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Review

Glutamate metabotropic receptors as targets for drug therapy in epilepsy

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Abstract

Metabotropic glutamate (mGlu) receptors have multiple actions on neuronal excitability through G-protein-linked modifications of enzymes and ion channels. They act presynaptically to modify glutamatergic and γ-aminobutyric acid (GABA)-ergic transmission and can contribute to long-term changes in synaptic function. The recent identification of subtype-selective agonists and antagonists has permitted evaluation of mGlu receptors as potential targets in the treatment of epilepsy. Agonists acting on group I mGlu receptors ($mGlu_1$ and $mGlu_5$) are convulsant. Antagonists acting on $mGlu_1$ or $mGlu_5$ receptors are anticonvulsant against 3,5-dihydroxyphenylglycine (DHPG)-induced seizures and in mouse models of generalized motor seizures and absence seizures. The competitive, phenylglycine $mGlu_{1/5}$ receptor antagonists generally require intracerebroventricular administration for potent anticonvulsant efficacy but noncompetitive antagonists, e.g., (3a*S*,6a*S*)-6a-naphthalen-2-ylmethyl-5-methyliden-hexahydrocyclopenta[*c*]furan-1-on (BAY36-7620), 2-methyl-6-(phenylethynyl)pyridine hydrochloride (MPEP), and 2-methyl-6-(2-phenylethenyl)pyridine (SIB-1893) block generalized seizures with systemic administration. Agonists acting on group II mGlu receptors ($mGlu_2$, $mGlu_3$) to reduce glutamate release are anticonvulsant, e.g., 2*R*,4*R*-aminopyrrolidine-2,4-dicarboxylate [(2*R*,4*R*)-APDC], (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740), and (−)-2-oxa-4-aminobicyclo[3.1.0]-hexane-4,6-dicarboxylate (LY379268). The classical agonists acting on group III mGlu receptors such as L-(+)-2-amino-4-phosphonobutyric acid, and L-serine-*O*-phosphate are acutely proconvulsant with some anticonvulsant activity. The more recently identified agonists (*R*,*S*)-4-phosphonophenylglycine [(*R*,*S*)-PPG] and (*S*)-3,4-dicarboxyphenylglycine [(*S*)-3,4-DCPG] and (1*S*,3*R*,4*S*)-1-aminocyclopentane-1,2,4-tricarboxylic acid [ACPT-1] are all anticonvulsant without proconvulsant effects. Studies in animal models of kindling reveal some efficacy of mGlu receptor ligands against fully kindled limbic seizures. In genetic mouse models, $mGlu_{1/5}$ antagonists and $mGlu_{2/3}$ agonists are effective against absence seizures. Thus, antagonists at group I mGlu receptors and agonists at groups II and III mGlu receptors are potential antiepileptic agents, but their clinical usefulness will depend on their acute and chronic side effects. Potential also exists for combining mGlu receptor ligands with other glutamatergic and non-glutamatergic agents to produce an enhanced anticonvulsant effect. This review also discusses what is known about mGlu receptor expression and function in rodent epilepsy models and human epileptic conditions.

Keywords: Glutamate receptor, metabotropic; Epilepsy; Anticonvulsant; DBA/2 mouse; Temporal lobe epilepsy; Kindling

1. Introduction

1.1. Glutamate metabotropic receptors

Glutamate is the principal excitatory neurotransmitter in the brain. Initially, it was thought that synaptically released glutamate acted only on ionotropic receptors opening cation-permeable channels. From 1985 onwards, however, evidence accumulated that glutamate, like acetylcholine, dopamine, serotonin, and noradrenaline, could also act via G-protein-coupled metabotropic glutamate (mGlu) receptors to induce phosphoinositide hydrolysis (Sladeczek et al., 1985; Sugiyama et al., 1987) or to decrease adenylate cyclase activity (Tanabe et al., 1992). Since the cloning and sequencing of $mGlu_1$ in 1991 (Masu et al., 1991; Houamed et al., 1991), seven other mGlu receptors have been characterised and sequenced. These eight receptors fall into three groups according to their sequence homology, transduction mechanisms, and agonist pharmacology (see Table 1). The functional unit appears to be a homomeric dimer, with a large amino (N)-terminal extracellular do-

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Table 1
Identified mGlu receptors, transduction systems, and selective agonists

Group	Subtypes	Transduction	Pharmacology
I	$mGlu_1$	Gq	agonists: DHPG, CHPG, (1*S*,3*R*)-ACPD
	$mGlu_5$	↑ PLC, ↑ Ca^{2+}, ↓ K^+, ↓ VOCC, ↑ L-VOCC	antagonists: AIDA, CPCCOEt, BAY36-720, SIB1893, MPEP, LY367385, LY456236
II	$mGlu_2$	Gi/o	agonists: APDC, NAAG,
	$mGlu_3$	↓ AC, ↓ VOCC, ↑ K^+	DCG-IV, LY354740, LY379268, LY389795 antagonists: LY341495, EGlu
III	$mGlu_4$	Gi/o	agonists: (*R,S*)-PPG,
		↓ AC, ↓ VOCC, ↑ K^+	(*S*)-DCPG, L-AP4,
	$mGlu_6$		L-SOP, ACPT-1
	$mGlu_7$		antagonists: MAP4, MSOP,
	$mGlu_8$		MPPG, MCPA, CPPG

Key to symbols: ↑, stimulation; ↓, inhibition; AC, adenylate cyclase; Ca^{2+}, intracellular calcium concentration; K^+, intracellular potassium concentration; VOCC, voltage-operated calcium channels; L-VOCC, L-type voltage-operated calcium channels; PLC, phospholipase C.
Agonists and antagonists: *1S,3R*-ACPD, (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylate; APDC, 2*R*,4*R*-4-aminopyrrolidone-2,4-dicarboxylate; AIDA, (*RS*)-1-aminoindan-1,5-dicarboxylate; BAY36-720, (3a*S*,6a*S*)-6a-naphthalen-2-ylmethyl-5-methyliden-hexahydrocyclopenta[c]furan-1-on; CPCCOEt, 7-(hydroxyimino)cyclopropan[b]chromen-1α-carboxylic ethyl ester; CHPG, (*R*,*S*)-2-chloro-5-hydroxyphenylglycine; DCG-IV, (2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarbocyclopropyl)glycine; DHPG, (*R*,*S*)-3,5-dihydroxyphenylglycine; Eglu, 2*S*-α-ethylglutamate; LY341495, (2*S*,1′*S*,2′*S*)-2-(9-xanthylmethyl)-2-(2′-carboxycyclopropyl)glycine; LY354740,(+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; LY-367385, (*S*)-(+)-α-amino-4-carboxy-2-methylbenzeneacetic acid; LY379268, (−)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylate; LY389795, (−)-2-thia-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylate; LY456236, (4-methoxy-phenyl)-(6-methoxy-quinazolin-4-yl)-amine, HCl; MPEP, 2-methyl-6-(phenylethynyl)pyridine hydrochloride; NAAG, *N*-acetylaspartylglutamate; SIB1893, 2-methyl-6-(2-phenylethenyl)pyridine.

main—a bilobed structure which functions as a "Venus Flytrap" that is converted from the open to the closed configuration by agonist binding—and an intracellular carboxy (C)-terminal with numerous phosphorylation sites and/or Homer-ligand domains (see Pin and Acher, 2002).

