Agonists and Antagonists of Metabotropic Glutamate Receptors: Anticonvulsants and Antiepileptogenic Agents?

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Abstract: Anticonvulsant and neuroprotective effects of agonist and antagonist of metabotropic glutamate receptors (mGluRs) have been known for more than 10 years from multiple studies. However, it is not certain whether these candidate drugs are also antiepileptic and antiepileptogenic, as few studies included the chronic stages to determine whether spontaneous recurrent seizures could be prevented or stopped. Even in the acute stage, differences in experimental design such as timing and route of administration of candidate drugs, age, species and strain of experimental animal and experimental model make it difficult to determine the anticonvulsant and neuroprotective effects of each candidate drug. This paper, reviews *in vivo* neuropharmacological studies on agonsists and antagonists of mGluRs in different seizure and epilepsy models in last more than ten years. By combining with our neuropharmacological studies on the effect of mGluR agonists and antagonists in the mouse pilocarpine model of temporal lobe epilepsy, an ideal model for future development of mGluR agonists and antagonists as antiepileptogenic drugs will be proposed.

INTRODUCTION

Pharmacotherapy is considered the mainstay of treatment for most epilepsy patients, although neurosurgery and vagal nerve stimulation are options for those who are not adequately controlled by existing anticonvulsants. Unfortunately, for more than a hundred years since the introduction of the first antiepileptic drug, bromides in 1857, most novel, clinically effective anticonvulsants have been found by screening (i.e. serendipity) or structure variation of known drugs and not by rational strategies based on knowledge of processes involved in generation of seizures or in development of epilepsy. By rational design of anticonvulsant drugs targeting on GABAergic inhibition, vigabatrin, an inhibitor of GABA aminotransferase, and tiagabine, GABA uptake blocker were marketed as new clinically effective anticonvulsant drugs. However, the side effect of tolerance, dependence, and induction of psychotic reactions has made it problematic for clinical use [43]. Ionotropic glutamate receptors (iGluR) or ion channels - directed strategies failed to produce any clinically effective drugs with advantages over existing drug treatments due to the side effects [60]. However, metabotropic glutamate receptors (mGluRs) located at the periphery of pre- or post-synaptic membrane, "modulate" rather than "mediate" excitatory synaptic transmission under particular circumstances such as synaptic hyperactivity (as seen in epilepsy) [31, 57], rarely present in target organs of the autonomic nervous system, and have been considered as promising drug targets in the treatment of not only epilepsy, but also other neurological disorders [14, 45, 47,51, 56].

CHANGES OF MGLURS IN ANIMAL MODEL OF SEIZURES, STATUS EPILEPTICUS, AND IN BOTH ANIMAL AND HUMAN TEMPORAL LOBE EPILEPSY, GUIDES FOR TIMING WHEN AGONISTS OR ANTAGONISTS OF MGLURS SHOULD BE ADMINISTERED TO STOP SEIZURES?

It has been known that group I mGluRs are involved in initiating epileptogenesis [1,10,48,49,69]. In the rat kindling model, an initial up regulation in mGluR1mRNA in the dentate gyrus, CA3, and CA4 areas, and down regulation in mGluR5 mRNA in CA4, CA1, CA3 areas and dentate gyrus of the hippocampus were observed 24 h after the last kindled seizure. By 28 days, mGluR1 mRNA levels had returned to control levels, however, mGluR5 mRNA level was still lower than the control, suggesting that the mRNAs for mGluR1 and mGluR5 are differentially regulated by kindling, and may contribute to kindling epileptogenesis [1]. Increases in the expression of functional mGluR1 and perhaps mGluR3 receptors in the supraoptic nucleus were also found in kindled seizures, which may contribute to the development of long-lasting plastic changes associated with seizure activity [2]. Keele *et al*. [35] showed that group I mGluRs would facilitate, while group II mGluRs attenuate epileptiform activity. Up regulation of mGluR3 and 5 in reactive astrocytes in kindling model suggests that glial-neuronal communication may play a role in the course of epileptogenesis [5]. However, in neuronal elements of the basolateral amygdala in kindling model, and in the hippocampus of the rat and mouse pilocarpine models and of patients with mesial temporal lobe epilepsy, group II mGluRs were down regulated [34,64]. Decreased sensitivity to group III mGluR agonists in the lateral perforant path in kindling [24,29,37,40] and pilocarpine [13] models indicates the loss of feedback inhibition mediated by group III mGluRs, particularly that of subtype mGluR8 or mGluR7 respectively. It was supported by our study in the rat pilocarpine model showing drastic reduction of mGluR8 in the outer one-third of the molecular layer of the dentate gyrus [68]. This model also showed up regulation of mGluR1 in the stratum oriens [69], mGluR2/3 in the stratum lacunosum molecular [64] and mGluR8 in the entire molecular layer of the dentate gyrus [68] 24 h after pilocarpine induced status epilepticus. However, in the mouse pilocarpine model, Chen *et al*. [21], showed an increased expression of inhibitory mGluR 4 and downregulation of excitatory mGluR 1 in epileptic CD1 mice and a decrease of the excitatory mGluRs 1 and 5 in C57BL/6, but not in the FVB/N strain, suggesting differential expression of group I and III mGluR in different species and strains of animals. In

