however, the rPPIs are an exciting development in the quest for the optimal anti-secretory drug.

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VIEWPOINT

Therapeutic potential of excitatory amino acid antagonists: channel blockers and 2,3-benzodiazepines

Michael A. Rogawski

NMDA and non-NMDA (AMPA/kainate) antagonists have potential in the treatment of a diverse group of neurological disorders associated with excessive activation of excitatory amino acid receptors. Here Michael Rogawski *reviews recent progress in the development of therapeutically useful NMDA receptor channel blockers and a new class of selective AMPA/kainate receptor antagonists, the 2,3-benzodiazepines. Research on these novel noncompetitive excitatory amino acid antagonists has opened promising new avenues for the development of drugs to treat epilepsy, ischaemia, neurodegeneration and Parkinson's disease.*

The pathogenesis of a diverse group of neurological disorders has been linked to excessive activation of excitatory amino acid receptors (or to a defect in the cellular mechanisms that protect against the potentially toxic consequences of normal levels of receptor activation). These disorders include epilepsy, focal and global ischaemia, CNS trauma, neuropathic pain and various forms of neurodegeneration including Huntington's disease, amyotrophic lateral sclerosis and Parkinson's disease. Not surprisingly, there has been intense interest in the development of excitatory amino acid receptor antagonists as therapeutic agents[1].

Historically, NMDA receptor antagonists have been at the centre of attention, and drug development efforts continue in this area. However, the initial enthusiasm has been dampened somewhat by increasing awareness of the various toxicities of NMDA receptor antagonists (see below). In addition, it is now recognized that NMDA receptor blockade is only partially protective in some focal ischaemia models and may be ineffective in severe global ischaemia[2]. Coinciding with the more realistic appraisal of the clinical potential of NMDA receptor antagonists has been the development of potent and selective quinoxalinedione AMPA/kainate receptor antagonists, such as NBQX. The availability of these compounds has generated experimental evidence supporting a role for AMPA/kainate receptor antagonists, either alone or in combination with NMDA receptor antagonists, in the treatment of cerebral ischaemia.

To date, clinical development efforts have focused largely on competitive NMDA recognition site antagonists. Recently, however, noncompetitive antagonists have attracted increasing attention, with much effort directed toward the glycine site of the NMDA receptor[3]. Noncompetitive antagonists have the theoretical advantage that their blocking action would not be overcome by high levels of glutamate, as may occur during seizures and ischaemia. In the case of drugs acting in a channel blocking fashion, there is the additional theoretical advantage that their inhibitory action may be potentiated specifically at sites of excessive glutamate receptor activation. In this review, recent progress in the development of therapeutically useful channel blocking NMDA antagonists is discussed. Noncompetitive