Immunogold studies show that the neuronal location of mGlu receptors relative to the synaptic cleft varies according to the group and the subtype of mGlu receptor (review: Shigemoto and Mizuno, 2000). Group I mGlu receptors are found predominantly postsynaptically, with a location adjacent to the margins of the synaptic cleft, and $mGlu_5$, but not $mGlu_1$, is also found on glia. The $mGlu_{1\alpha}$ isoform is particularly prominent on γ-aminobutyric acid (GABA)-ergic interneurons in hippocampus and cerebellum (Shigemoto et al., 1997), while $mGlu_5$ expression is prominent in the limbic cortex and basal ganglia. Group II receptors are predominantly presynaptic, with strong evidence for $mGlu_2$ of location on presynaptic axons in cerebellum, neocortex, and thalamus. While $mGlu_3$ shares a similar pattern of distribution throughout the brain, this subtype is also expressed on glia (Tamaru et al., 2001). Group III mGlu receptors are also presynaptic with $mGlu_4$, $mGlu_7$, and $mGlu_8$ mRNA being located in the basal ganglia motor loop (Messenger et al., 2002); however, $mGlu_6$ expression appears to be largely restricted to retinal neurons.

1.2. mGlu receptor function

Group I mGlu receptors are coupled to a stimulatory G-protein (G_q) and activate inositol phosphate hydrolysis. G-protein activation of PLC will generate inositol-1,4,5-triphosphate and diacylglycerol from phosphatidylinositol-4,5-biphosphate. Inositol-1,4,5-triphosphate then activates protein kinase C (PKC). Inositol phosphates are known to regulate membrane trafficking, glucose metabolism, cytoskeletal organisation, and most importantly, intracellular Ca^{2+} homeostasis—particularly the release of stored Ca^{2+} via inositol-1,4,5-triphosphate-sensitive receptors. Secondary activity induced by these pathways includes activation of plasma membrane voltage-operated Ca^{2+} channels (VOCC) and the induction of K^+ efflux via Ca^{2+}-sensitive K^+ channels. Groups II and III mGlu receptors act via an inhibitory G-protein (G_i) to inhibit adenylate cyclase activity and decrease the formation of cyclic adenosine monophosphate (cAMP), which can result in the inhibition of VOCCs (Table 1).

Metabotropic glutamate (mGlu) receptors have an enormous diversity of effects on neurons and glia (reviews: Winder and Conn, 1996; Conn and Pin, 1997; Anwyl, 1999; Cartmell and Schoepp, 2000; Schoepp, 2001) and exhibit activity-dependent plasticity, including a process of desensitisation related to phosphorylation and internalisation of the receptor molecules (particularly, group I mGlu receptors; review: Dale et al., 2002).

Neuronal group II mGlu receptors are predominantly presynaptic on the axons rather than in close proximity to the synapses. They have a high affinity for glutamate and apparently respond to synaptic glutamate "spillover." It is not clear if, or to what extent, $mGlu_2$ desensitises due to protein kinase phosphorylation (Schaffhauser et al., 2000), since in some in vitro systems, $mGlu_2$ is resistant to agonist-induced desensitisation (S. Lennon, personal communication, 2003). Of group III mGlu receptors, $mGlu_7$ has a low affinity for glutamate, whereas $mGlu_8$ has a high glutamate affinity. However, $mGlu_7$, like $mGlu_1$ and $mGlu_5$, interacts with calmodulin in the C-terminal tail region in a Ca^{2+}-dependent manner (O'Connor et al., 1999; Minakami et al., 1997). For $mGlu_5$ and $mGlu_7$, this interaction is prevented by PKC-induced phosphorylation. A review of mGlu receptor-associated interactions with other G-protein receptors via intracellular signalling has been published (Moldrich and Beart, 2003).

The modulation of neurotransmitter release by mGlu receptor ligands has been reviewed by Cartmell and Schoepp (2000). In short, group I mGlu receptor agonists are able to increase glutamate release in neocortical, striatal, and hippocampal in vitro cultures or slices, while groups II

and III mGlu receptor agonists are able to inhibit glutamate release in such preparations.

1.3. Selective mGlu receptor agonists and antagonists

The large number of pharmacological agents with specific agonist or antagonist actions at mGlu receptors has been reviewed by Schoepp et al. (1999), while relationships between mGlu receptor structure and activation mechanisms have been reviewed by Pin et al. (1999), Bräuner-Osbourne et al. (2000), and Pin and Acher (2002). It is notable that competitive agonists and antagonists that bind to the "Venus Flytrap" module show some group selectivity, but rather limited subtype specificity, largely because the amino acids that contribute to the agonist binding domain are highly conserved between mGlu receptor subtypes. Recently, various noncompetitive antagonists or allosteric modulators that bind to the heptahelical transmembrane domain have been described (Hermans et al., 1998; Pagano et al., 2000). These can show a high degree of subtype selectivity presumably because of the lower degree of sequence homology in this region. Structures that are glutamate homologues, or are derived from, or analogous to phenylglycine, tend to penetrate the blood–brain barrier poorly, whereas some of the noncompetitive antagonists and heterobicyclic carboxylates penetrate well and show activity when administered systemically. Allosteric modulators can be antagonists, often with inverse agonist action related to constitutive activity of the receptor (e.g., Carroll et al., 2001). Very recently, positive allosteric modulators of mGlu receptors and other group I mGlu receptor noncompetitive antagonists have been described (Britton et al., 2002; Cosford et al., 2002; Li et al., 2002; Lesage et al., 2002; Mutel et al., 2002), but their actions in models of epilepsy have yet to be reported.

1.4. Role of mGlu receptors in epilepsy

Present clinically efficacious antiepileptic drugs act by inducing prolonged inactivation of the Na^+ channel (e.g., phenytoin, carbamazepine, lamotrigine or valproate) by blocking Ca^{2+} channel currents (e.g., ethosuximide) or by enhancing inhibitory GABAergic neurotransmission (e.g., diazepam, vigabatrin or tiagabine) (Meldrum and Chapman, 1999). Some antiepileptic drugs act via a number of different mechanisms, which may include antagonism of (*S*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (e.g., felbamate, phenobarbitone or topiramate). Most often, therapeutic regimes for epileptic patients will involve a change of first-line and/or add-on (adjunct) antiepileptic drugs. Most antiepileptic drugs are associated with adverse effects, such as sedation and ataxia and weight loss (e.g., topiramate) or weight gain (valproate, tiagabine, and vigabatrin). Rare adverse effects can be life threatening such as rashes leading to Stevens–Johnson syndrome (e.g., lamotrigine) or aplastic anemia (e.g., felbamate) (Bourgeois, 1998). Some epileptic patients are unresponsive to antiepileptic drug treatment. For this reason, research continues into safe and more effective antiepileptic drugs.

Excessive glutamatergic neurotransmission is understood to be one of the primary metabolic and pathological mechanisms behind the aetiology of numerous types of epilepsy (Chapman et al., 1996). A number of early studies showed that glutamate and kainate were capable of inducing epilepsy in animals that correlated with human symptoms (Johnston, 1973; Ben-Ari, 1985; Meldrum, 1991). Since then, a number of functional changes in excitatory amino acid neurotransmission have been reported in seizure-susceptible animals including increased excitatory amino acid-induced Ca^{2+} influx, altered excitatory amino acid binding, enhanced glutamate and aspartate release, and modulation of glutamate transporter expression and function (review: Meldrum et al., 1999).