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1570-159X/05 $50.00+.00

the kainic acid model of pup and adult rats, status epilepticus induced a reduction in expression of mGluR2 mRNA in granule cells of the dentate gyrus. In pup but not adult rats, mGluR4 mRNA expression was enhanced in CA3 pyramidal neurons. It suggests that status epilepticus affects mGluR expression in a gene- and cell-specific manner, and that these changes vary with the developmental stage [4]. Blumcke *et al*. [9] demonstrated a striking up regulation of mGluR1 mRNA and protein expression in the hippocampus in kainic acid model and human patients suggesting that this up regulation may significantly contribute to hippocampal hyperexcitability in focal human epilepsies. However, up regulation of mGluR4 in patients with temporal lobe epilepsy may counteract excitatory hippocampal activity [42]. In our study, no obvious increase of mGluR4 protein was observed in the hippocampus from patients with the same subtype of epilepsy [66]. Similar to the kindling model, mGluR5 and mGluR2/3 were also increased in astrocytes in kainate-induced epileptic seizures, [25,75]. However, in the pilocarpine model, no upregulation of mGluR2/3 and mGluR5 in astrocytes was demonstrated [64]. In the hippocampi of epileptic patients, Glazier *et al.* [32] reported decrease in levels of mGluR1 and mGluR2. However, in patients with focal cortical dysplasia (FCD) induced intractable epilepsy, Aronica *et al*. [3] found high expression of mGluR1alpha and mGluR5 in dysplastic neurons, and suggested a possible contribution of group I mGluRs to the intrinsic and high epileptogenicity of dysplastic cortical regions. Combined mRNA and protein expression patterns of group I mGluRs at acute stages, the induction of limbic seizure in animal model by group I mGluR agonists [15, 72] with the neuroprotective effect of antagonists of group I mGluRs [14], it suggests that timely administration of antagonists of group I mGluRs at the early stage of seizures or brain damage may produce anticonvulsive and /or neuroprotective effect, and possibly prevent epileptogenesis. However, at chronic stages, down regulation of group II and III mGluRs may make it difficult to use their agonists to control epilepsy.

