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Review Article

Competitive AMPA antagonism: a novel mechanism for antiepileptic drugs?

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Introduction

Epilepsy is one of the most common neurological disorders, with a prevalence in excess of 0.5% of the world population. Despite a variety of antiepileptic drugs (AEDs) available, there is still a high medical need for improved treatments of epilepsy. About 40% of the patients consider their seizures inadequately controlled (1), and many of those who become free of seizures suffer from adverse effects of which the most frequent are cognitive impairment and a decrease in overall energy level (2, 3).

Glutamate is the main excitatory neurotransmitter in the human brain, and acts at 2 families of ionotropic and metabotropic receptors. There are 3 subtypes of ionotropic glutamate receptors, which are pharmacologically classified as NMDA and non-NMDA (AMPA and kainate) receptors. It has been shown that competitive NMDA receptor antagonists have potent anticonvulsant effects in a variety of animal models (4). In clinical trials, however, they lack anticonvulsant action and elicited unacceptable neurotoxic side effects (5, 6).

AMPA/kainate receptor antagonists also possess a broad spectrum of anticonvulsant activity in preclinical models of epilepsy and, although no clinical data on their antiepileptic potential is available, there is some evidence that they may be better tolerated in humans (7, 8). As it is now well established that the activation of AMPA receptors is involved in the initiation and propagation of seizures (9-11), antagonism of AMPA receptors may represent a promising mechanism for AED action.

Effect of antiepileptic drugs on AMPA receptors

Clinically used AEDs exert their action mainly via inhibition of voltage-sensitive sodium or calcium channels or by enhancement of γ-aminobutyric acid (GABA)ergic inhibition (12, 13). Some of these drugs also interact with AMPA receptors (Fig. 1). For instance, even though the anticonvulsant effect of barbiturates is mainly derived from their potentiation of GABAergic inhibition, pentobarbital (14, 15) and thiopental (16) have been shown to noncompetitively antagonize AMPA receptors at clinically relevant concentrations. However, no clear correlation between the anticonvulsant effect of barbiturates and AMPA receptor inhibition could be found, suggesting that the action of these drugs on AMPA receptors only plays a minor part in their anticonvulsant activity (16). Topiramate, which appears to act mostly via enhancement of GABAergic transmission and a voltage- and use-dependent block of sodium channels (17), has also been shown to be an allosteric AMPA/kainate negative modulator in cultured hippocampal neurons (18, 19). Finally, there is *in vitro* evidence based on autoradiographic studies in the human hippocampus that valproate, which exerts its anticonvulsive action mainly via blockade of

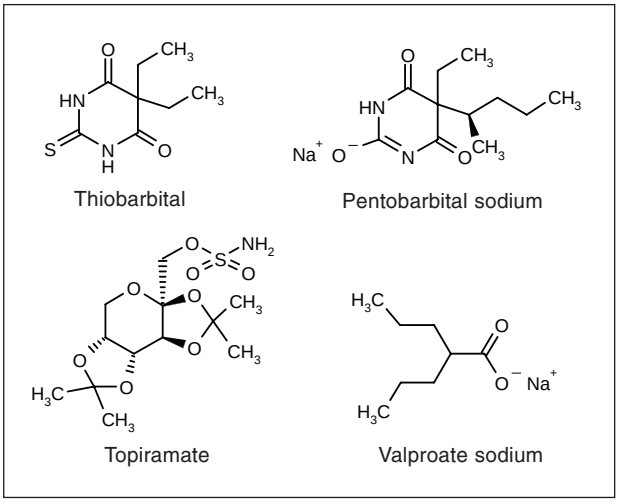

Fig. 1. AEDs that nonselectively interact with AMPA receptors.

voltage-sensitive sodium channels and potentiation of GABA responses (20, 21), also interacts with AMPA receptors at therapeutic concentrations (22).

In conclusion, some AEDs were shown to interact with AMPA receptors, but since they all have multiple mechanisms of action, the extent to which their pharmacological properties are influenced by their interaction with AMPA receptors is unknown.