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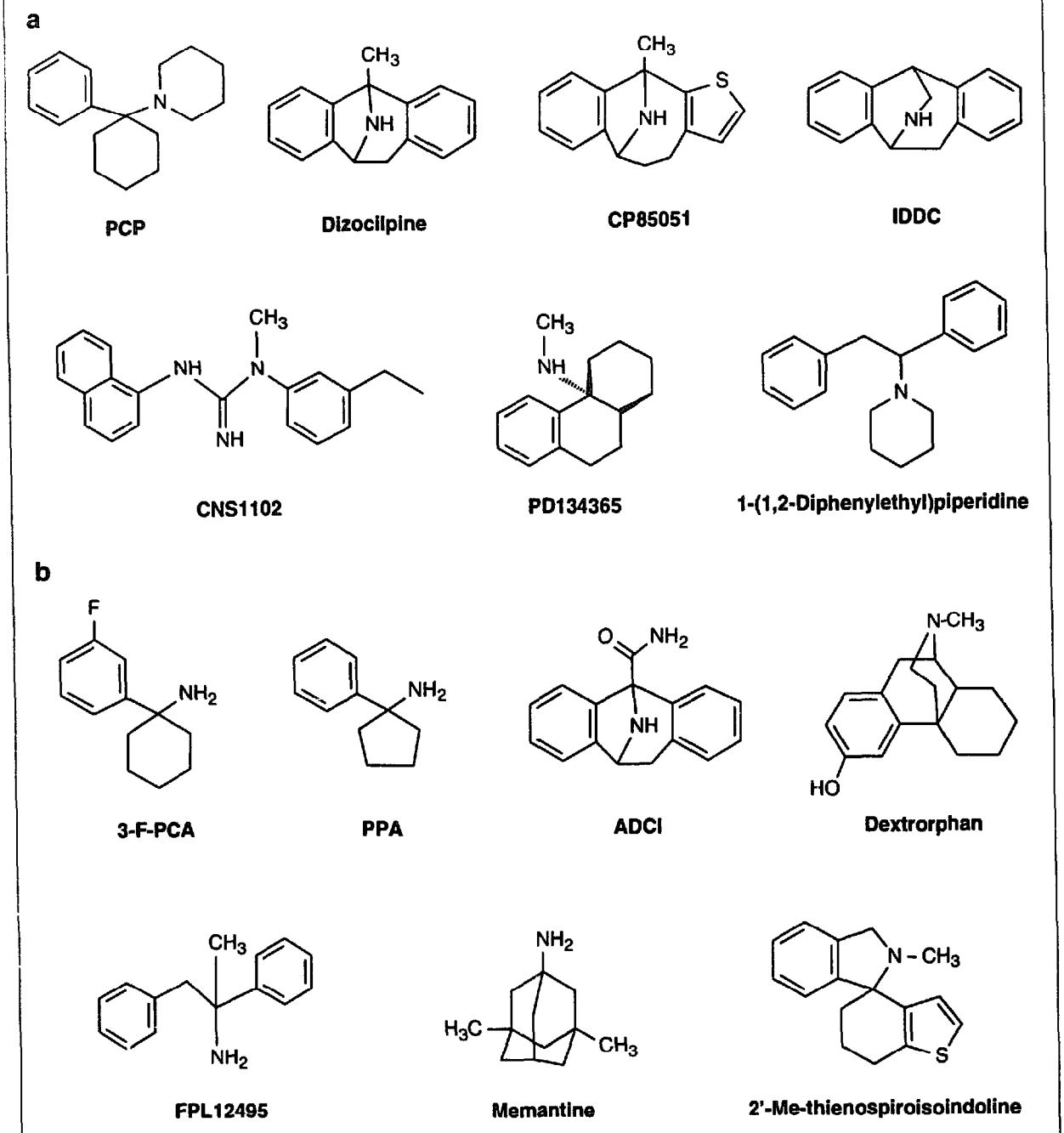


Fig. 1. **a:** *Structures of channel blocking NMDA antagonists with high affinity for the dissociative anaesthetic binding site on NMDA receptors.* **b:** *Structures of low-affinity channel blocking NMDA antagonists. See Table I for affinity values of these and related compounds.*

antagonists that interact with other sites on the NMDA receptor are reviewed elsewhere[4]. Recently, a series of 2,3-benzodiazepines has been identified as potent and selective noncompetitive antagonists at AMPA/kainate receptors. In the second part of this review, the possibilities for these compounds in the treatment of neurological disorders are explored.

Low-affinity NMDA receptor channel blockers

Dissociative anaesthetics, such as phencyclidine (PCP), ketamine and the dissociative anaesthetic-like agent dizocilpine (Fig. 1a), antagonize NMDA receptor mediated responses by an 'open channel' mechanism[5], i.e. they are use-dependent (uncompetitive) antagonists. Despite the effectiveness of dissociative anaesthetics in test systems which evaluate anticonvulsant and neuroprotective activity, such compounds have high neurobehavioural toxicity, and in humans may induce cognitive, sensory and various schizophrenia-like neuropsychological deficits even at low doses[6]. In animals, dissociative anaesthetics produce hyperlocomotion, stereotypies and disturbances of motor function at doses equal to, or less

TABLE I. Affinities of channel blockers for inhibition of [^{3}H]dizocilpine[a] or [^{3}H]TCP (1-[1-(2-thienyl)cyclohexyl]piperidine)[b] binding to NMDA receptors in brain membranes. The values are only roughly comparable since experimental conditions differ.