ANTICONVULSIVE, BUT NOT ANTIEPILEPTIC EFFECT OF AGONISTS AND ANTAGONISTS OF MGLURS: *IN VIVO* STUDIES IN PAST TEN YEARS

A wealth of *in vitro* studies has suggested that agonists and antagonists of mGluRs could modulate epileptiform activity [13,24,35,40,48,49]. Parallel *in vivo* studies showed anticonvulsive effect of agonists and antagonists of mGluRs in different animal models (Tables **1**-**4**). However, most of previous studies were done in genetically epilepsy-prone mice [17-19, 22,50,52-53, 62-63, 71], or group I mGluR agonists- [17,19,36,52,54,62,72] and electrical stimulation (including kindling)–induced [6-8,13,22,30,44,55] seizure instead of epilepsy models (Tables **1**-**4**). In this case, few of previous experiments were designed to show if agonists and antagonists of mGluRs could stop spontaneously recurrent seizures or epilepsy or prevent epileptogenesis. The timing (before seizure induction) and routes (i.a.m., IC, i.c.v., IH) of administration of agonists and antagonists of mGluRs (Tables **1**-**4**) in previous studies are also not a routine way used in clinical practice. Combined with our recent study showing that when group I mGluR antagonists AIDA, LY 367385, SIB 1757, SIB 1893 (Tang *et al*. unpublished data) or group II mGluR agonist 2R, 4R- APDC [64] were administered systemically during pilocarpine induced status epilepticus, no anticonvulsive effect was observed; it suggests that further studies have to be done before the conclusion that agonists and antagonists of mGluRs are antiepileptic is drawn.

AGONISTS AND ANTAGONISTS OF MGLURS AS CANDIDATE DRUGS TO PREVENT EPILEPTOGENESIS: FUTURE STUDY

In clinical practice, systemic administration of existing anti-epileptic drugs could control two-thirds of temporal lobe epilepsy patients, but none of these drugs is antiepileptogenic. To develop agonists and antagonists of mGluRs as antiepileptic or/and antiepileptogenic drugs, it was important to 1) test if systemic administration of the candidate drugs could prevent neuronal loss after acute brain insults and prevent and/or stop spontaneously recurrent seizures in different animal models of epilepsy by long-term video camera and EEG monitoring, 2) conduct pharmacodynamic, pharmacokinetic studies, so as to show how stable these candidate drugs are in the body, or poisonous to different organs of experimental animals; what is the best dosage range, if these candidate drugs could pass through blood-brain barrier, 3) perform behavioral test to see if they produce any behavioral change on the experimental animals.

Neuroprotective effect of agonists and antagonists of mGluRs in brain trauma, ischemia, stroke, status epilepticus and various other neurodegenerative disorders is well-known [14], which makes them more attractive to epileptologists than other antiepileptic drugs. Both anticonvulsive (Tables **1**-**4**) and neuroprotective [14] effects exerted by agonists and antagonists of mGluRs strongly suggest that these candidate drugs will be not only antiepileptic (symptomatic), but also antiepileptogenic (etiological) when administered at a right time point after different brain insults. Otherwise, temporal lobe epilepsy may be developed. One of ideal models for developing agonists and antagonists of mGluRs as anti-epileptogenic (anti-neurodegenerative and anticonvulsive) drugs is the mouse pilocarpine model, which employs status epilepticus to induce epilepogenesis and has many features similar to human temporal lobe epilepsy. In this model, days to weeks (with average latent period of 14.4±11.9 days) following an episode of pilocarpine induced status epilepticus, animals begin having spontaneous recurrent seizures and continue to have seizures for life [16,73-74]. Many of the pathophysiological changes observed in epileptic human brain tissue have been shown to be present in pilocarpine-induced epileptic mice, including hippocampal neuronal death, sclerosis and axon reorganization, in particular, mossy fiber sprouting [64-65]. Behavioral and cognitive changes occur soon after pilocarpine induced status epilepticus [33,41,59,61,77]. It has been known that this model develops refractoriness to many first-line treatments as seizure duration increases, rendering it a good model for drug screening [59], and fully satisfying the criteria for an "ideal model of epilepsy" proposed by White [76]. There are other chronic models of temporal lobe epilepsy such as kindling and kainite models of epilepsy. In kindling model, no significant brain damage (particularly in CA1 and CA3 areas of the hippocampus) was reported; this is quite different

Table 1. Agonists and Antagonists of mGluRs on KA, DL-HCA and PTZ Induced Seizures in Immature Rats