Because metabotropic glutamate receptor ligands are relatively novel compared for example to benzodiazepines or Na^+ channel inhibitors, the potential of mGlu receptor ligands to attenuate epileptic seizures has not yet been fully investigated. At present, no identified mGlu receptor ligand is in clinical use for the amelioration of epileptic seizures. (The possibility that current antiepileptic drugs may be allosteric modulators of mGlu receptors has not been fully explored.) Interest in ionotropic glutamate receptor antagonists as potential antiepileptic drugs increased with the discovery of competitive and noncompetitive *N*-methyl-D-aspartic acid (NMDA) receptor antagonists, such as D-CPPene, (E)-4-(3-phosphonopropyl)piperazine-2-carboxylic acid and MK-801, (5*S*,10*R*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine maleate and the noncompetitive AMPA receptor antagonist 4-(8-methyl-9*H*-1,3-dioxolo[4,5-h][2,3]benzodiazepin-5-yl)-benzenamine dihydrochloride (GYKI 52466). These glutamate antagonists all show therapeutic potential in animal models of epilepsy (Chapman et al., 1991; Meldrum et al., 1992), but they failed early clinical trials and ionotropic glutamate receptors have since lost favour as sole therapeutic targets for antiepileptic drugs. Ionotropic glutamate receptors continue, however, to be investigated to further understand the role of glutamate in the aetiology of epilepsy. Reports that group III and later group II mGlu agonists could block glutamatergic transmission initiated new interest in mGlu receptors as targets for novel antiepileptic drugs. It is also known that mGlu receptors are expressed in the key epileptogenic regions of the brain including the cerebral cortex, the thalamus, the amygdala, and the hippocampus, and even the basal ganglia which receives inputs from these regions (e.g., Rouse et al., 2000).

Numerous publications describe the modulation of epileptiform discharges by mGlu receptor ligands in slice preparations. This review is, however, primarily concerned with mGlu receptors as potential targets for antiepileptic drugs; thus, the emphasis here is on in vivo studies in animal

models of epilepsy. Doherty and Dingledine (2002) have recently provided a broad review of the role of mGlu receptors in epilepsy.

2. Group I mGlu receptors

2.1. Group I mGlu receptor agonists are convulsant

Compounds which show group I mGlu receptor agonist activity are uniformly convulsant when injected focally into the brain or into the cerebral ventricles. In the case of the prototypic group I mGlu receptor agonist, quisqualate, some of this proconvulsant effect may be due to nonselective AMPA receptor activation. Similarly, conclusions about the focal convulsant effect of (1*S*,3*R*)-ACPD, (1S,3R)-1-amino-cyclopentane-1,3-dicarboxylic acid (Tizzano et al., 1993, 1995), must be limited because it is not specific for group I mGlu receptors. Thus, data relating to convulsant activity of 3,5-dihydroxyphenylglycine (DHPG) (Tizzano et al., 1995; Camón et al., 1998) are particularly valuable since this agonist is relatively devoid of activity at non-group I mGlu receptors and is approximately equipotent at $mGlu_1$ and $mGlu_5$ (Schoepp et al., 1999). (*R*,*S*)-2-chloro-5-hydroxy-phenylglycine (CHPG) activates $mGlu_5$ and not $mGlu_1$ receptors (Doherty et al., 1997), but is comparable to DHPG as a convulsant when given intracerebroventricularly to mice.

The convulsant effect of group I mGlu receptor agonists may result from a number of direct excitatory actions. These include block of accommodation and activation of cationic nonselective channels, L-type Ca^{2+} channels, and inactivation of Ca^{2+}-activated and non-Ca^{2+}-activated K^+ channels or an enhancement of Na^+/Ca^{2+} exchange. Alternatively, group I mGlu receptors can modulate excitatory actions indirectly by potentiating the activation of NMDA and/or AMPA receptor responses. For example, in cortical pyramidal neurons $mGlu_1$ activation potentiates NMDA responses via a calmodulin-dependent, but PKC-independent, mechanism involving tyrosine phosphorylation of NR2A subunits (Heidinger et al., 2002). In contrast, in hippocampal pyramidal neurons, NMDA potentiation occurs through $mGlu_5$ activation by a PKC-dependent mechanism (Mannaioni et al., 2001). There is also evidence (in *Xenopus* oocytes) for $mGlu_1$ potentiation of NMDA responses by insertion of new NMDA receptors into the surface membrane (Lan et al., 2001). Activation of NMDA receptors has also been shown to reverse desensitisation of $mGlu_5$ receptors by activation of a protein phosphatase (Alagarsamy et al., 2001). An enhancement of AMPA receptor-mediated responses has been described at various brain and spinal cord sites (Anwyl, 1999). Additionally, presynaptic actions of group I mGlu receptors may be important, either by impairing inhibitory GABAergic postsynaptic potentials (Marino et al., 2001) or by enhancing glutamate release (Cartmell and Schoepp, 2000).

2.2. Group I mGlu receptor antagonists are anticonvulsant

Initial experiments showing the anticonvulsant effects of (*S*)-4-carboxy-3-hydroxyphenylglycine and (*S*)-4-carboxy-phenylglycine in sound-induced seizures in DBA/2 mice suggested that either $mGlu_1$ antagonism or group II mGlu receptor agonist activity might be anticonvulsant (Thomsen et al., 1994; Dalby and Thomsen, 1996). Experiments employing competitive antagonists with greater specificity for $mGlu_1$, e.g., (*S*)-(+)-*a*-amino-4-carboxy-2-methylbenzeneacetic acid (LY367385) and (*R*,*S*)-1-aminoindan-1,5-dicarboxylic acid (AIDA) confirmed that such action was anticonvulsant not only in models of generalised motor seizures but also in a model of absence epilepsy (Chapman et al., 1999a).

2-Methyl-6-(phenylethynyl)pyridine hydrochloride (MPEP) and 2-methyl-6-(2-phenylethenyl)pyridine (SIB-1893) are potent noncompetitive antagonists at $mGlu_5$ receptors (Varney et al., 1999; Kuhn et al., 2002; Gasparini et al., 2002) that suppress clonic seizures induced by the $mGlu_5$ selective agonist, CHPG, given at low doses intracerebroventricularly or intraperitoneally (Chapman et al., 2000b). These compounds are also effective against sound-induced seizures and DHPG-induced seizures in DBA/2 mice at significantly higher doses than are required to suppress CHPG-induced seizures. In lethargic mice (lh/lh), a genetic absence model, MPEP (50 mg/kg, i.p.), caused a marked reduction in the incidence of spontaneous spike-and-wave discharges. It has been suggested that MPEP and SIB-1893 both in vitro and in vivo act as NMDA receptor antagonists at somewhat higher doses than are required for $mGlu_5$ antagonism (O'Leary et al., 2000; Movsesyan et al., 2001). MPEP (6 mg/kg, intravenous) in the rat, however, suppresses neuronal firing triggered by DHPG, but not that triggered by NMDA (Gasparini et al., 2002). There is additional evidence that MPEP at high concentrations may act to modulate GABA neurotransmission, act at $mGlu_4$ and at norepinephrine receptors (Battaglia et al., 2001; Mathiesen et al., 2003). A related noncompetitive $mGlu_5$ antagonist, MTEP, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine, that lacks the nonspecific effects of MPEP has recently been described (Cosford et al., 2002), but its effect in seizures has yet to be reported.

