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The Preclinical Properties of a Novel Group II Metabotropic Glutamate Receptor Agonist LY379268

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ABSTRACT

Activation of group II metabotropic glutamate (mGlu2/3) receptors reduces excessive glutamate release that is often associated with neurodegenerative and psychiatric disorders. This finding encouraged the search for potent and selective agonists as potential therapeutic agents. The search led to the discovery of LY379268 {(-)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid}, which is a highly potent and systemically available mGlu2/3 receptor agonist. LY379268 was effective in several animal models of stroke, epilepsy, drug abuse, schizophrenia, and pain. Suppression of motor activity is the major side effect of LY379268. Upon repeated administration tolerance develops to this side effect, while the therapeutic effects of LY379268 remain. To date, no clinical data with LY379268 are available. This review article summarizes the preclinical pharmacology of LY379268.

INTRODUCTION

Besides its essential function in energy metabolism, glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (Watkins 2000). Glutamate is involved in nearly all aspects of brain function, particularly cognition, memory and learning. Abnormal changes in glutamatergic neurotransmission, especially excessive glutamate release,

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can consequently lead to a neuronal dysfunction resulting in a variety of neurological and psychiatric disorders. These include epilepsy, amnesia, motor neuron disease, stroke, traumatic brain injury, pain, anxiety, and psychosis. Therefore, there has been a great deal of interest in developing therapeutic strategies that can influence the function of glutamate receptors.

In the last decade, the members of group II metabotropic glutamate (mGlu2/3) receptors have emerged as potential therapeutic targets. First, converging results from *in situ* hybridization (Ohishi et al. 1993a, b) and immunochemical studies (Ohishi et al. 1998; Petralia et al. 1996) showed that mGlu2/3 receptors are localized extensively in brain areas associated with neuropsychiatric and neurological disorders, such as the neocortex, thalamus, striatum, amygdala, and hippocampus. Second, activation of mGlu2/3 receptors can suppress presynaptic glutamate release and postsynaptic excitation in a use-dependent manner (Conn and Pin 1997; Schoepp 2001). Furthermore these receptors have a predominant localization at the periphery of the synaptic area, where they monitor the glutamate that has escaped from the synaptic space. Thus, under normal conditions when glutamate is generally confined to the active zone of the synaptic space, activation of mGlu2/3 receptors is not detected. However, in conditions where glutamate spillover from the synapses occurs, for instance due to high-frequency stimulation or glutamate uptake blockade, mGlu2/3 receptors become activated, leading to suppression of glutamate release (Chen et al. 2001; Huang et al. 1997; Kew et al. 2001; Scanziani et al. 1997). The mGlu2/3 receptors may, therefore, provide a negative feedback to keep glutamate transmission within the physiological range, preventing hyperexcitability from interfering with normal brain function.

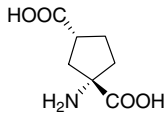
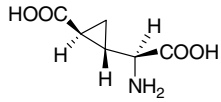
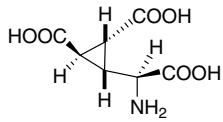
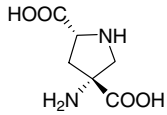
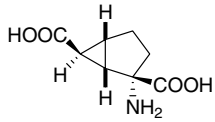
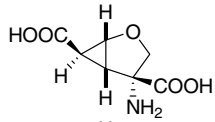
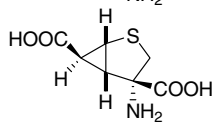
Initial studies investigating the function of mGlu2/3 receptors used nonselective ligands, such as L-CCG-I, (1S,3R)-ACPD, and DCG-IV (Table 1), which are not sufficiently potent (generally μM concentrations are required) or not systemically bioavailable *in vivo* (Schoepp et al. 1999; Spooren et al. 2003). The discovery of novel subtype-selective ligands, which have *in vivo* activity following systemic administration, was crucial in the determination of the role of mGlu2/3 receptors in neuronal function. The first potent and selective agonist described was LY354740, followed by its more potent derivative, LY379268 (Monn et al. 1997, 1999). This review presents an overview of the currently available literature on the pharmacology of LY379268, with particular emphasis on its effects in preclinical models with abnormal glutamate transmission.