Drug candidate	Selectivity	Route	Timing	Dose	Model	Age of animal	Effect on seizure control	Ref.
AIDA	mGluR1 antagonist	i.p.	B	1.8mg/kg	KA	P20, P30	-, SRS: +	58
2R,4R-APDC	group II mGluR agonist	i.c.v.	B	0.6 or 0.05nmol	DL-HCA	P12	+	26, 28
(S)-4-C3HPG	mGluR1 antagonist mGluR2 agonist	i.c.v.	B	0.6nmol	DL-HCA	P12	+	28
Cyclobutylene AP5	group III mGluR agonist	i.c.v.	B	32nmol	DL-HCA	P12	+	28
DCG IV	group II mGluR agonist	i.c.v.	B	0.6nmol 5-100 nmol	DL-HCA	P12	+/- --	28
MPEP	mGluR5	i.p.	B	10-80mg/kg	PTZ	P12 P25	+ +	49
(R, S)-PPG	group III mGluR antagonist	i.c.v.	B	10nmol	DL-HCA	P12	+	27

+: effective; +/-: partialy effective; -: not effective; --: proconvulsive

A: drug candidate was given after seizures had come out

B: drug candidate was given before seizure induction

i.p.: intraperitoneal injection

i.c.v.: intracerebroventricular injection

AIDA:1-aminoindan-1,5-dicarboxylic acid

2R,4R-APDC: (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate

(S)-4-C3HPG: (S)-4-carboxy-3-hydroxyphenylglycine

Cyclobutylene AP5: (RS)-1-amino-3-(phosphonomethylene) cyclobutane-carboxylic acid

DCG IV: (2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine

DL-HCA: DL-homocysteic acid

MPEP: 2-methyl-6-(phenylethynyl)-pyridine

KA: Kainic acid

(R, S)-PPG: (R,S)-4-phosphonophenylglycine

PTZ: pentylenetetrazol

SRS: spontaneous recurrent seizures

Table 2. Group I mGluR Antagonists on the Adult Rat and Mouse Models of Seizures

Drug candidate	Selectivity	Route	Timing	Dose (ED50)	Model	Effect on seizure control	Ref.
(S)-4-C3HPG	mGluR1α antagonist	i.c.v.	B	110nmol	DBA/2	+	71
	mGluR2 agonist	i.c.v	B	325-500nmol*	PTZ	+	22
		i.c.v	B	180nmol	DMCM	+	22
		i.c.v.	B	30-500nmol*	NMDA	-	22
		IC	B	4.3nmol	GEPR	+	63
(S)-4CPG	mGluR1 antagonist	i.c.v.	B	500nmol*	DBA/2	+	22
		i.c.v.	B	500nmol*	DMCM	+	22
		i.c.v.	B	500nmol*	PTZ	+	22

(Table 2. contd….)

Drug candidate	Selectivity	Route	Timing	Dose (ED50)	Model	Effect on seizure control	Ref.
AIDA	mGluR1	i.c.v.	B	465nmol	PTZ	+	70
		i.c.v.	B	79nmol	DBA/2	+	20
		i.c.v.	B	500nmol	1h/1h	+	20
		IC	B	100nmol	GEPR	+	20
		i.c.v.	B	477nmol	DHPG	+	36
		i.c.v.	B	800nmol*	pilocarpine	+	67
		i.v.	A	25-400mg/kg*	pilocarpine	-	Tang *et al.*, unpublished
LY367385	mGluR1	i.c.v	B	12nmol	DBA/2	+	20
		i.c.v.	B	250nmol*	1h/1h	+	20
		IC	B	160nmol*	GEPR	+	20
		i.c.v.	B	122nmol	DHPG	+	36
		i.c.v.	B	0.3-500nmol*	6Hz	-	8
		IH	B	1mM*	DHPG	+	62
		i.c.v.	B	0.40µmol*	PTZ(40mg/kg)	+	55
		i.c.v.	B	0.40µmol*	Kindling	+	55
		i.v.	A	25-200mg/kg*	pilocarpine	-	Tang *et al.*, unpublished
BAY36-7620	mGluR1	i.p.	B	163mg/kg	DBA/2	+	17
		i.p.	B	10mg/kg	PTZ	+	23
LY339840	mGluR1, 5	i.c.v.	B	138 nmol	DHPG	+	36
LY339764	mGluR1,5	i.c.v.	B	43 nmol	DHPG	+	36
LY367366	mGluR1,5	i.c.v.	B	39 nmol	DHPG	+	36
LY367335	mGluR1,5	i.c.v.	B	35 nmol	DHPG	+	36
LY393053	mGluR1,5	i.c.v.	B	9 nmol	DHPG	+	36
MPEP	mGluR5	i.p.	B	0.42mg/kg	CHPG	+	17
		i.p.	B	22mg/kg	DHPG	+	17
		i.c.v.	B	110nmol	DHPG	+	17
		i.p.	B	18mg/kg	DBA/2	+	17
		i.p.	B	50mg/kg	1h/1h	+	17
		i.p.	B	17.4mg/kg	6Hz	+	8
		i.p.	B	72.4mg/kg	MES	+	8
		i.c.v	B	50mg/kg*	DHPG	+	62
		i.c.v.	B	0.06µmol*	PTZ(40mg/kg)	+	55
		i.c.v.	B	0.06µmol*	kindling	-	55
SIB1983	mGluR5	i.p.	B	0.19mg/kg	CHPG	+	17
		i.p.	B	31mg/kg	DHPG	+	17
		i.c.v.	B	95nmol	DHPG	+	17
		i.p.	B	27mg/kg	DBA/2	+	17
		i.p.	B	0.5-2mg/kg*	ES	--	44
		i.p.	B	40mg/kg*	ES	+	44
		i.p.	B	0.25-10mg/kg*	PTZ	-	12
		i.p.	B	20-40mg/kg*	kindling	-	11
		i.v.	A	25-200mg/kg*	pilocarpine	-	Tang *et al.*, unpublished
SIB1757	mGluR5	i.v.	A	25-200mg/kg*	pilocarpine	-	Tang *et al.*, unpublished