A group of second-generation phenylglycine-like $mGlu_{1/5}$ antagonists have demonstrated potent anticonvulsant activity in models of DHPG-induced limbic seizures (order of potency: LY393053 > LY339764=LY367335= LY367366>LY367385, LY339840>AIDA; Kingston et al., 2002). Whereas such phenylglycine derivatives require intracerebroventricular administration to demonstrate anticonvulsant activity, the noncompetitive $mGlu_1$ antagonist, (3a*S*,6a*S*)-6a-naphthalen-2-ylmethyl-5-methyliden-hexahydrocyclopenta[*c*]furan-1-on (BAY36-7620) was found to be anticonvulsant following systemic administration (Chapman et al., 2000a). Similarly, a series of aminopyridine derivatives have been described that are potent noncom-

petitive antagonists with high selectivity for $mGlu_1$ (Li et al., 2002). One such compound, LY456236, has been shown to be anticonvulsant against sound-induced seizures in DBA/2 mice and limbic seizures in the 6 Hz, mouse focal seizure model following intraperitoneal administration, and anticonvulsant against amygdala-kindled seizures in the rat with oral administration (Shannon and Peters, 2002).

It is likely that no subtype of group I mGlu receptors primarily mediates the anticonvulsant action of group I mGlu ligands, since subtype selective antagonists for $mGlu_1$ and $mGlu_5$ are equally potent and non-subtype-selective antagonists appear to be the most potent anticonvulsants of this class. The complex interaction between $mGlu_1$ and $mGlu_5$ on neuronal burst frequency and duration is, however, only starting to be understood (e.g., Lanneau et al., 2002; Merlin, 2002; Thuault et al., 2002; Stoop et al., 2003). A summary of the anticonvulsive activity of group I mGlu receptor antagonists is presented in Table 2.

Table 2
Anticonvulsant activity of group I mGlu receptor antagonists

Antagonist	Selectivity	Model	Dose and route
(*S*)-4CPG	1>5	DBA/2(S)[a]	500 nmol i.c.v.
	(agon. $mGlu_{2/3}$)	DMCM[a]	ED_{50}>500 nmol i.c.v.
		PTZ[a]	500 nmol i.c.v.
(*S*)-4C3HPG	1>5	DBA/2(S)[b]	ED_{50} 110nmol i.c.v.
	(agon. $mGlu_{2/3}$)	DMCM[a]	ED_{50} 180nmol i.c.v.
		PTZ[a]	150 nmol i.c.v.
LY367385	1>5	DBA/2(S)[c]	ED_{50} 12nmol i.c.v.
		GEPR(S)[c]	160 nmol i.c.
		lh/lh SWD[c]	250 nmol i.c.v.
		DHPG[d]	$ED_{50} \approx 122$ nmol i.c.
AIDA	1=5	DBA/2(S)[c]	ED_{50} 79 nmol i.c.v.
		GEPR(S)[c]	100 nmol i.c.
		Lh/lh SWD[c]	500 nmol i.c.v.
		DHPG[d]	$ED_{50} \approx 477$ nmol i.c.
SIB-1893	5	DBA/2(S)[e]	ED_{50} 27mg/kg i.p.
		DHPG[e]	ED_{50} 31mg/kg i.p.
		CHPG[e]	ED_{50} 0.19mg/kg i.p.
MPEP	5	DBA/2(S)[e]	ED_{50} 18mg/kg i.p.
		DHPG[e]	ED_{50} 22mg/kg i.p.
		CHPG[e]	ED_{50} 0.42mg/kg i.p.
		Lh/lh SWD[e]	50 mg/kg i.p.
BAY36-7620	1	DBA/2(S)[e]	ED_{50} 163 mg/kg i.p.
LY456236	1	DBA/2 (S)[f]	30–100 mg/kg i.p.
		Am-K rat[f]	60 mg/kg p.o.
LY339840	1>5	DHPG[d]	$ED_{50} \approx 138$ nmol i.c.
LY339764	1=5	DHPG[d]	$ED_{50} \approx 43$ nmol i.c.
LY367366	1=5	DHPG[d]	$ED_{50} \approx 39$ nmol i.c.
LY367335	1=5	DHPG[d]	$ED_{50} \approx 35$ nmol i.c.
LY393053	1=5	DHPG[d]	$ED_{50} \approx 9$ nmol i.c.

Abbreviations: agon., agonist; Am-K, amygdala-kindled; DMCM, methyl-6,7-dimethoxy-4-ethyl-β-carboline-2-carboxylate; GEPR, genetically epilepsy-prone nine rats; lh/lh, lethargic mice; (S), sound-induced seizures; SWD, spike-wave discharge.

Antagonists (see also Table 1): (*S*)-4C3PG, (*S*)-4-carboxy-3-hydroxyphenylglycine; (*S*)-4CPG, (*S*)-4-carboxyphenylglycine; LY339840, (*R*,*S*)-2-methyl-3-hydroxy-4-carboxyphenylglycine; LY339764, (*R*,*S*)-2-amino-2-(4-carboxyphenyl)3-(9*H*-xanthen-9-yl)propanoic acid; LY367366, (*R*,*S*)-2-amino-2-(4-carboxyphenyl)-3-(9*H*-thioxanthen-9-yl) propanoic acid; LY367335, 2-amino-2-(3-*cis* and *trans*-carboxycyclobutyl)-3(9*H*-xanthen-9-yl) propionic acid; LY393053, 2-amino-2-(3-*cis* and *trans*-carboxycyclobutyl)-3-(9*H*-thio-xanthen-9-yl)propionic acid.

[a] Dalby and Thomsen, 1996.
[b] Thomsen et al., 1994.
[c] Chapman et al., 1999a.
[d] Kingston et al., 2002.
[e] Chapman et al., 2000b.
[f] Shannon and Peters, 2002.