Animal models to characterize AMPA antagonists

The most frequently used epilepsy models for the characterization of AMPA antagonists are the maximal electroshock seizure test (MES) which is highly predictive for the activity of drugs against generalized tonic-clonic seizures, the subcutaneous pentylenetetrazole test (PTZ) which identifies compounds acting against generalized absence and myoclonic seizures, and the electrical kindling model of temporal lobe epilepsy (23, 24). The pharmacological sensitivity of kindled animals to anticonvulsant drugs is considered predictive for complex partial seizures, the largest subtype of therapy-resistant epilepsies in humans (11, 25-27). In addition, the development of convulsive sensitivity associated with repetitive electrical stimulation of the brain, *i.e.*, the kindling process itself, is thought to be relevant to the study of epileptogenesis (25). The kindling model permits the evaluation of drug efficacy in animals displaying a seizure susceptibility close to truly epileptic animals, whereas the MES and PTZ tests, for instance, reflect the effect of drugs against seizures in a nonepileptic brain. Interestingly, the sensitivity of rats to the neurotoxic effects of some drugs, *e.g.*, NMDA antagonists, is increased by kindling. As a similar difference in tolerability has been observed with NMDA antagonists between healthy volunteers and epileptic patients (5, 6), it has been suggested that this model might help avoid overestimating the therapeutic index of new AEDs (28). NMDA antagonists were shown to retard kindling development, but were not effective against kindled seizures (11). In contrast, AMPA antagonists like NBQX, YM90K or LU 115455 are active against both (11, 29, 30). Such drugs might benefit patients suffering from complex partial seizures and may be clinically useful in preventing epileptogenesis, for instance, after traumatic brain injury.

A number of chemically induced convulsion tests are used for the characterization of potential AEDs. These tests give, to a certain extent, an indication of the mechanism of anticonvulsant action. Not surprisingly, most AMPA antagonists have been tested against AMPA-, NMDA- or kainate-induced convulsions. Their protective action has also been demonstrated against tonic and clonic seizures induced by strychnine, picrotoxin, 4-aminopyridine, isoniazide, 3-mercaptopropionate and other convulsant agents (31-33).

In addition, AMPA antagonists demonstrated anticonvulsant effects in 2 classes of genetic models of epilepsy as described below (34).

Models of reflex epilepsy

DBA/2 (Dilute Brown Agouti) mice are an inbred strain that experience seizures upon exposure to a loud, high-frequency sound (35). This sensitive test for anticonvulsant action does not discriminate between the different drug mechanisms, even though the seizure response is particularly sensitive to GABAergic and monoaminergic agents (35). Several AMPA antagonists, such as NBQX, S 17625 and YM90K, were shown to be protective in this model (36-38).

Genetically epilepsy-prone (GEP) rats are bred from Sprague-Dawley stock and are known as GEPR-3s, which express moderate seizures in response to an acoustic stimulus, or GEPR-9s, which develop more severe seizures (39). GEP rats are more sensitive to anticonvulsant drugs acting in humans on generalized tonic-clonic seizures, simple partial and complex partial seizures than on absence-type and myoclonic seizures (40). The reference AMPA receptor antagonist NBQX was shown to protect GEP rats from audiogenic seizures (41).

Papio papio baboons from the Casamance area in Senegal can be reproducibly induced to exhibit myoclonic seizures after intermittent light stimulation. In general, there is a good correlation between the effective plasma level of AEDs in baboons and epileptic patients (42). NBQX potently reduced the light-induced epileptic response in this model (41). Photosensitivity, which is encountered in approximately 5% of epileptic patients, has also been used for the clinical evaluation of AEDs (43).

Models of absence epilepsy

Two strains of albino rats, the GAERS (genetic absence epilepsy rats from Strasbourg) (44-46) and WAG/Rij rats (47, 48) are considered useful models of absence epilepsy. The electroencephalograms of these rats show spontaneous spike-wave discharges, similar to those observed in human patients suffering from absence epilepsy. The frequency of these seizures is, as commonly observed in children with absence epilepsy, dependent on the level of arousal, and disappear during active behavior. There is evidence from pharmacological studies in WAG/Rij rats that AMPA receptors are involved in this type of epilepsy (49) and AMP397A proved active in this model (50, 51).