(Table 2. Contd….)

*: not an ED50 value

DBA/2: sound –induced seizures in DBA/2 mice

DHPG: 3, 5-dihydroxyphenylglycine

DMCM: methyl-6,7-dimethoxy-4-ethyl-beta-carboline-2-carboxylate

1h/1h: lethargic mice

ES: electroshock seizure

GEPR: genetically epilepsy prone rats

IC: inferior colliculum

IH: intrahippocampal perfusion

MES: maximal electroshock model

ACPT-1: (1S,3R,4S)-1-aminocyclopentane-1,2,4-tricarboxylic acid

BAY36-7620: (3aS,6aS)-6a-naphthalen-2-ylmethyl-5-methyliden-hexahydrocyclopenta[c]furan-1-on

(S)-4CPG: (S)-4-carboxyphenylglycine

CHPG:(R,S)-2-chloro-5-hydroxyphenylglycine

LY339764: (R.S)-2-amino-2-(4-carboxycyclobutyl-3-(9-xanthen-9-yl) propanoic acid

LY339840: (R.S)-2-methyl-3-hydroxy-4-carboxyphenylglycine

LY367335: 2-amino-2-(3-cis and trans-carboxycyclobutyl-3-(9-xanthen-9-yl) propionic acid

LY367366: (R.S)-2-amino-2-(4-carboxycyclobutyl-3-(9H-thioxanthen-9-yl) propanoic acid

LY 367385: (S)-2-methyl-4-carboxyphenylglycine

LY393053: 2-amino-2-(3-cis and trans-carboxycyclobutyl-3-(9-thioxanthyl) propionic acid