Compound	Affinity (μM)	References
High-affinity		
Dizocilpine	0 003[a]	Grant, K. A., Snell, L. D., Rogawski, M. A., Thurkauf, A. and Tabakoff, B. (1989) *J. Pharmacol. Exp. Ther.* 260, 1017–1022
PD134365	0.015[b]	Malone, T. C., Ortwine, D. F., Johnson, G. and Probert, A. W., Jr (1993) *Bioorg. Med. Chem. Lett.* 3, 49–54
CP85051	0.032[b,c]	Robinson, R. P. *et al.* (1990) *Amer. Chem. Soc. Abst.* MEDI111
CNS1102	0.037[a]	Minematsu, K. *et al.* (1993) *Neurology* 43, 397–403
1-(1,2-Diphenylethyl)piperidine	0.039[b]	Gray, N. M. and Cheng, B. K. (1989) European Patent Application 89110572.8 (EP 0 346 791 A1)
IDDC	0.041[a]	Hu, L-Y. *et al.* (1992) *Amer. Chem. Soc. Abst.* MEDI106; Weber, E. and Keana, J. F. W. (1992) *U.S. Patent 5, 011,834*
PCP	0.063[b]	Rogawski, M. A. *et al.* (1989) *J. Pharmacol. Exp. Ther.* 249, 708–712
Low-affinity		
Dextrophan	0.17[b]	Coughenour, L. L. *et al.* (1988) in *Frontiers in Excitatory Amino Acid Research* (Cavalheiro, E. A., Lehmann, J. and Turski, L., eds), pp. 563–566, Alan R. Liss
FPL12495	0.48[a]	Palmer, G. C., *et al.* (1992) *Epilepsy Res.* 12, 9–20
2'-Me-thienospiroisoindoline	0.49[b]	Bare, T. M. *et al.* (1993) *Bioorg. Med. Chem. Lett.* 3, 55–60
Memantine	0.54[a]	Kornhuber, J., Bormann, J., Hübers, M., Rusche, K. and Riederer, P. (1991) *Eur. J. Pharmacol.* 206, 297–300
PCA	0.53[b]	Rogawski, *et al.* op cit.
3-F-PCA	0.68[b]	Thurkauf, A. *et al.* (1990) *J. Med. Chem.* 33, 1452–1458
Dextromethorphan	1.5[b]	Coughenour, *et al.*, op cit.
PM-THIQ	5.4[b]	Rogawski, *et al.*, op cit.
ADCI	9.3[a]	Grant, *et al.*, op cit.
PPA	10.5[b]	Thurkauf, *et al.*, op cit.
Remacemide	68[a]	Palmer, *et al.*, op cit.

PD134365, *cis*-1,3,4,9,10,10*a*-hexahydro-*N*-methyl-4*a*(2*H*)-phenanthreneamine; **CP85051**, 5-methyl-4,5,6,11-tetrahydrobenzo[6,7]cycloocta-[1,2-*b*]thiophen-6,11-imine; **CNS1102**, *N*-(1-napthyl)-*N'*-(3-ethylphenyl)-*N'*-methylguanidine); **IDDC**, 10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene); **PD134355**, *cis*-1,3,4,9,10,10*a*-hexahydro-*N*-methyl-4*a*(2*H*)-phenanthreneamine); **PCA**, 1-phenylcyclohexylamine; **3-F-PCA**, 1-(3-fluorophenyl)cyclohexylamine; **PPA**, 1-phenylcyclopentylamine; **PM-THIQ**, 1,1-pentamethylenetetrahydroisoquinoline (a conformationally restricted analogue of PCA).