CHEMISTRY AND PHARMACOLOGY

LY379268 {(-)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid} is a heterobicyclic amino acid. Its chemical structure is shown in Table 1. Conformational constraint of the glutamate pharmacophore into a fused bicyclic [3.1.0] ring system resulted in LY354740 {(+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid} (Monn et al. 1997). LY379268 is structurally related to this compound with the C4-methylene unit being replaced with an oxygen atom (Monn et al. 1999).

As measured by specific displacement of the group II-selective antagonist radioligand [^{3}H]LY341495 {(2*S*,1′*S*,2′*S*)-2-(9-xanthylmethyl)-2-(2′-carboxycyclopropyl)glycine}, LY379268 binds with high ($IC_{50} \sim 10$ nM) affinity to mGlu2/3 receptors expressed in native rat brain homogenates and to recombinant human mGlu2 and mGlu3 receptor subtypes. This affinity of LY379268 compares favorably with that of the parent carbocyclic

TABLE 1. mGlu2/3 receptor agonists

Agonist	Chemical structures	mGlu2/3 affinity (EC_{50})	Selectivity
1*S*,3*R*-ACPD		1–10 μM	Nonselective mGlu receptor agonist at the same dose range
L-CCG-I		0.1–0.4 μM	Nonselective mGlu receptor agonist at low micromolar concentrations
DCG-IV		0.1–0.4 μM	NMDA receptor agonist and antagonist of group I and III mGlu (IC_{50} = 20–40 μM) receptors
2*R*,4*R*-APDC		0.3–10 μM	Selective mGlu2/3 agonist
LY354740		10–50 μM	Weak agonist effects on mGlu6 (EC_{50} = 3 μM) and mGlu8 (EC_{50} = 36 μM) receptors
LY379268		3–6 μM	Weak agonist effects on mGlu4 (EC_{50} = 20 μM), mGlu6 (EC_{50} = 400 μM), and mGlu8 (EC_{50} = 2 μM) receptors
LY389795		4–8 μM	Agonist responses in mGlu6 (EC_{50} = 2 μM) and mGlu8 (EC_{50} = 7 μM) receptor expressing cells

1S,3R-ACPD: 1S,3R-1-amino-cyclopentane-1,3-dicarboxylic acid; DCG-IV: (2S,2′R,3′R)-2-(2′,3′-dicarboxycyclopropyl)glycine; LCCG-I: (2S,1′S,2′S)-2-(carboxycyclopropyl)glycine; 2R,4R-APDC,2R: 2R,4R-4-aminopyrrolidine-2,4-dicarboxylic acid; LY354740: (1S,2S,5R,6S)-(+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; LY379268: (-)-2-oxa-4-aminocyclo[3.1.0]hexane-4,6-dicarboxylic acid; and LY389795: (-)-2-thia-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid.

amino acid LY354740, binding more potently to both native group II and recombinant mGlu3 receptors. Although an enhanced affinity was also observed for LY379268 relative to LY354740 at recombinant mGlu2 receptors, it was of a more modest (approximately 2–5-fold) nature. Accordingly, LY379268 possesses a significantly different mGlu2/mGlu3 receptor selectivity ratio (K_i ratio for mGlu2/mGlu3 = 2.4) compared to the parent amino acid (K_i ratio for mGlu2/mGlu3 = 0.8). As a result, LY354740 possesses approximately equal affinity for both mGlu2 and mGlu3 receptor, while LY379268 is considerably more mGlu3 receptor selective.