SIB-1757: 6-methyl-2-(phenylazo)-3-pyridinol,

SIB-1893: 2-methyl-6-(2-phenylethenyl)pyridine

Table 3. Group II mGluR Agonists on the Adult Rat and Mouse Models of Seizures

Drug candidate	Selectivity	Route	Timing	Dose (ED50)	Model	Effect on seizure control	Ref.
1S,3R-APDC	mGluR2 agonist	i.c.v.	B	150-500nmol*	DBA/2	+	22
		i.c.v.	B	500nmol*	DMCM	+	22
		i.c.v.	B	50-500nmol*	ES	-	22
		IC	B	5-40nmol*	GEPR	-: <1h	63
		IC	B	9nmol	GEPR	+: 2h	63
		i.c.v.	B	30-300nmol*	PTZ	--	70
2R, 4R-APDC	mGluR2/3 agonist	i.a.m.	B	10nmol	Amygadala-kindled	+	6
		i.c.v.	B	20nmol	DBA/2	+	53
		i.p.	B	100mg/kg	DBA/2	+	53
		i.p.	A	25-600mg/kg*	Pilocarpine	-	64
L-CCG-1	mGluR2 agonist	i.c.e.	B	100-400nmol*	DHPG	+	72
		i.c.v.	B	500nmol*	DBA/2	+	22
		i.c.v.	B	500nmol*	DMCM	-	22
		i.c.v.	B	0.2-600nmol*	PTZ	-	22
(S)-4-C3HPG	mGluR1α antagonist	i.c.v.	B	110nmol	DBA/2	+	71
	mGluR2 agonist	i.c.v.	B	325-500nmol*	PTZ	+	22
		i.c.v.	B	180nmol	DMCM	+	22
		i.c.v.	B	30-500nmol*	NMDA	-	22
		IC	B	4.3nmol	GEPR	+	63
DCG IV	mGluR2/3 agonist	i.a.m	B	0.01-1.0nmol*	Amygadala-kindled	+	7

(Table 3. Contd….)

Drug candidate	Selectivity	Route	Timing	Dose (ED50)	Model	Effect on seizure control	Ref.
LY354740	mGluR2/3 agonist	i.p.	B	4.8mg/kg	PTZ	+	38, 39
		i.p.	B	6.3mg/kg	Picrotoxin	+	
		i.p.	B	16mg/kg	NMDA	-	
LY 379268	mGluR2/3 agonist	i.p.	B (1h)	19mg/kg	1S,3R-APDC	+	54
		i.p.	B (2h)	6mg/kg	1S,3R-APDC	+	54
		i.p.	B (4h)	26mg/kg	1S,3R-APDC	+	54
		i.c.v.	B	0.3pmol	DHPG	+	52
		i.c.v.	B	0.08nmol	DBA/2	+	52
		i.p.	B	2.9mg/kg	DBA/2	+	52
		i.c.v.	B	1nmol	1h/1h	+	52
		i.p.	B	6.34mg/kg	6Hz	+	8
		i.p.	B	>100mg/kg	6Hz	+	8
		i.p.	B	0.1-1mg/kg*	GEPR	-	62
		i.p.	B	10mg/kg*	DHPG	--	62
LY 389795	mGluR2/3 agonist	i.p.	B (1h)	14mg/kg	1S,3R-APDC	+	54
		i.p.	B (2h)	15mg/kg	1S,3R-APDC	+	54
		i.p.	B (4h)	14mg/kg	1S,3R-APDC	+	54
		i.c.v.	B	0.03nmol	DHPG	+	52
		i.c.v.	B	0.82nmol	DBA/2	+	52
		i.p.	B	3.4mg/kg	DBA/2	+	52
		i.c.v.	B	10nmol	1h/1h	+	52
		i.p	B	0.1-1mg/kg*	GEPR	-	52
		i.p.	B	10mg/kg*	Amygadala-kindled	+/-	52
		i.p.	B	15.7mg/kg	6Hz	+	8
		i.p.	B	>200mg/kg	MES	+	8

1S,3R-APDC: (1S,3R)-1-aminocyclopentane dicarboxylic acid

L-CCGI: (2S, 3S, 4S) alpha -(carboxycyclopropyl) glycine

LY354740: hexane-2,6-dicarboxylic 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

Table 4. Group III mGluR Agonists on the Adult Rat and Mouse Models of Seizures

Drug candidate	Selectivity	Route	Timing	Dose (ED50)	Model	Effect on seizure control	Ref.
ACPT-1	mGluR4, 6, 8, 7	i.c.v.	B	5.6nmol	DBA/2	+	19
		i.c.v.	B	0.60nmol	DHPG	+	19
		i.c.v.	B	49.3nmol	MSOP	+	19
		IC	B	0.08nmol (1h)	GEPR	+	19
		IC	B	0.33nmol (2h)	GEPR	+	19
		IC	B	0.03nmol (1d)	GEPR	+	19
L-AP4	mGluR4, 6, 8 agonist	i.c.e.	B	400-000nmol*	DHPG	+	72
		i.c.v.	B	36.8nmol	6Hz	+	8
		i.c.v.	B	223nmol	MES	-	30

(Table 4. Contd….)