3. Group II mGlu receptors

3.1. Group II mGlu receptor agonists are anticonvulsant

Following the evidence that (*S*)-4-carboxy-3-hydroxyphenylglycine [(*S*)-4C3HPG] was anticonvulsant and an agonist at group II mGlu receptors, further compounds with some preferential action on group II mGlu receptors were tested in various epilepsy models (see Table 3). Interpretation of early experiments is complicated by the nonselective actions of these compounds, but the anticonvulsant effect of low doses of (2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)-glycine (DCG-IV) against chemoconvulsant-induced seizures was reversed by the group II antagonist (*R*,*S*)-α-methyl-4-tetrazolylphenylglycine (MTPG) (Folbergrová et al., 2001). DCG-IV is, however, unable to inhibit kainic acid-induced seizures when administered intracerebroventricularly (Miyamoto et al., 1997) despite being 70-fold more potent than lamotrigine at inhibiting [^{3}H]D-aspartate release (Attwell et al., 1998a). Data from experiments with (2*R*,4*R*)-4-aminopyrrolidine-2,4-dicarboxylate [(2*R*,4*R*)-APDC] and the Eli Lilly aminobicyclo dicarboxylates (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate, LY354740, (−)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylate, LY379268, and (−)-2-thia-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylate, LY389795) confirm the anticonvulsant effect of group II mGlu receptor activation (Klodzinska et al., 1999; Moldrich et al., 2001b,c). Anticonvulsant effects are seen with these agonists in generalised seizure models including some but not all chemical-induced seizure models. Interestingly, a loss of anticonvulsant activity was seen with (2*R*,4*R*)-APDC at doses twofold higher than those which produced full anticonvulsant effects in sound-induced seizures of DBA/2 mice (Moldrich et al., 2001c). A similar anticonvulsant–proconvulsant effect was seen following intra-amygdaloid injection of (2*R*,4*R*)-APDC in amygdala-kindled rats, which correlated with a biphasic (2*R*,4*R*)-APDC-induced inhibition of [^{3}H]D-aspartate release (Attwell et al., 1998b). This effect seems, however, particular to (2*R*,4*R*)-APDC since no such proconvulsant activity was seen with LY379268 or LY389795 (Moldrich et al., 2001b) and may be due to potentiation of group I mGlu receptor activity (Schoepp et al., 1996). Neugebauer et al. (2000) reported that (2*S*,1′*S*,2′*S*)-2-(carboxycyclopropyl)glycine (L-CCG-I) had an increased potency to inhibit EPSP in hippocampal neurons following kindling, but LY379268 was only weakly effective (intraperitoneal) against amyg-

Table 3
Anticonvulsant activity of group II mGlu receptor agonists

Agonist	Selectivity	Model	Dose and route
L-CCG-1	2>1=3	DBA/2(S)[a,b]	20–500 nmol i.c.v.
DCG-IV	2 (NMDAR agon.)	HCA[c]	0.6 nmol i.c.v.
(1*S*,3*R*)-ACPD	1=2=3	DBA/2(S)[a,b]	150–700 nmol i.c.v.
(*S*)-4C3HPG	2 antag. $mGlu_1$	PTZ[a]	325–500 nmol i.c.v.
(2*R*,4*R*)-APDC	2	DBA/2(S)[d]	20 nmol i.c.v.
			100 mg/kg i.p.
		DHPG[d]	20 nmol i.c.v.
LY354740	2	PTZ[e]	4–16 mg/kg i.p.
LY379268	2=3>4, 6, 8	DBA/2(S)[f]	ED_{50} 0.08 nmol i.c.v.
		DHPG[f]	ED_{50} 2.9 mg/kg i.p.
		Am-K rat[f]	ED_{50} 0.3 pmol i.c.v.
		lh/lh SWD[f]	10 mg/kg i.p.
			10 mg/kg i.p.
			1–10 nmol i.c.v.
LY389795	2=3>6, 8	DBA/2(S)[f]	ED_{50} 0.82 nmol i.c.v.
		DHPG[f]	ED_{50} 3.4 mg/kg i.p.
		Am-K rat[f]	ED_{50} 0.03 nmol i.c.v.
		lh/lh SWD[f]	10 mg/kg i.p.
			10 mg/kg i.p.
			1–10 nmol i.c.v.

Abbreviations: agon., agonist; Am-K, amygdala-kindled; antag., antagonist; GEPR, genetically epilepsy-prone nine rats; HCA, DL-homocysteic acid; lh/lh, lethargic mice; NMDAR, NMDA receptor; (S), sound-induced seizures; SWD, spike-wave discharge; PTZ, pentylenetetrazol.
Agonist: LCCG-I, (2*S*,1′*S*,2′*S*)-2-(carboxycyclopropyl)glycine.
[a] Dalby and Thomsen, 1996.
[b] Meldrum et al., 1996.
[c] Folbergrová et al., 2001.
[d] Moldrich et al., 2001c.
[e] Klodzinska et al., 1999.
[f] Moldrich et al., 2001b.

dala-kindled seizures in rats (Moldrich et al., 2001b). Spike wave discharges are reduced in lethargic (lh/lh) mice up to 90 min following intracerebroventricular infusion with either LY379268 or LY389795 (Moldrich et al., 2001b). High doses of (2*R*,4*R*)-APDC, LY379268, and LY389795 (>1 μmol, i.c.v.) produced clonus, but these doses were 1000-fold higher than anticonvulsant doses and far beyond those that induced sedation and as such were most likely toxic due to "off-target" effects (Moldrich et al., 2001a,b). By comparison, very little epilepsy research has been undertaken with LY354740. This is in part due to the poor bioavailability of this compound and also to the fact that a highly bioavailable prodrug of LY354740 is in human trials (Levine et al., 2002).

3.2. Effects of group II mGlu receptor antagonists

The group II mGlu receptor antagonist (2*S*)-2-amino-2-[(1*S*,2*S*)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid (LY341495) (which is also a potent agonist at $mGlu_8$) produces clonic and tonic seizures when injected at low doses (0.3–1 μmol, i.c.v.) in DBA/2 mice (Moldrich, Chapman, and Meldrum, unpublished observation) and completely reverses the anticonvulsant effects of LY379268 and LY389795 in sound-induced seizures in DBA/2 mice at 100 nmol i.c.v. (Moldrich et al., 2001b). This compound, however, antagonises other mGlu receptors at higher concentrations, and the dose-selectivity of this antagonist for $mGlu_{2/3}$ has not been established in vivo. The more selective group II antagonist (2α)-ethylglutamic acid, EGlu, is also convulsive when given intracerebroventricularly (3–7 μmol) to DBA/2 mice (Meldrum et al., 1996). The group II mGlu receptor selective antagonist, (*R*,*S*)-1-amino-5-phosphonoindan-1-carboxylic acid (APICA) given intracerebroventricularly up to 2.5 μmol did not produce seizure activity (Moldrich, Chapman, and Meldrum, unpublished observation). Given the differing selectivity, results, and high doses required of group II mGlu receptor antagonists to induce seizures, it would be premature to conclude that antagonism of group II mGlu receptors induces seizures.

4. Group III mGlu receptors

4.1. Group III mGlu receptor agonists are anticonvulsant

Initial studies employing intracerebroventricular administration of the two classic group III mGlu receptor agonists, L-(+)-2-amino-4-phosphonobutyric acid (L-AP4), and *O*-phospho-L-serine (L-SOP) emphasized the early proconvulsant effect of these compounds (Ghauri et al., 1996). Focal injection into the amygdala of the group II/III agonist (1*S*,3*S*)-ACPD or the group III agonist L-AP4 blocks kindled seizures (Attwell et al., 1995; Abdul-Ghani et al., 1997; Suzuki et al., 1996). Interestingly, one of the studies with L-AP4 in the amygdala (Suzuki et al., 1996) and a study with focal injection of the similar group III agonist L-SOP in the inferior colliculus of genetically epilepsy-prone (GEP) rats showed a very prolonged anticonvulsant effect (1–3 days) (Tang et al., 1997) that was unlikely to be related to the local persistence of the compound. Experiments looking at changes in mGluR mRNA and protein suggest that enhanced synthesis of mGlu receptor protein, particularly $mGlu_7$, may occur after agonist activation (Yip et al., 2001).