Group II metabotropic receptors are negatively coupled to adenylate cyclase via G_i protein and thereby inhibit the production of cAMP. LY379268 potently suppressed

forskolin-stimulated cAMP formation in cells expressing recombinant human mGlu2 (EC_{50} = ~3 nM) and mGlu3 (EC_{50} = ~6 nM) receptors, indicative of group II mGluR agonist activity (Monn et al. 1999). Like LY354740, LY379268 did not show any measurable affinity for native iGlu receptors, nor did it produce agonist or antagonist effects at concentrations up to 100 μM in cells expressing recombinant mGlu1, mGlu5, or mGlu7 receptors. LY379268, however, elicited weak agonist responses in cells expressing mGlu4 (EC_{50} = ~20 μM) and mGlu8 (EC_{50} = ~2 μM) receptors. Moreover, LY379268 can be clearly differentiated from LY354740 in its agonist potency in cells expressing mGlu6, an mGlu receptor subtype localized primarily in the retina (Laurie et al. 1997). Thus, while LY354740 produced agonist responses in this cell line at micromolar concentrations (EC_{50} = ~3 μM), LY379268 more potently suppressed the stimulated cAMP response with an EC_{50} value of 401 nM, approximately two orders of magnitude higher than that required for mGlu2/3 receptor activation.

In vivo microdialysis in the prefrontal cortex (PFC) of freely moving rats was utilized to assess the ability of LY379268 (10 mg/kg s.c.) to reach receptor active level in the brain (Schoepp et al. 2001). Within 1 h post-drug administration, LY379268 peaked at levels of 600–800 nM in the extracellular fluid of the brain, then declined over the next 5 h to <30 nM. As the above-mentioned *in vitro* studies showed, 30 nM is more than necessary to activate mGlu2/3 receptors. Thus, systemic administration of this drug gives insight into its functional consequences and therapeutic potential *in vivo*.

NEUROCHEMICAL EFFECTS

According to the function of mGlu2/3 receptors in the excitatory synaptic transmission (see Introduction), activation of these receptors by LY379268 could suppress both 5-HT-induced and electrically evoked EPSPs (EC_{50}: ~230–276 nM) in rat PFC slices that were associated with reduced presynaptic glutamate release (Marek et al. 2000; Aghajanian and Marek 1999). Additionally an *in vivo* microdialysis study showed that by either systemic or local administration LY379268 could reverse the NMDA antagonist, ketamine-evoked glutamate release in the PFC, while LY379268 did not change basal glutamate level (Lorrain et al. 2003a). These findings supported the concept that synaptic glutamate spillover is necessary for mGlu2/3 receptor-mediated reduction in glutamate release.

Cartmell et al. demonstrated by systemic administration that LY379268 produced increases in the release of dopamine, 5HT, and their metabolites in the PFC of freely moving rats (Cartmell et al. 2000d, 2001). It is unlikely that these effects of LY379268 are mediated by nonselective actions, as the increases in monoamine neurotransmission were attenuated by the selective mGlu2/3 receptor antagonist LY341495 (Cartmell et al. 2000d). Furthermore, the effects of systemic LY379268 on monoamine release were not locally mediated in the PFC, as perfusion of LY379268 through the microdialysis probe had no effects on either dopamine or 5-HT release (Cartmell et al. 2001). Also, LY379268-induced increases in dopamine and 5-HT could still be elicited in the presence of dopamine and 5-HT reuptake blockers, indicating these effects of LY379268 are not mediated via alterations in monoamine transporter activity. The cellular mechanism(s) underlying these changes and their functional relevance to the behavioral actions of mGlu2/3 receptor agonists are not yet clear.

Extrasynaptic localization of mGlu2/3 receptors on nonglutamatergic neurons has been described, suggesting a possible presynaptic heteroreceptor role for these receptors. Indeed, electrophysiological and biochemical studies have shown that nonselective mGlu receptor agonists suppress the release of GABA from neurons (Anwyl 1999; Cartmell and Schoepp 2000) and reversibly reduce the amplitude of GABA-mediated inhibitory postsynaptic potentials in a number of tissues including cerebral cortex, hippocampus, thalamus, and spinal cord (Anwyl 1999). A recent report also demonstrated that by either intrahippocampal or systemic administration of LY379268 induced a significant sustained decrease in hippocampal GABA levels (~65% of basal GABA release) (Smolders et al. 2004).