[c]Similar to IC_{50} for dizocilpine reported in this study (0.030 μM).

than, those that are anticonvulsant and neuroprotective[7]. Moreover, dissociative anaesthetics can produce transient and reversible, but nevertheless striking, histolopathological changes in certain brain areas. Although neuronal vacuolization is the primary effect seen, destruction of neurones can occur with high doses[8]. Interestingly, there is complete tolerance to these effects with repeated dosing.

Recently, certain phenylcyclohexylamines (PCAs; primary amine analogues of PCP), were found to be effective anticonvulsants while producing substantially less motor impairment than PCP[9]. Similarly, an analogue of dizocilpine, ADCI has been shown to be a broad spectrum anticonvulsant and, like other NMDA receptor antagonists, to retard the development of kindled seizures, but to have low neurological toxicity[10]. A common characteristic of these compounds is that they block NMDA receptor-mediated responses in a use-dependent and voltage-dependent manner[11,12]. However, the affinity of the PCA analogues and ADCI for the dissociative anaesthetic binding site associated with the NMDA receptor is in the low-micromolar range, whereas dizocilpine has low nanomolar affinity (Table I). At equieffective concentrations, the low-affinity antagonists would exhibit faster apparent rates of block and unblock, and this could, at least in part, contribute to their lower toxicity; other factors could also be important (see Box). Optimization of receptor affinity is a fundamental principal of drug development. However, in the case of channel blocking NMDA antagonists, it may be reasonable to violate this rule and to focus on low- to moderate-affinity compounds that, because of their reduced toxicity, may be more desirable therapeutic agents.

In recent years, a number of potentially clinically important anticonvulsants and neuroprotective agents have been recognized as low-affinity NMDA receptor channel blockers. Among the first such compounds to be described were the dextrorotatory morphinan, dextromethorphan, and its *O*-demethylated metabolite, dextrorphan. Although essentially inactive at opioid receptors, both morphinans are low-affinity uncompetitive NMDA antagonists[13] with anticonvulsant[7] and neuroprotective[14] activity. The available electrophysiological data suggest that dextrorphan[15] and dextromethorphan[16] may block more rapidly than dizocilpine, and in line with the hypothesis discussed above, they have somewhat reduced toxicity in comparison with dissociative anaesthetics[7]. Dextrorphan is a higher-affinity antagonist than dextromethorphan (Table I), and its relative toxicity is correspondingly higher[7]. Dextromethorphan is reasonably well tolerated in humans[18], although the drug does produce ataxia and other neurobehavioural side effects at high doses[19]. Both dextrorphan and dextromethorphan are currently in clinical trials.

Also in clinical development is remacemide, an anticonvulsant that, like dextromethorphan, appears to be a prodrug for a metabolite with higher affinity as a channel blocking NMDA antagonist. Originally synthesized in an attempt to target the pharmacophore of the antiepileptic drug phenytoin, remacemide is effective in the maximal electroshock seizure test and has relatively low

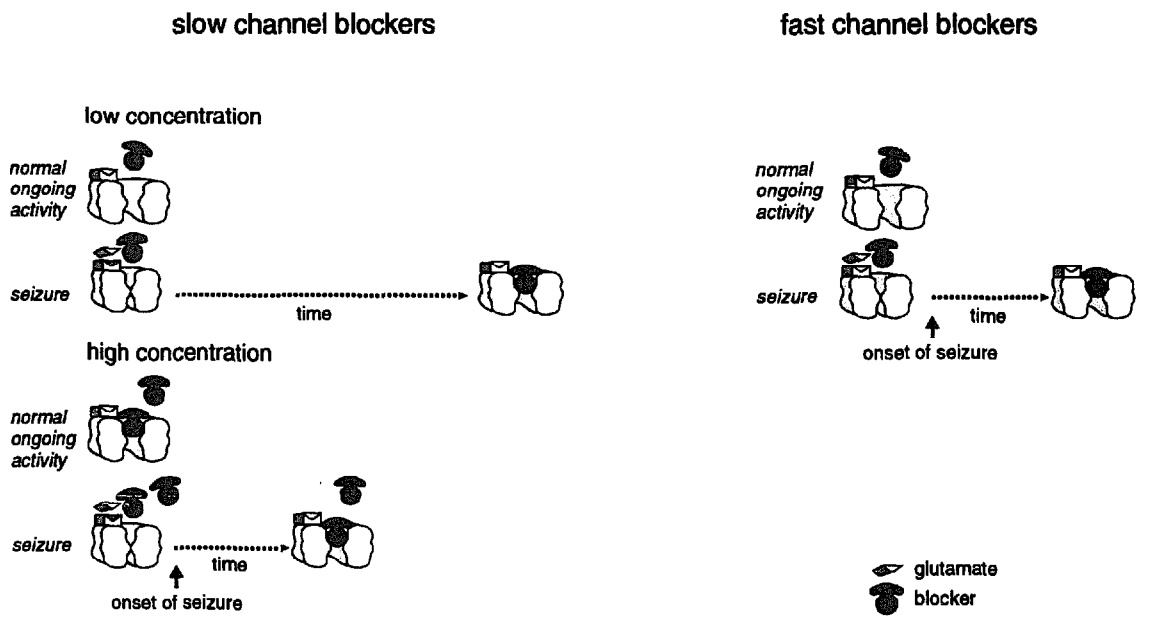
Why might low-affinity uncompetitive NMDA antagonists have diminished toxicity?