Preclinical data

As described below in more detail, the broad-spectrum anticonvulsive activity of AMPA antagonists in preclinical models is now clearly established. The identification of NBQX, the first truly selective AMPA antagonist (52), was instrumental in unveiling the role of this mechanism in the initiation and propagation of seizures. Unfortunately, the clinical development of NBQX was

Table I: In vitro *affinities of AMPA receptor antagonists (IC_{50} or K_i when stated [μM]).*

Antagonist	Company	AMPA receptors [^{3}H]AMPA	AMPA receptors [^{3}H]CNQX	Kainate receptors [^{3}H]kainate	NMDA receptors binding sites Glutamate	NMDA receptors binding sites Glycine
AMP397A	Novartis	0.29	0.014	4.2	0.49[e]	1.16[h]
Indenone 1	Aventis	0.76	-	-	-	3[g]
Indenone 4f	Aventis	0.018	-	-	-	7.2[g]
LU 112313	BASF	K_i = 0.019	-	K_i = 5	-	K_i = 20[f]
LU 115455	BASF	K_i = 0.018	-	K_i = 7.95	-	K_i = 20 [f]
LY293558	Eli Lilly	1.33	1.01	28	12[c]	-
NBQX	Novo Nordisk	0.15	-	4.8	>90[a]	>100[f]
NS 229	Neurosearch	1.8	-	27	-	-
NS 257	Neurosearch	0.07	-	13	44[b]	>100[f]
PNQX	Parke-Davis	0.063	-	0.368	-	0.37[f]
S 16678	Servier	0.09	-	-	-	1.4[f]
S 17625	Servier	0.09	-	-	-	111[f]
SPD502	Neurosearch	0.043	-	81	>30[d]	>30[f]
YM90K	Yamanouchi	0.084	-	2.2	>100[b]	37 [f]
YM872	Yamanouchi	0.096	-	4.6	>100[b]	>100[f]
ZK200775	Schering	0.12	0.032	2.5	2.8[a]	2.8[g]

Tritiated ligands: [a]CPP; [b]Glutamate; [c]NMDA; [d]CGS19755; [e]CGP39653; [f]Glycine; [g]DCKA; [h]MDL-105519.

prevented by its low solubility in water at physiological pH, which combined with a fast renal excretion would have caused crystallization in the kidneys at therapeutic doses (53). Later, introduction of hydrophilic side chains on the quinoxalinedione nucleus led to improved drug candidates, such as ZK200775 (54) and YM872 (55). These compounds entered clinical development as neuroprotective agents, but because of their lack of activity after oral administration, would be of limited use for the treatment of human epilepsy. Recently, AMP397A, another quinoxalinedione derivative with good water solubility and potency, was shown to be active after oral administration (50, 51). Clinical results with such compounds might soon confirm the value of AMPA antagonism as a novel alternative for the development of AEDs. The most representative competitive AMPA antagonists are briefly discussed hereafter. *In vitro* potencies are listed in Table I and structures are shown in Figures 2 and 3. It should be kept in mind that the receptor selectivity profiles of these antagonists are not always fully described and that pharmacokinetic properties may differ. Direct comparisons of *in vivo* results should therefore be made with caution, especially when models, pretreatment times and modes of administration vary.

NBQX was the first potent and selective AMPA antagonist described (52) and its anticonvulsant profile has been thoroughly characterized. It shows activity in the MES, PTZ and in a number of other chemically induced convulsion tests (31, 56), as well as in amygdala-kindled rats (57, 58). NBQX is also active in DBA/2 mice against sound-induced seizures (59), in GEP-9 rats (41) and in photosensitive baboons (41). Due to its lack of oral activity, however, it was never considered a potential AED and entered clinical development as a neuroprotectant (53). When it was shown that NBQX reaches the limit of its solubility in urine at doses that were clearly below the expected therapeutic dose (60), clinical development was discontinued.

Structurally unrelated to NBQX, LY293558 was discovered in the course of studies on the structure-activity relationship of a series of NMDA antagonists (61). The compound displays a 10-fold selectivity for AMPA *versus* NMDA receptors (62). It is protective in the MES test after i.v. dosing (ED_{50} = 2.9 mg/kg, 5 min), but inactive after oral administration (62). The development of LY293558 as a potential AED was not pursued, but limited clinical trials were conducted to evaluate its effect on pain perception. Side effects were mild, with transient visual obscurations defining the maximal tolerated dose. There were no effects on cognition and neurological functions at effective plasma concentrations (7, 8).

NS 229, an isatin oxime, only has a relatively low affinity for AMPA receptors and lacks sufficient water solubility, but was the first AMPA antagonist to demonstrate anticonvulsant activity after oral administration (63). Chemical optimization of NS 229 led to NS 257, a more potent and better water-soluble derivative (64). NS 257 is not orally active, but after i.v. administration proved to be as potent as NBQX against AMPA-induced convulsions (ED_{50} = 10 mg/kg, 5 min). It was considered a potential candidate for the treatment of stroke until follow-up compounds with better affinities and more promising pharmacological profiles were identified.