As measured by cerebral glucose use technique, while LY379268 reduced glucose utilization in certain limbic regions, it also elicited increases in glucose use in the hippocampus, some auditory relay nuclei, and locus coeruleus (Lam et al. 1999). Empirically a reduction in GABAergic neurotransmission may account for this enhanced neuronal activity following LY379268 administration. On the other hand, coincident heterosynaptic inhibition of GABA release by LY379268 (or other mGlu2/3 receptor agonist) contributes to countering any direct decreases in excitatory glutamatergic synaptic transmission on principal cells. Thus, overall, the actions of these types of drugs may be dependent on the relative importance of mGlu2/3 receptors in modulation of presynaptic suppressions of glutamate versus GABA release in that functional circuit.

NEUROPROTECTION

Neuroprotection studies demonstrated that mGlu2/3 receptor agonists including LY379268 protect neurons against NMDA toxicity in cell cultures (D'Onofrio et al. 2001; Kingston et al. 1999a,b). Systemic LY379268 was also effective in reducing MK801 (a noncompetitive NMDA antagonist)-induced cell injury in the retrosplenial cortex in adult rats. This effect was mimicked by local infusion of LY379268 into the retrosplenial cortex or the anterior thalamus (Carter et al. 2004). Initially, these neuroprotective effects of LY379268 were attributed to reduction in the release of endogenous glutamate via presynaptic activation of mGlu2/3 receptors.

In contrast to the function of mGlu2/3 receptors expressed in neurons, much less is understood about the role of glial mGlu2/3 receptors. It is clear, however, that mGlu3 but not mGlu2 receptor is expressed in glial cells (Liu et al. 1998; Mineff and Valtschanoff 1999; Ohishi et al. 1993a,b; Shigemoto et al. 1997). Given the major contribution of glia to the uptake and the synthesis of glutamate, and that the affinity of LY379268 is higher to mGlu3 versus mGlu2, activation of glial mGlu3 receptors by LY379268 is likely to result in significant functional effects (Winder and Conn 1996). In fact, LY379268 was more effective against excitotoxic death in mixed cultures than in pure neuronal cultures (Kingston et al. 1999a).

To date, most of the investigations of mGlu2/3 receptor-mediated inhibition of cAMP production were performed in pure neuronal cultures or brain slices where neuronal versus glial events cannot be separated. However, Moldrich et al. (2002) demonstrated that mGlu2/3 receptor signaling is somewhat different in astrocytes compared to neurons. While LY379268 and 2R,4R-APDC (a less potent mGlu2/3 receptor agonist) inhibited stimulated cAMP production in astrocytes under Ca^{2+}-free conditions, these agonists also potentiated stimulated cAMP production in the presence of physiological concentrations of Ca^{2+}, which was associated with adenosine release.

Adenosine has been shown to be neuroprotective in glial cells because of its regulatory role on the Ca^{2+}- and cAMP-dependent intracellular signaling (Schubert et al. 1996). For example, adenosine receptor-mediated intracellular cAMP rise could lead to increased expression of glutamate transporters (Eng et al. 1997; Schlag et al. 1998). An increased expression of glial glutamate transporters EAAT1 and EAAT2 might be important in preventing excitotoxicity, since they are the predominant transporters responsible for the clearance of extracellular glutamate (Danbolt 2001).

Synthesis and release of different proteins are also involved in the neuroprotective effects of glial mGlu3 receptor activation. For instance, the neuroprotectant effects of mGlu2/3 receptor agonists were abolished when protein synthesis in astrocytes was inhibited by cycloheximide or when the glial medium was heated (Bruno et al. 1997). Among the factors released in response to mGlu3 receptor activation, tumor growth factor-β (TGF_{β}) appears to mediate neuroprotection (Bruno et al. 1998). First, application of anti–$TGF_{ß1}$ or anti– $TGF_{ß2}$ antibodies prevents neuroprotection induced by mGlu2/3 receptor agonists, including LY379268, in glial medium. Second, mGlu2/3 receptor agonists enhance the synthesis and release of $TGF_{ß1}$ and $TGF_{ß2}$ in cultured astrocytes (Bruno et al. 1998; D'Onofrio et al. 2001). The possible underlying mechanism in response to glial mGlu3 receptors is activation of the mitogen-activated protein (MAP) kinase and the PI-3-kinase pathways. Inhibitors of these transduction pathways reduced the ability of LY379268 to enhance the synthesis of $TGF_{ß}$ in astrocytes and to protect neurons against NMDA toxicity (D'Onofrio et al. 2001).