(1) For drug concentrations producing equivalent levels of channel block, lower affinity antagonists reach equilibrium more rapidly than higher affinity antagonists. Given certain assumptions (see Ref. 12), rapid block might be advantageous for a drug intended to treat seizures. At the onset of the seizure discharge, the low-affinity, rapidly blocking antagonist would almost immediately achieve complete steady-state block. In contrast, high-affinity, slowly blocking antagonists would require relatively higher concentrations to achieve the same degree of block within a sufficiently rapid period of time to abort the seizure. The higher concentrations would produce greater interference with ongoing NMDA receptor-mediated neurotransmission, thus resulting in toxicity.

(2) For certain channel blockers, the level of block of NMDA receptors may increase proportionately with agonist (glutamate) concentration[25]. Thus, under conditions of excessive glutamate release, the block may be enhanced.

(3) Inhibition by dissociative anaesthetics and related compounds is reduced by membrane depolarization[5]. A theoretical disadvantage of this voltage-dependence is that blocking effectiveness may be diminished when neurones are strongly depolarized by excessive glutamate. Certain low-affinity channel blockers may block by binding to both a voltage-independent site as well as to a voltage-dependent site (Subramamiam, S., Donevan, S. D. and Rogawski, M. A., unpublished observations). Since the block produced at the voltage-independent site would be maintained irrespective of the level of depolarization, effectiveness would not be diminished under pathological conditions.

(4) Synergism between effects on NMDA receptors and on other targets might enhance the desired therapeutic activity of channel blockers and allow the drug to be used at doses below those that would produce toxicity by virtue of its action at any of the targets individually. For example, use-dependent block of voltage-dependent Na^+ channels is a putative anticonvulsant mechanism, which in combination with NMDA receptor antagonism, could enhance anticonvulsant activity. Although synergism between effects on NMDA receptors and voltage-dependent Na^+ channels may enhance anticonvulsant activity, side-effects might not be synergistic if the toxicity produced by inhibition of NMDA receptors and Na^+ channels were predominantly mediated by distinct brain systems. Thus, the motor impairment of NMDA receptor antagonists may be largely due to interference with sensorimotor integration in thalamocortical and corticospinal systems, whereas the ataxia induced by use-dependent Na^+ channel blockers may be more dependent upon perturbation of cerebellar function (because cerebellar neurones fire at high rates and are therefore particularly susceptible to use-dependent block). If effects on secondary targets are of low-affinity, their relative importance would be greater for NMDA antagonists with similarly low-affinity.