YM90K, another quinoxalinedione selected as a potential treatment for cerebrovascular ischemia (65), has been less extensively evaluated in epilepsy models than NBQX. In DBA/2 mice, it proved 2- to 3-fold more potent than NBQX (ED_{50} = 2.5-5.4 mg/kg *vs.* 7.2-10.6 mg/kg i.p., 15 min), but this effect was of a short duration of approximately 30 min (38). YM90K caused a marked retardation of kindling development at 7.5 mg/kg i.p. and a decrease in afterdischarge duration and seizure severity at 15 mg/kg (29). In healthy human volunteers, i.v.

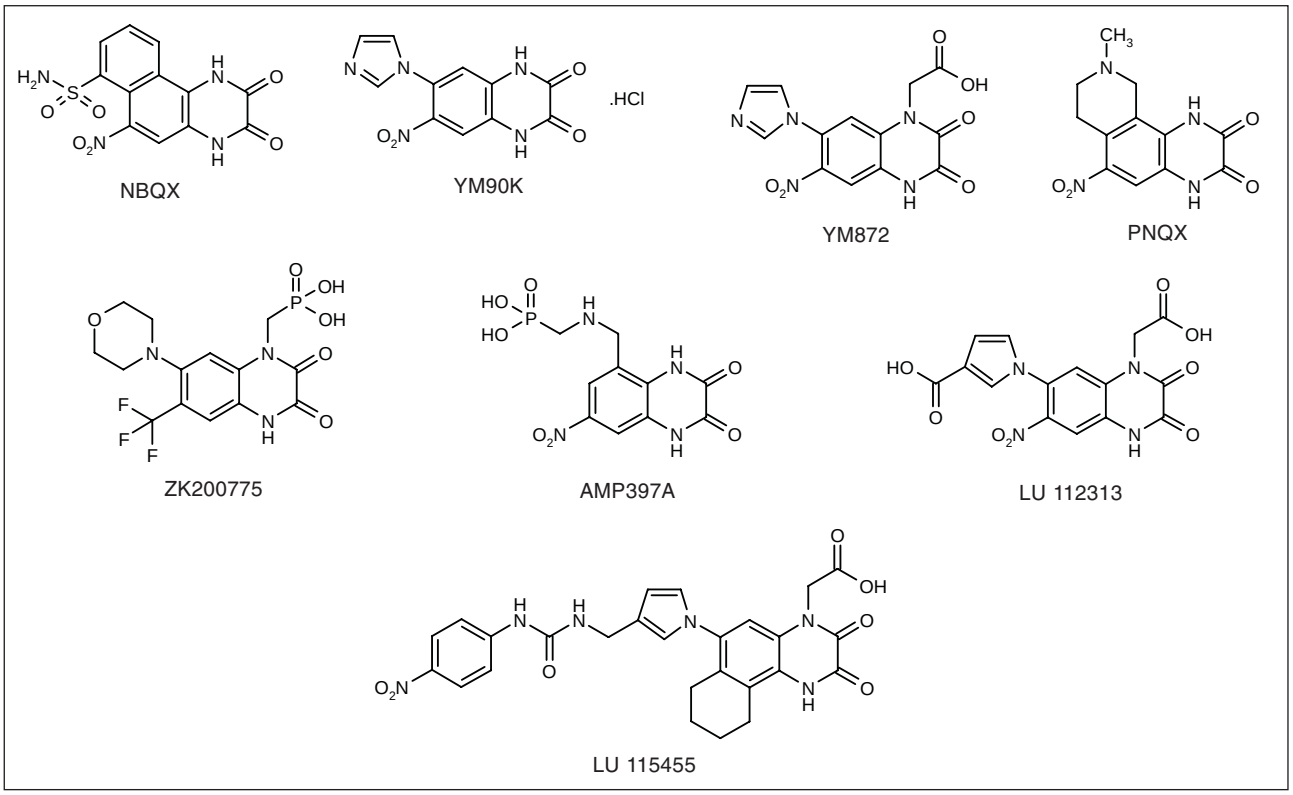

Fig. 2. AMPA receptor antagonists of the quinoxalinedione family.