The novel group III mGlu receptor agonist (1*S*,3*R*,4*S*)-1-aminocyclopentane-1,2,4-tricarboxylic acid (ACPT-1), with a high affinity for $mGlu_4$, $mGlu_6$, and $mGlu_8$ (similar to L-SOP and L-AP4) shows potent anticonvulsant action in similar animal models with little evidence for proconvulsant actions, suggesting that something other than group III mGlu receptor agonist action may be responsible for the convulsant effect of L-SOP and L-AP4 (Chapman et al., 2001).

Two novel group III mGlu receptor agonists, (*R*,*S*)-4-phosphonophenylglycine [(*R*,*S*)-PPG] and (*S*)-3,4-dicarboxyphenylglycine [(*S*)-3,4-DCPG], with some selectivity for $mGlu_8$ have been studied as anticonvulsants. (*R*,*S*)-PPG is a potent anticonvulsant against sound-induced seizures in DBA/2 mice and against electroshock seizures in mice, with little evidence of any excitant or proconvulsant actions (Chapman et al., 1999b, Gasparini et al., 1999). An inter-

esting difference between the anticonvulsant actions of (*R*,*S*)-PPG and ACPT-1 is that the effects of ACPT-1 are reversed by moderate doses of selective group III mGlu receptor antagonists, such as (*R*,*S*)-α-methylserine-*O*-phosphate (MSOP), (*R*,*S*)-α-methyl-4-phosphonophenylglycine (MPPG) and (*S*)-2-methyl-2-amino-4-phosphonobutanoate (MAP4), but those of (*R*,*S*)-PPG are not (Chapman et al., 2001). Such differences may be explained according to the agonist and antagonist pharmacology in vivo (e.g., $mGlu_4$ selectivity versus $mGlu_8$) (Saugstad et al., 1997). For example, MAP4 blocks L-AP4-induced effects in the lateral perforant path (mediated by $mGlu_8$) and glutamate-induced currents in *Xenopus* oocytes expressing $mGlu_8$. (*R*,*S*)-PPG given intracerebroventricularly in normal mice protects against pentylenetetrazol seizures, but this effect is lost in $mGlu_7$, but not in $mGlu_8$ or $mGlu_4$, knockout mice, suggesting that $mGlu_7$ plays an important role in the anticonvulsant action of (*R*,*S*)-PPG against pentylenetetrazol (Sansig et al., 2001). This may not, however, be the case for the anticonvulsant effect of (*R*,*S*)-PPG in sound-induced seizures in DBA/2 mice where efficacy is seen at lower doses of PPG.

(*S*)-3,4-DCPG is a group III mGlu receptor agonist with a more marked preferential action on $mGlu_8$ than (*R*,*S*)-PPG (Thomas et al., 2001). Like (*R*,*S*)-PPG, (*S*)-3,4-DCPG is anticonvulsant against sound-induced seizures in DBA/2 mice (Moldrich et al., 2001a). The (*R*)-isomer of 3,4-DCPG is an AMPA receptor antagonist and is a slightly weaker anticonvulsant than (*S*)-3,4-DCPG. The racemate (*R*,*S*)-3,4-DCPG is significantly more potent anticonvulsant than either the (*S*) or (*R*) isomers. A potentiation of anticonvulsant effect by combining $mGlu_8$ activation and AMPA receptor antagonism was demonstrated by combining (*R*,*S*)-PPG and (*R*)-3,4-DCPG (Moldrich et al., 2001a). This potentiating effect has subsequently been observed with noncompetitive AMPA and NMDA receptor antagonists (De Sarro et al., 2002). A summary of the anticonvulsive activity of group III mGlu receptor agonists is presented in Table 4.

Table 4
Anticonvulsant activity of group III receptor agonists

Agonist	Selectivity	Model	Dose and route
(*R*,*S*)-PPG	8>4=6>7	DBA/2 (S)[a]	ED_{50} 3.4 nmol i.c.v.
		GEPR[a]	5–10 nmol i.c.
		ECS mouse[b]	ED_{50} 78 nmol i.c.v.
		PTZ[c]	ED_{50} 634 nmol i.c.v.
		HCA[d]	5–10 nmol i.c.v.
(*S*)-3,4-DCPG	8>4	DBA/2(S)[e]	ED_{50} 0.11 nmol i.c.v.
(*R*,*S*)-3,4-DCPG	8>4 AMPAR antag.	DBA/2 (S)[e]	ED_{50} 0.004 nmol i.c.v.
			ED_{50} 86 mg/kg i.p.
L-SOP	4=6=8>7	DBA/2(S)[f]	convulsant
L-AP4	4=6=8>7	DBA/2(S)[f]	convulsant
ACPT-1	4=6=8>7	DBA/2(S)[g]	ED_{50} 2.9 nmol i.c.v.
		DHPG[g]	ED_{50} 0.6 nmol i.c.v.
		GEPR[g]	ED_{50} 0.08 nmol i.c.

Abbreviations: AMPAR, AMPA receptor; antag., antagonist; ECS, electroconvulsive shock; GEPR, genetically epilepsy-prone nine rats; HCA, DL-homocysteic acid; PTZ, pentylenetetrazol; (S), sound-induced seizures; SWD, spike-wave discharge.
[a] Chapman et al., 1999b.
[b] Gasparini et al., 1999.
[c] Sansig et al., 2001.
[d] Folbergrová et al., 2003.
[e] Moldrich et al., 2001a.
[f] Ghauri et al., 1996.
[g] Chapman et al., 2001.

4.2. Group III mGlu receptor antagonists are proconvulsant and anticonvulsant

Compounds that are potent selective antagonists of the effect of L-AP4 on excitatory transmission in hippocampal slices or spinal cord preparations (e.g., MAP4, MPPG, and MSOP) are convulsant when injected intracerebroventricularly in mice (1–4 μmol i.c.v.; Ghauri et al., 1996; Chapman et al., 2001). In contrast, MCPA [(*S*)-α-methyl-3-carboxyphenylalanine] is relatively inactive in electrophysiological assays of group III mGlu receptor antagonism, but is a potent and selective antagonist of L-AP4-induced depression of forskolin-stimulated cAMP production in rat cerebrocortical brain slices and is anticonvulsant in a range of seizure models, including sound-induced seizures in DBA/2 mice, NMDA- and DHPG-induced seizures (1–3 μmol i.c.v.; Ghauri et al., 1996). The $mGlu_4$ selective antagonist (*R*,*S*)-*a*-cyclopropyl-4-phosphonophenylglycine (CPPG) prevents pentylenetetrazol-induced absence seizures (5 nmol, focal infusion; Snead et al., 2000; discussed below).

5. Changes in mGlu receptors in animal models of epilepsy

The most detailed studies of changes in the expression and function of mGlu receptors in animal models of acquired epilepsy concern electrical kindling of limbic seizures in the rat. A potentiation of responses to group I agonists has been repeatedly described in amygdala-kindled rats. Initial reports (Akiyama et al., 1989, 1992) described an increase in phosphoinositide hydrolysis induced by quisqualate or ibotenate, which was transient in the hippocampus but sustained in the amygdala. A sustained increase in protein kinase C activity was also observed in the hippocampus (Akiyama et al., 1995). In situ hybridisation of mRNA expression has shown a transient upregulation of hippocampal $mGlu_1$ (at 24 h) and $mGlu_5$ (at 7 days) following amygdala kindling (Akbar et al., 1996).