motor toxicity[20]. More recently, the drug has also been demonstrated to have neuroprotective activity in various ischaemia models[21], and to have a synergistic effect with L-dopa in an animal model of Parkinson's disease[22]. Although remacemide itself is an extremely weak uncompetitive NMDA antagonist, it is rapidly deglycinated *in vivo* to form 1,2-diphenyl-2-propylamine (FPL12495) which is 140-fold more potent as an inhibitor of [^{3}H]dizocilpine binding (Table I). FPL12495 can be viewed as a conformationally flexible homeomorph of dizocilpine and it presumably binds to the same site in the ion channel of the NMDA receptor-channel complex, but with lower affinity. A number of FPL12495 analogues, including 1,2-diphenylethylamine, 1-phenyl-2-thienylethylamine and their cyclic and *N*-alkyl congeners, appear to have similar properties[23]. An inverse relationship between affinity and toxicity has been demonstrated for this class of compounds[24]. In animals, remacemide and FPL12495 are only very weak at inducing adverse behavioural effects such as hyper-

activity, ataxia and stereotypies, and they produce a low incidence of neuronal vacuolization even at high doses. Clinical trials with remacemide in epilepsy have been promising and there have been few adverse incidents.

A similar series of studies has recently been reported for memantine, an adamantane analogue that is marketed as an anti-Parkinsonian and antispasticity agent. Although structurally quite different from other NMDA channel blockers (Fig. 1b), memantine inhibits [^{3}H]dizocilpine binding to brain membranes (Table I), and blocks NMDA receptor-mediated responses in a use-dependent fashion[25]. Memantine also blocks other neurotransmitter-gated ionotropic receptors, including nicotinic acetylcholine receptors[26] and 5-hydroxytryptamine 5-HT$_3$ receptors[27]. The broad spectrum of channel blocking activity exhibited by memantine could contribute to its more complex behavioural profile in comparison with other NMDA receptor antagonists. Thus, although memantine is an effective anticonvulsant[29] and neuroprotective agent[30], it may induce seizures at high doses[31]. Moreover, memantine strongly induces behaviours typical of the dissociative anaesthetics, including locomotor stimulation[32] and stereotypies[33], and the drug produces PCP- and dizocilpine-like discriminative stimulus effects in rats[34]. As is consistent with these animal studies, recent case reports indicate that memantine can induce agitation, confusion and psychotic symptoms in some Parkinsonian patients taking the drug[35,36]. The extent to which other low-affinity channel blocking NMDA antagonists will produce similar side-effects is at present unknown.

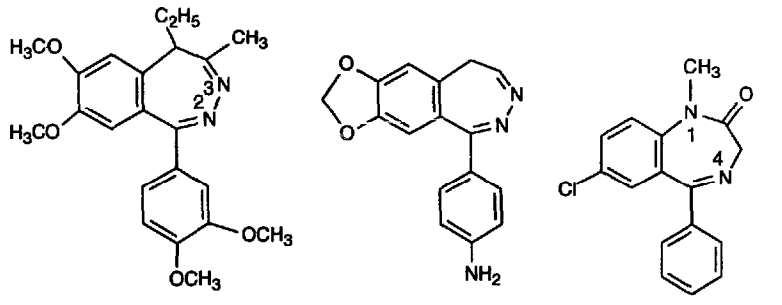


Fig. 2. Comparison of the structures of the 2,3-benzodiazepines, tofisopam and GYKI52466, and the conventional 1,4-benzodiazepine, diazepam.

AMPA/kainate receptor antagonists

Until recently, selective antagonists of AMPA/kainate receptors were not available. Watkins and co-workers described a variety of weak non-NMDA receptor antagonists[37], such as γ-D-glutamylaminomethyl sulfonate (GAMS) and several 1-benzoyl-piperazine-2,3-dicarboxylates, but these compounds were only partially selective. Nevertheless, the observation that intracerebroventricular injection of these compounds protected against audiogenic seizures[38] provided the first suggestion that AMPA/kainate receptor antagonists could have anticonvulsant activity. More recently, certain quinoxalinediones have been identified as potent and selective competitive AMPA/kainate receptor antagonists. One of these, NBQX, which is active when administered systemically and is over 500 times more selective for AMPA than for NMDA recognition sites, has been particularly useful in demonstrating the potential utility of AMPA/kainate receptor antagonists in neurological therapeutics. Thus, NBQX has neuroprotective activity in a wide variety of brain ischaemia models (see e.g. Ref. 39); is anticonvulsant in diverse seizure models (see e.g. Ref. 40); and may potentiate the effects of dopamine receptor agonists in animal models of Parkinson's disease (see e.g. Ref. 41). The neuroprotective activity of AMPA/kainate antagonists, such as NBQX, in transient global ischaemia models is particularly noteworthy in that most investigators have found that NMDA antagonists fail to afford the neuroprotection in these models that they confer in focal ischaemia[2].