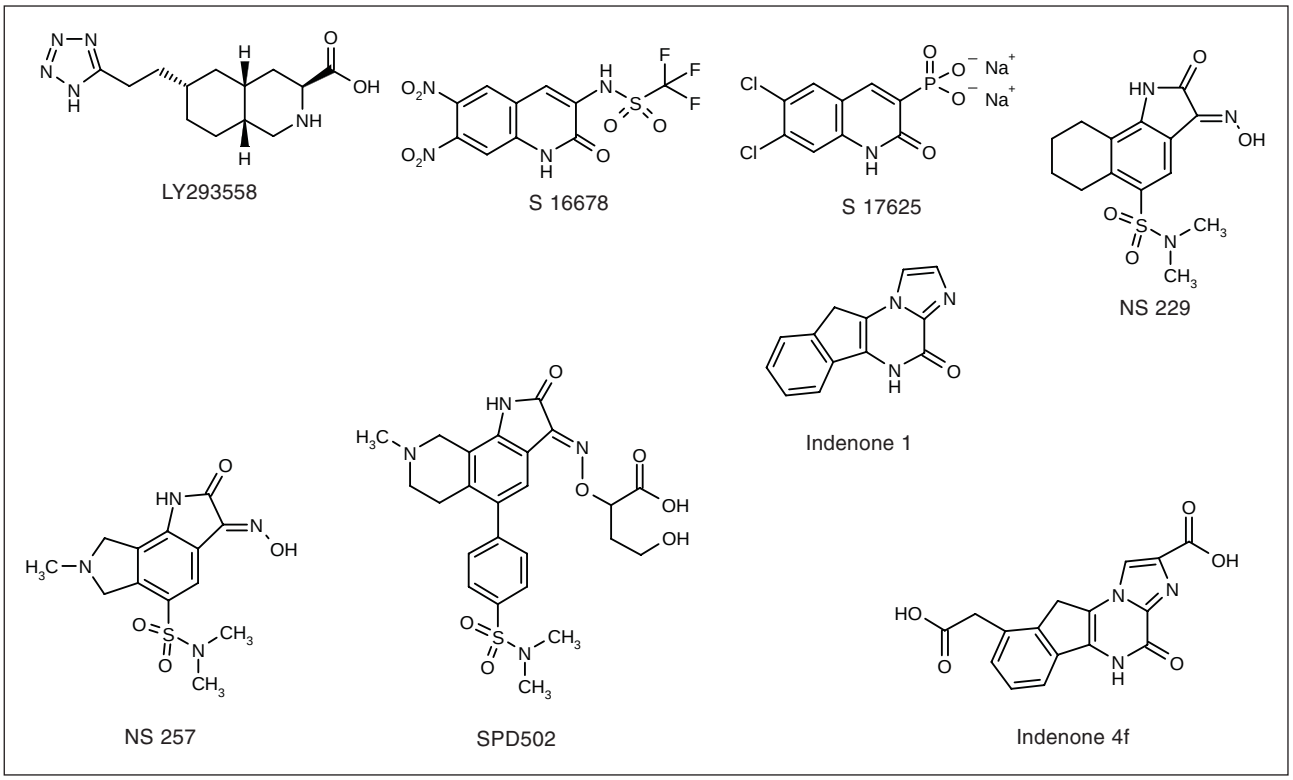

Fig. 3. Nonquinoxalinedione AMPA receptor antagonists.

doses up to 36 mg (in a 600 ml infusion volume) were well tolerated (66), but like NBQX, YM-90K reached saturating concentrations at doses which were not expected to be sufficient for neuroprotection. Further chemical optimization led to an equipotent and 500-fold better water-soluble derivative, YM872 (55), which is currently undergoing clinical trials for cerebrovascular ischemia. No details regarding the anticonvulsant profile of YM872 have been published.

PNQX resulted from an effort to direct the chemical derivatization of the quinoxalinedione backbone of NBQX or YM90K, using the first detailed pharmacophore model of the binding pocket of AMPA receptors (67). This compound is significantly more potent in the MES test 30 s after i.v. injection than NBQX (ED_{50} = 0.44 *vs.* 13.1 mg/kg). The affinities of both antagonists for AMPA and kainate receptors are similar. Assuming that pharmacokinetic parameters are not markedly different, the high anticonvulsant activity of PNQX might result from its additional affinity for the glycine-binding site of NMDA receptors (67). Despite the presence of a nitrogen atom in its saturated ring, PNQX has a low water solubility at physiological pH (8.6 mg/l). It also has a very short duration of action in the MES test after i.v. injection of about 10 min. The synthesis of acyclic derivatives allowed the identification of compounds with improved water solubility, but these were devoid of *in vivo* activity in the MES test (68).