A more prolonged upregulation of $mGlu_1$ mRNA (1 month) has been observed in the rat supraoptic nucleus following amygdala kindling (Al-Ghoul et al., 1998). Electrophysiological studies in the amygdala, contralateral to the site of kindling, reveal that the depolarising effect of group I mGlu receptor agonists is potentiated, an effect that is at least partially dependent on potentiation of Na^+/Ca^{2+} exchange (Holmes et al., 1996; Keele et al., 2000). Another

reason for the potentiation may be due to the increased competition between the short-form Homer1a and the longer form of Homer proteins with respect to group I mGlu receptor function. For example, an induced increase in Homer1a expression was thought to be responsible for preventing $mGlu_1$ internalisation by the longer forms of Homer in cerebellar purkinje neurons and thereby potentiating $mGlu_1$ function (Minami et al., 2003). Massively parallel signal sequencing experiments have shown an upregulation of Homer1a mRNA in kindled rats (Potschka et al., 2002); however, the same study showed that overexpressing Homer1a mutant mice were more resistant to induction of electrically stimulated seizures, thereby concluding that the overexpression was an intrinsic countermeasure to epileptogenesis due to competition between short and long forms of Homer variants. While more research is required, it appears that the time of induction and the level of Homer protein expression play an important part in the role of group I mGlu receptors in epileptogenesis.

Studies in amygdala-kindled rats have shown that the hyperpolarising response evoked by group II agonists (such as L-CCG-1 and (1*S*,3*R*)-ACPD) is decreased in the basolateral amygdala contralateral to the site of kindling (Holmes et al., 1996). In contrast, the presynaptic inhibitory effects of group II and group III agonists are potentiated in the contralateral amygdala (Neugebauer et al., 1997). In the dentate gyrus in amygdala-kindled rats, the effect of the group III agonist, L-AP4, on synaptic transmission is unchanged (Friedl et al., 1999), whereas in the hippocampal-kindled rat, the effect of the group III agonist L-SOP in the dentate gyrus is decreased (Klapstein et al., 1999). The latter effect matches observations in the human epileptic hippocampus with mesial temporal sclerosis (see below).

Spontaneous seizures following status epilepticus induced in the rat by kainate, pilocarpine or prolonged electrical stimulation are regarded as models of human temporal lobe epilepsy associated with hippocampal sclerosis. After status epilepticus induced by electrical stimulation of the angular bundle, immunolabelling studies show upregulation of the expression of $mGlu_{2/3}$ and $mGlu_5$ (corresponding to astrocytic activation shown by glial fibrillary acidic protein (GFAP) co-localization) (Aronica et al., 2000). Enhanced astrocytic expression of $mGlu_5$ has also been seen after kainate-induced status epilepticus (Ulas et al., 2000). Both $mGlu_8$ and $mGlu_1$ were found to be upregulated in the hippocampus of the rat pilocarpine model of status epilepticus (Tang et al., 2001a,b). In this model, study of field excitatory postsynaptic potentials in hippocampal slices has shown that the effect of the group III agonists L-AP4 and PPG was much reduced in rats showing spontaneous seizures compared with those not showing seizures (Kral et al., 2003). This was interpreted as demonstrating that presynaptic $mGlu_8$ was reduced, thereby decreasing the normal negative feedback on glutamate release. This is not inconsistent with the data indicating that the immunoreactivity of $mGlu_8$ is increased in this model, since this occurs in reactive astrocytes and is of unknown functional significance.

Studies in genetically modified mice have mostly shown modest effects on seizure threshold. Mice lacking $mGlu_7$ have been described as seizure prone with an increase in excitability in cortical tissue (Sansig et al., 2001). No such trait has been reported in $mGlu_4$ or $mGlu_6$ knockout mice (Nakanishi et al., 1998). In $mGlu_4$ knockout mice, Snead et al. (2000) reported a resistance to low-dose pentylenetetrazol-induced absence seizures, which was supported by administration of the $mGlu_4$ antagonist CPPG in wild-type mice. The authors of that study proposed that $mGlu_4$ on thalamic relay neurons regulates the recurrent GABA-ergic inhibitory activity within the nucleus reticularis thalami, thereby providing decreased hypersynchrony and preventing absence seizures (proposed by Huguenard and Prince (1994)). The protective effect of a high dose of PPG against pentylenetetrazol seizures is lost in $mGlu_7$ knockout mice, suggesting that this effect is dependent on $mGlu_7$ receptors. More recently, $mGlu_8$ knockout mice were found to be no more susceptible to pentylenetetrazol-, kainate- or pilocarpine-induced seizures than their wild-type counterparts (Gerlai et al., 2002). While such knockout studies indicate the importance of $mGlu_7$ (amongst group III mGlu receptors) at inhibiting seizures, the mGlu receptor expression profile has not been fully characterised for these animals.

6. Changes in mGlu receptors in human epilepsy syndromes

In human epilepsy syndromes, subtle differences in mGlu receptor expression have been described. Differences in group II and group III mGlu receptor expression have been found in human patients with mesial temporal lobe epilepsy (Tang and Lee, 2001). In this study, receptor expression of $mGlu_{2/3}$ or $mGlu_8$ appeared confined to presynaptic terminals in the molecular layer or CA2 of the hippocampus, respectively. Furthermore, $mGlu_{2/3}$, $mGlu_4$, and $mGlu_8$ were found on astrocytes in the hippocampus of these mesial temporal lobe epilepsy patients, which the authors concluded may relate to gliosis. In a similar series of experiments, increased immunoreactivity of group I mGlu receptors in mesial temporal lobe epilepsy patients suggested that these receptors may facilitate an associated increase in hippocampal excitability at postsynaptic terminals (Tang et al., 2001c). Increased $mGlu_1$, but not $mGlu_5$, labelling was observed within the dentate gyrus molecular layer of chronic temporal lobe epilepsy patients, which correlated with the expression pattern found in animals with induced limbic seizures (Blumcke et al., 2000).

In electrophysiological studies on hippocampal slices, Dietrich et al. (1999) found that the effect of L-AP4 on dentate granule cell responses to perforant path stimulation was lost in material from patients with mesial

temporal sclerosis compared to those with other pathologies. This corresponds to the finding of diminished group III mGlu receptor sensitivity in hippocampal-kindled rats (Klapstein et al., 1999). The specific receptor involved is not known but is likely to be $mGlu_8$ because of its known location on the lateral perforant pathway. Immunohistochemical studies have indicated that $mGlu_4$ is upregulated in the dentate gyrus in temporal lobectomy specimens (Lie et al., 2000).