As in the case of noncompetitive NMDA receptor antagonists, noncompetitive AMPA/kainate receptor antagonists could have advantages over competitive antagonists. However, until recently, selective noncompetitive AMPA/kainate receptor antagonists were not available. Certain low molecular weight, polyamine-containing, arthropod toxins isolated from venoms of orb-web spiders (argiotoxins and Joro spider toxin) and the Egyptian digger wasp (philanthotoxin) have been purported to be as selective open channel blockers of AMPA/kainate receptors in mammalian neurones as they are at invertebrate neuromuscular junctions[42]. However, it is now clear that in mammalian neurones these toxins are even more potent antagonists at NMDA receptors than at AMPA/kainate receptors[43]. Nevertheless, the recent observations that the spider toxins specifically target certain of the AMPA/kainate receptor subunits[44,45] may provide important leads to the development of subunit-specific agents. Barbiturates also appear to block AMPA/kainate receptors in a noncompetitive fashion[46]. However, these compounds are not useful experimental tools because of their promiscuous actions on other ion channel systems, including GABA$_A$ receptors and voltage-dependent Ca^{2+} channels[47]. Nevertheless, the AMPA/kainate receptor blocking activity of barbiturates could contribute to their efficacy in the treatment of status epilepticus as well as to their neuroprotective activity in certain types of brain injuries. Because of their adverse cardiovascular side effects and a paucity of studies showing long term benefit, barbiturates have not gained widespread clinical acceptance as neuroprotective agents; whether selective AMPA/kainate receptor antagonists will prove to offer clinically significant neuroprotection without the adverse systemic side effects is worthy of investigation.

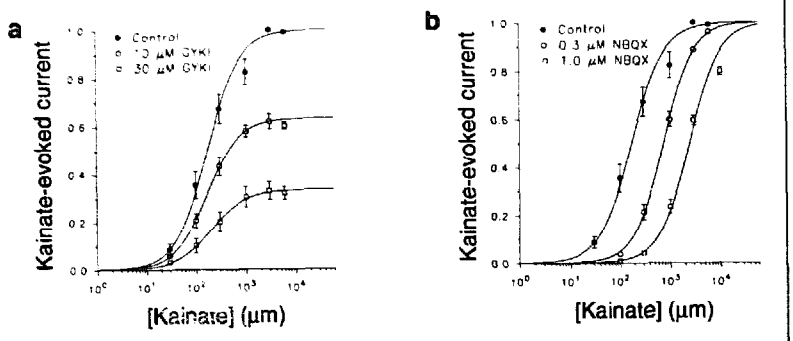


Fig. 3. Comparison of the effects of **a**: *GYKI52466 and* **b**: *NBQX on kainate concentration–response curves obtained in voltage-clamp recordings from cultured hippocampal neurones. GYKI52466 causes a concentration-dependent reduction in the maximal response, indicating that it acts noncompetitively. The rightward shift produced by increasing concentrations of NBQX is consistent with its competitive antagonism at the kainate recognition site.* (Reproduced with permission from Ref. 53.)