S 16678, one of the first quinolones with high *in vitro* affinity for AMPA, had a very disappointing *in vivo* pharmacology (69). The subsequent introduction of a phosphonic acid side chain improved *in vivo* properties, leading to S 17625, an AMPA antagonist active against clonic seizure in DBA/2 mice with an ED_{50} of 45 mg/kg after oral dosing (37). S 17625 was not further profiled as an anticonvulsant agent and more attention was directed towards its neuroprotective effect after cerebral ischemia (37).

LU 112313 belongs to a series of 6-pyrrolylquinoxalinediones with high affinity for AMPA receptors (70, 71). It is a very selective antagonist, with a 400-fold preference for AMPA over kainate rat forebrain receptors and no affinity for the glycine-binding site of NMDA receptors (30). LU 112313 is highly potent in the MES test (ED_{50} = 2.4 mg/kg i.p., 30 min) and against AMPA-induced convulsions in mice (ED_{50} = 1.4 mg/kg i.p., 1 h). LU 115455, a derivative showing less selectivity with regard to the low-affinity kainate receptor subunits, was able to display anticonvulsant protection in the kindling model at doses inducing no unwanted effects on motor coordination, suggesting an increased safety window for combined AMPA and kainate receptor antagonism in this model (11).

ZK200775 (33, 54) is a potent and selective AMPA antagonist. Its excellent water solubility was obtained with the introduction of a phosphonate-containing side chain on the quinoxalinedione nucleus. Despite previous experience with glutamate antagonists suggesting that such a modification would increase affinity for NMDA receptors, the selectivity for AMPA receptors remained unchanged. ZK200775 is active in the MES (ED_{50} = 13 mg/kg i.v., 5 min) and PTZ tests (ED_{50} = 8 mg/kg s.c., 30 min), as well as in several other chemically induced convulsion tests. This potent antagonist is not active after oral administration and was selected for development as a neuroprotective agent after stroke and brain trauma based on its neuroprotective activity in the rat middle cerebral artery occlusion and gerbil transient global ischemia models, as well as in a percussion model of traumatic brain injury in the rat.

SPD502 is an isatine oxime derivative (72) belonging to the same structural family as NS 257. It is very selective for AMPA receptors and has practically no affinity for kainate receptors or for the glutamate and glycine binding sites of NMDA receptors. SPD502 is anticonvulsant in the MES test where it increased seizure threshold in mice at a dose of 50 mg/kg i.v. This compound appears to possess a more attractive profile in models of neuroprotection and was under consideration for development as an antiischemic agent.

The chemical optimization of Indenone 1, a mixed antagonist with affinity for both AMPA receptors and the glycine-binding site of NMDA receptors (73), led to the identification of high affinity derivatives with improved selectivity and *in vivo* potency (74-76). The exploration of the structure-activity relationship of this interesting series culminated in the identification of Indenone 4f (32), which has a high affinity (IC_{50} = 18 nM) and selectivity for AMPA receptors and is a potent anticonvulsant agent. In the MES test, it was shown to be one of the most potent derivatives described so far (ED_{50} = 1.2 mg/kg i.p., 30 min). It is also active in a number of chemically induced seizure models such as the PTZ test (ED_{50} = 1.7 mg/kg i.p., 30 min) and in DBA/2 mice (ED_{50} = 0.8 mg/kg i.p., 30 min), among others. It is not known whether Indenone 4f is active after oral administration.

Finally, AMP397A is the first AMPA antagonist that combines high affinity for the receptors (IC_{50} = 14 nM), good *in vivo* potency and oral activity (50, 51). Its high solubility in water is due to the presence of an aminophosphonic acid, which also imparts AMP397A with an improved pharmacokinetic profile and a longer duration of action as compared to the corresponding amino carboxylic acid (77). *In vivo*, it demonstrated anticonvulsant activity in a broad range of animal models of epilepsy (50, 51), including the MES test (ED_{50} = 9 mg/kg p.o., 2 h), the PTZ test (ED_{50} = 14 mg/kg i.p., 1 h), against tonic and clonic seizures in DBA/2 mice (ED_{50} = 5.4 and 1.9 mg/kg p.o., 1 h), absence seizures in WAG/Rij rats and in the rat kindling model.