7. Prospects for therapeutic advances in epilepsy related to mGlu receptors

Ligands acting at mGlu receptors have shown antiepileptic efficacy in animal models of generalized seizures (including clonic, clonic-tonic, and absence seizures) and temporal lobe epilepsy (such as those induced by kainate or kindling). Furthermore, in the DBA/2 mouse model of primary generalized seizures some mGlu receptor ligands show equal or greater potency than clinical antiepileptic drugs in this system when administered intraperitoneally (see Table 5). Further comparisons with mGlu receptor ligands across other animal models are made difficult since very different preclinical animal models have often been used to test antiepileptic drugs. Another important consideration when assessing the therapeutic potential of mGlu receptor ligands is to establish the therapeutic index of such ligands—the anticonvulsant potency of the ligand compared to its ataxic or sedative potency. Current clinical antiepileptic drugs such as diazepam, carbamazepine, lamotrigine, and sodium valproate exhibit therapeutic indexes of approximately 41, 15, 23, and 7 in DBA/2 mice, respectively (intraperitoneally; De Sarro et al., 1996, 2000). Similarly, in DBA/2 mice, group I mGlu receptor antagonists demonstrate a 5–20-fold therapeutic index (MPEP, intraperitoneally; Chapman et al., 2000b) and group II mGlu receptor agonists demonstrate a therapeutic index of 2–30 (LY379268 and LY389795, intracerebroventricularly; Moldrich et al., 2001b). The duration of antiepileptic effect produced by mGlu receptor ligands should ideally be long term (e.g., to be able to achieve twice-daily dosing in humans). Most mGlu receptor ligands have demonstrated transient anticonvulsant activity (15 min to 1 h), while some group III mGlu receptor ligands have shown anticonvulsant activity days after administration (the initial acute proconvulsant effect associated with these agonists would need to be overcome). Other considerations towards evaluating the therapeutic potential of mGlu receptor ligands as antiepileptic drugs, which are yet to be investigated, include drug interactions, absorption with food, metabolism, hepatoxicity, and protein binding.

The preclinical data positively support the therapeutic potential of mGlu receptor ligands in epilepsy and more data are required concerning the efficacy of subtype specific agents in different epilepsy models. Compounds with more appropriate pharmacokinetics are required. Pharmacological data are conspicuously lacking in animal models of epileptogenesis. That $mGlu_1$ and probably also $mGlu_5$ play a significant role in the development of kindled seizures seems clear. Indeed, experiments with $mGlu_1$ and $mGlu_3$ antisense oligonucleotides have shown that daily injections in the hippocampus (that decrease mGlu immunoreactivity) in the case of $mGlu_1$ do not alter the local afterdischarge duration but significantly slow epileptogenesis, but are without effect on either parameter in the case of $mGlu_3$ (Greenwood et al., 2000). Nevertheless, there are no published data showing an effect of group I antagonists on the rate of epileptogenesis in the kindling model. Published data involving the focal injection of groups II and III agonists in the amygdala show that such agents decrease local after discharge duration and the limbic seizure expression (Abdul-Ghani et al., 1997; Attwell et al., 1995, 1998a,b). They do not, however, establish the presence of an antiepileptogenic effect, as the slowing of epileptogenesis may be a simple consequence of the suppression of the local afterdischarge, an effect seen with the local or systemic administration of antiepileptic agents such as tiagabine.

Table 5
Comparison of the inhibition of sound-induced clonic seizures in DBA/2 mice of clinical anti-epileptic drugs and mGlu receptor ligands

Drug	Clinical use	ED_{50} (mg/kg, i.p.)
Diazepam	partial and generalized seizures	0.28 [0.20–0.39][a]
Phenytoin	generalized convulsive and partial seizures	2.5 [1.8–3.5][b]
LY379268	n.a.	2.9 [0.9–9.6][c]
Phenobarbital	partial and generalized seizures	3.4 [2.3–5.0][b]
LY389795	n.a.	3.4 [1.0–11.7][c]
Lamotrigine	generalized seizures and Lennox–Gastaut syndrome	3.5 [2.4–5.1][b]
Carbamazepine	generalized convulsive and partial seizures	4.4 [3.6–5.4][b]
Levetiracetam	adjunct for partial seizures	8.6 [6.2–11.2][d]
Topiramate	adjunct for partial/ generalized seizures	16.2 [11.3–23.1][b]
SIB 1893	n.a.	27 [17–44][e]
Sodium valproate	partial and generalized seizures	43 [33–56][a,b]
LY456236	n.a.	30–100[f]
(2*R*,4*R*)-APDC	n.a.	75 [25–116][g]
(*R*,*S*)-3,4-DCPG	n.a.	86 [74–101][h]

Drugs are listed in decreasing order of potency according to ED_{50} values with 95% confidence intervals. n.a.: not applicable.

[a] De Sarro et al., 1996.
[b] De Sarro et al., 2000.
[c] Moldrich et al., 2001b.
[d] Gower et al., 1992.
[e] Chapman et al., 2000a,b.
[f] Shannon and Peters, 2002.
[g] Moldrich et al., 2001c.
[h] Moldrich et al., 2001a.

The potential of mGlu receptor ligands as adjuncts to current anti-epileptic drugs should be explored, in particular, and further experiments investigating the ability of mGlu receptor ligands to potentiate the anticonvulsant effect of current antiepileptic drugs needs to be addressed.

Prolonged epileptic seizures produce a similar histopathological pattern to that of ischaemic damage (Meldrum, 1991). Few studies have investigated the correlation of the antiepileptic effect of mGlu receptor ligands with neuroprotection. The early studies of Schoepp's group emphasized the focal neurodegeneration seen after the intracerebral injection of convulsant doses of group I agonists (Tizzano et al., 1995). Camón et al. (1998) showed that proconvulsant doses of DHPG induced severe neuronal loss in the CA1 and CA3 of rats, and that DHPG-induced toxicity was comparable to that induced by kainate (Camón et al., 2001); mGlu receptor antagonists were not, however, used to prevent seizures or cellular loss. Kainate-induced status epilepticus induces progressive apoptosis and neuronal loss of the hippocampus, amygdala, and surrounding cortex, which is associated with gliosis (Mayat et al., 1994). Similar experiments by Miyamoto et al. (1997), however, found little or no neuroprotection provided by DCG-IV (DCG-IV did not inhibit kainate-induced seizures in this study). The $mGlu_{1/5}$ antagonist AIDA has been shown to improve the performance of rats in the water maze following convulsant doses of kainate, which was correlated with a significant reduction in neuronal loss in the CA1, compared to kainate-treated alone (Renaud et al., 2002). Other studies have reported neuroprotection in vivo and in vitro with group I mGlu receptor antagonists and group II/III mGlu receptor agonists (e.g., Movsesyan et al., 2001; Gasparini et al., 1999; D'Onofrio et al., 2001). It is possible, therefore, that neuroprotective effects may be associated with administration of antiepileptic doses of mGlu receptor ligands and therefore add to the therapeutic potential of this class of drugs.

Another important consideration regarding the therapeutic relevancy of mGlu receptor ligands arose from the studies of Moldrich et al. (2001c) and De Sarro et al. (2002). In these studies, action on multiple targets involved in glutamatergic neurotransmission was found to be more efficacious than action on only one target. Ultimately, it appears that a marginal presynaptic reduction in glutamatergic transmission with a marginal postsynaptic block can have an enhanced functional effect on preventing generalised seizures. Additionally, combining group I mGlu receptor antagonists with group II/III mGlu receptor agonists could provide greater therapeutic value yet again. Testing with the recently developed mGlu receptor allosteric modulators may provide even more opportunity for obtaining the maximum therapeutic value. It will be interesting to see which combination of glutamate ligands produces the best therapeutic value according to the animal model of seizures. Whereas selective activation or inactivation of mGlu receptors can provide information of the therapeutic contribution of each receptor subtype alone and help map epileptic circuitry in the brain, ultimately, antiepileptic drugs directed at the glutamatergic system are likely to be most beneficial when they involve a combination of agents including mGlu receptor ligands.

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