

4. CONCLUSIONS

The field of epilepsy research has been an important beneficiary of the fundamental progress in research on glutamate neurotransmission of the past half century. Ionotropic glutamate receptor antagonists and modulators have been enormously important tools for investigating neuronal mechanisms involved in seizures and epilepsy. These tools have made it possible to demonstrate that glutamatergic neurons, acting via both NMDA and non-NMDA receptors, are involved in seizure initiation and propagation. Not surprisingly, ionotropic glutamate receptor antagonists have been a major focus of attention in the search for new antiepileptic drugs. Initially, most of the interest was directed on NMDA receptor antagonists, and several such agents entered clinical trials. However, despite the anticonvulsant potency and favorable therapeutic ratios of some of these compounds in animal models, NMDA receptor antagonists have shown no convincing antiepileptic efficacy in clinical trials, and in some cases there was a disturbingly high incidence of adverse effects. Interestingly, these disappointing results from clinical trials had been correctly predicted from experiments in kindled rats, demonstrating that models of chronic epilepsy, such as the kindling model, should be a component of the battery of tests used in the preclinical assessment of investigational anticonvulsants *(58)*. Based on their preclinical profiles, including excellent activity in the kindling model, and preliminary results in one clinical trial, non-NMDA receptor antagonists look much more promising. Nevertheless, although they target a molecularly and functionally distinct class of receptors and have entirely different behavioral actions, non-NMDA antagonists seem to have been tarred with the same brush as NMDA antagonists, so that it has been difficult to generate enthusiasm for their evaluation in epilepsy, although there are limited trials ongoing for other indications such as stroke, chronic pain and multiple sclerosis.

One interesting idea resulting from the evaluation of various categories of ionotropic glutamate receptor antagonists and modulators is that drugs that interact with more than one anticonvulsant target (e.g., sodium channels or $GABA_A$ receptors and NMDA receptors; NMDA and AMPA receptors; or AMPA and kainate receptors) may show synergistic anticonvulsant actions but may not have increased toxicity. Indeed, highly effective, broad-spectrum antiepileptic drugs such as felbamate and topiramate, may act through such multiple mechanisms. Thus, screening for drugs that have combined actions on several anticonvulsant targets could be a valuable strategy for the future.

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