Discussion

The discovery of a first generation of selective AMPA antagonists (*e.g.*, NBQX, YM90K) allowed the study of the therapeutic potential of compounds acting via this mechanism, in particular as anticonvulsant and neuroprotective agents. In view of the promising pharmacological

profile of these earlier compounds, a major effort has been made to find derivatives with improved physicochemical and pharmacokinetic properties and several new drugs with better water solubility and longer duration of action were identified (*e.g.*, NS 257, ZK200775). Their neuroprotective action in animal models of ischemia and traumatic brain injury indicate that AMPA antagonists might be of benefit for the treatment of stroke and trauma in humans. On the other hand, the clinical evaluation of AMPA antagonists as potential AEDs was hampered by the lack of orally active drugs. This problem appears to be solved at last by one of the most recently identified AMPA antagonist, AMP397A. Another reason for not pursuing epilepsy as a possible indication so far, is the potential of AMPA antagonists to cause unwanted effects, especially during chronic treatment. AMPA receptors play a major role in the excitatory processes in the brain, including the neurotransmission governing cognition, memory, motor activity and autonomic functions. It is, therefore, not surprising that pharmacological profiling in animal experiments suggests a potential to cause neurotoxic side effects in human patients (78). In this respect, the first 2 clinical trials performed with NBQX (60) and YM90K (66) showed no unwanted effects in healthy volunteers, but the maximal plasma concentrations reached were considerably below the expected therapeutic concentration. More recently, clinical trials with LY293558 showed that doses effective against hyperalgesia (7) and postoperative pain (8) produce only mild and reversible side effects, indicating that competitive AMPA antagonists may be well tolerated in humans. It remains to be seen, however, whether drugs acting via this mechanism display the same safety profile in epileptic patients.

For treatment-resistant patients, polytherapy has become a recognized approach to enhance effectiveness of AED treatment and several combinations were shown to be of clinical benefit (79). Along these lines, there is also evidence that competitive AMPA receptor antagonists potentiate the anticonvulsant effect of AEDs in preclinical models of epilepsy. For instance, NBQX demonstrated this effect in the MES test at 10 mg/kg, a dose which is inactive by itself. When combined with valproate, carbamazepine, phenobarbital, diphenylhydantoin or diazepam, NBQX decreased the ED_{50} values of the antiepileptic drug by 25-50% of their original values. This effect was observed in the absence of a pharmacokinetic interaction, with AED plasma levels remaining unchanged (80, 81).

Interestingly, multiple action at different ionotropic glutamate receptors seems to have the same effect. For instance, AMPA and NMDA receptor antagonists can act synergistically in the MES test (82) or against kindling-induced seizures (83, 84). This overadditive effect might, in part, explain the unusually high anticonvulsant activity of some nonselective AMPA and NMDA antagonists (67, 85, 86). There is also indirect evidence that a combined action at AMPA and kainate receptors leads to similar overadditive properties (30). Taken together, these observations suggest that the most efficacious antagonists might be those combining a high affinity for AMPA receptors, together with a weaker affinity for NMDA and, possibly, kainate receptors.

Finally, an added benefit of AMPA receptor antagonists for the treatment of epilepsy is their potential neuroprotective activity. It has been shown in animal models that prolonged seizure activity can lead to neuronal death; likewise, status epilepticus in humans is associated with extensive neuronal necrosis both in the hippocampus and other brain regions (87).

Conclusions

More than a decade after the identification of NBQX, results obtained in a variety of animal models demonstrate that AMPA antagonism is indeed a promising novel mechanism for anticonvulsant drug action. So far, clinical trials of competitive AMPA antagonists have been hampered by low water solubility, short duration of action and lack of activity after oral administration. The identification of drug candidates fulfilling these criteria remains a challenge for medicinal chemists. AMP397A, an orally active drug candidate, is a recent step in this direction and may confirm in human patients the promising results obtained in preclinical models of epilepsy with this class of compounds. If this approach proves viable, competitive AMPA antagonists would become the first AEDs acting selectively on the excitatory glutamatergic system, and potentially be of benefit for the treatment of those patients not responding to current therapies.

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