GYKI52466: a selective AMPA/kainate antagonist

Identification of a class of highly selective, noncompetitive AMPA/kainate receptor antagonists was the fortuitous by-product of structure–activity studies of the atypical anxiolytic, tofisopam (Fig. 2). Tofisopam is a 2,3-benzodiazepine (homophthalazine) that differs pharmacologically from conventional 1,4-benzodiazepines, such as diazepam, in that it lacks sedative-hypnotic, muscle relaxant and anticonvulsant activity and does not bind to benzodiazepine receptors[48] (although it does bind to a novel homophthalazine site[49]). Tarnawa and his collaborators recognized that the structurally related homophthalazine, GYKI-52466 was unlike tofisopam and its other analogues in that it had muscle relaxant and anticonvulsant activity[50,51]. Electrophysiological studies in rat cortical slices revealed that GYKI52466 was a selective antagonist of quisqualate evoked responses[52]. More recently, the mechanism of the GYKI52466 block has been investigated in whole-cell voltage-clamp recordings from cultured hippocampal neurones[53]. These studies have confirmed that GYKI52466 is a highly selective AMPA/kainate antagonist (IC_{50} for kainate, 7.5 μM) which does not affect NMDA, metabotropic glutamate or $GABA_A$ receptor-mediated responses. Moreover, unlike the quinoxalinedione competitive antagonists, the blocking action of GYKI52466 cannot be overcome by raising the agonist concentration, indicating that it is a non-competitive antagonist (Fig. 3). The GYKI52466 block is largely voltage-independent and the drug appears to bind to closed and open channels equally effectively. GYKI52466 therefore appears to antagonize AMPA/kainate receptor-mediated responses by a novel allosteric blocking mechanism.

Like NBQX, GYKI52466 is effective in experimental models of both focal[54,55] and global ischaemia[56]. In addition, the drug has a broad spectrum of anticonvulsant activity in animal seizure models[57]. In the maximal electroshock test, a widely used screening test for anticonvulsant drugs, the dose-response curve for motor impairment nearly overlaps the curve for seizure protection[40], suggesting that neurological side effects could be an impediment to the clinical use of GYKI52466, or compounds with a similar mode of action. However, in certain seizure models, most notably audiogenic seizures in genetically epilepsy prone mice, GYKI52466 is more potent and, as a result, there is a greater separation between the anticonvulsant and toxic doses[57]. Interestingly, GYKI52466 had protective activity in seizures induced by the glutamate-releasing K^+ channel antagonist 4-aminopyridine or by systemic injection of the excitatory amino acid receptor agonists AMPA and kainate, whereas it has been difficult to show activity for NBQX in these models[40]. Because the competitive block produced by NBQX can be surmounted, it may be relatively less effective than GYKI52466 in the face of high synaptic or extrasynaptic agonist levels. Since the blocking action of GYKI52466 cannot be overcome by high levels of glutamate, it should be possible to administer the drug at relatively lower, less toxic doses. Structure–activity studies have revealed that the methyl-carbamoyl analogue, GYKI53655 is several-fold more potent than the parent compound[59], and since GYKI53566 is a racemate, one of the enantiomers may be even more potent. It can be expected that there will be intense interest in the medicinal chemistry of this class of compounds.

□ □ □

Adverse experiences encountered during clinical trials with competitive NMDA receptor antagonists[60] have focused attention on the need for fresh approaches to developing safe and effective excitatory amino acid receptor antagonists for use in the treatment of epilepsy, ischaemia and neurodegeneration, the major neurological disorders plaguing mankind. Results in animal studies provide reason for cautious optimism regarding the potential of noncompetitive NMDA and AMPA/kainate receptor antagonists. Numerous lead compounds are now available, and some low-affinity NMDA channel blockers (or their prodrugs), including dextromethorphan, remacemide and memantine, have already been demonstrated to be clinically acceptable. Therapeutic trials that are ongoing or planned for the near future will determine whether this optimism regarding the potential clinical utility of noncompetitive excitatory amino acid receptor antagonists is warranted.

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ADCI: (±)-5-aminocarbonyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine
AMPA: α-amino-3-hydroxy-5-phenyl-4-isoxazolepropionate
NBQX: 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(F)quinoxaline
GYKI52466: 1-(4-aminophenyl)-4-methyl-7,8-methylendioxy-5*H*-2,3-benzodiazepine

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