Drug candidate	Selectivity	Route	Timing	Dose (ED50)	Model	Effect on seizure control	Ref.
Cyclobutylene AP5	group III mGluR agonist	i.c.v.	B	4 μM	PTZ	+	70
(RS)-3,4-DCPG	mGluR8, 4 agonist	i.c.v.	B	0.004nmol	DBA/2	+	50
(S)-3,4-DCPG	mGluR8, 4 agonist	i.c.v.	B	0.11nmol	DBA/2	+	50
(R, S)-PPG	mGluR8, 4, 6,7 agonist	i.c.v	B	78nmol	MES	+	30
		i.p.	B	100mg/kg*	MES	-	30
		i.v.	B	10mg/kg*	MES	-	30
		i.c.v.	B	3.4nmol	DBA/2	+	18
		IC	B	5-10nmol*	GEPR	+	18
		i.c.v.	B	3.4nmol	DBA/2	+	19
		i.c.v.	B	3.7nmol	DHPG	+	19
		i.c.v.	B	40.2nmol	MSOP	+	19
		i.c.v.	B	32nmol	6Hz	+	8
		i.c.v.	B	112nmol	MES	+	8
L-SOP	mGluR4, 6, 8 agonist	i.c.e.	B	1600-3200nmol*	DHPG	+	72
		IC	B	36nmol*	GEPR	--: <10min	63
		IC	B	36nmol*	GEPR	+: > 1 day	63
		i.c.v.	B	218nmol*	MES	-	30

i.c.e.: intracerebral injection

ACPT-1: (1S,3R,4S)-1-aminocyclopentane-1,2,4-tricarboxylic acid

L-AP4: L-2-amino-4-phosphonobutyrate

(RS)-3,4-DCPG: (RS)-3,4-dicarboxyphenylglycines, (S)-3,4-DCPG: (S)-3,4-dicarboxyphenylglycines

L-SOP: L-serine-O-phosphate

from neuropathological changes in human intractable temporal lobe epilepsy, which shows characteristic neuronal loss in CA1 and CA3 areas of the hippocampus. The kainite model has recurrent spontaneous seizures and damage to limbic structures, but seizure may remit [16]. Pilocarpine injection induces bilateral damage, and may compromise additional brain regions not involved in human mesial temporal lobe epilepsy. However, this model does provide a platform for evaluating neuroprotective effect of antiepileptic drugs, as neuronal damage in brain trauma, ischemia, stroke, status epilepticus and various other neurodegenerative disorders may spread into a wide brain area. Nevertheless, prediction of a drug's efficacy should not rely on drug studies in one chronic model of epilepsy. Furthermore, the potential of animal models to predict efficacy in the treatment of prevention of human epilepsy should also not be overestimated. Clinical trials are still needed to confirm the drug effect in the humans.

CONCLUSION

In vivo studies in past more than ten years suggest that mGluR agonists and antagonists may be anticonvulsive and neuroprotective. To show if they are antiepileptic or antiepileptogenic, systemic administration of these candidate drugs in animal models of epilepsy, particularly temporal lobe epilepsy, should be made with video camera and EEG long-term monitoring. In order to produce better therapeutic effect, it may be necessary to combine mGluR agonists or antagonists with low dosages of ionotropic glutamate receptor antagonists or other neurotransmitter receptor agonists or antagonists. Of different animal models, the mouse pilocarpine model may be one of the ideal models for the development of antiepileptogenic drugs. By systemic administration of mGluR agonists or antagonists at different time points after pilocarpine induced status epilepticus, antiepileptogenic effect of candidate drugs may be evaluated, and a promising one will then be used for clinical trial in the human.

ACKNOWLEDGEMENTS

The study was supported by research grants (NMRC/0670/2002, NMRC/0777/2003, NMRC/0731/2003, NMRC/0768/2003) from the National Medical Research Council of Singapore.

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Received: 08 May, 2005 Accepted: 18 July, 2005

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