Taken together, LY379268 provides putative neuroprotection by a combination of actions such as activation of presynaptic mGlu2/3 receptors to inhibit glutamate release and via glial mGlu3 receptors to induce neuroprotective factors.

STROKE

In vivo studies provided evidence (Table 2) that systemic LY379268 was effective in preventing hypoxic brain damage in goldfish (Poli et al. 2003), in a gerbil global cerebral ischemia (Bond et al. 1999) and in a neonatal rat model of hypoxia-ischemia (Cai et al. 1999). Bond et al. (2000) also demonstrated in the gerbil model of global ischemia that the neuroprotective effect of LY379268 is long lasting, up to 28 days. Thus, it appears that LY379268 is blocking, rather than merely delaying, the process of cell death.

Interestingly, neither LY379268 nor LY354740 was protective in focal ischemia (Behrens et al. 1999; Bond et al. 1999; Lam et al. 1998). This result may indicate that the selective mGlu2/3 receptor agonists have no effect in conditions where there is a rapid development of neuronal cell loss such as focal ischemia (or acute excitotoxicity), but they appear to be most effective in circumstances of slowly developing neuronal cell death (i.e., global ischemia).

In the gerbil model of global ischemia, the mechanism of action of LY379268 was not associated with induction of $TGF_{\beta 1}$ or $TGF_{\beta 2}$ (or other neurotrophic factors such as bFGF, BDNF, and NGF) in the hippocampus (Bond et al. 2000). On the other hand, LY379268 was neuroprotective even when it was applied 48 h before ischemia induction, and this effect was prevented by co-administration of mGlu2/3-receptor antagonist LY341495. Thus, the authors concluded that the neuroprotective effect of LY379268 is likely coupled with receptor activation which may involve inhibition of glutamate release and/or activation of

TABLE 2. In vivo effects of LY379268 on animal models of neurodegenerative disorders.

Model	Dose/route	Effects	References
Stroke			
Neonatal rat model of hypoxia-ischemia	2, 5, or 10 mg/kg i.p.	Prevented reduction in the ipsilateral brain weight and in CA1 hippocampal neuron density.	Cai et al. (1999)
Gerbil model of global ischemia	10 or 20 mg/kg i.p.	Prevented loss of CA1 hippocampal neurons given 30–120 min post-occlusion	Bond et al. (1999)
	10 mg/kg i.p.	Long-lasting neuroprotective effect up to 28 days	Bond et al. (2000)
Endothelin-1 model of focal ischemia in rat	10 or 20 mg/kg i.p.	Ineffective in reducing the infarct volume	Bond et al. (1999)
Anoxic brain damage in goldfish	0.5 or 1 mg/kg i.p.	Highly protective against anoxic brain damage	Poli et al. (2003)
Chronic neurodegenerative disorders			
MPTP model of PD in rat	1 mg/kg, i.p. (acute) or s.c. (7 days)	Reduced the extent of nigrostriatal degeneration induced by high doses of MPTP	Battaglia et al. (2003)
Reserpine model of PD in rat	1–20 nmol/2 mL i.c.v. 0.1–10 mg/kg i.p.	Central administration, but not systemic, produced some alleviation of the reserpine-induced akinesia	Murray et al. (2002)
6-OHDA-induced lesions in nigrostriatal tract of rat	10 mg/kg i.p. (7–21 days)	Provided neuroprotection in animals bearing complete or partial lesion of the nigrostriatal tract.	Murray et al. (2002)
Transgenic mouse model of HD	1.2 mg/kg p.o. (chronic)	Increased survival time and reduced the early pathological spontaneous locomotor deficit	Schiefer et al. (2004)
Epilepsy			
Mouse model of limbic seizure	10–100 mg/kg i.p.	Dose-dependently reduced limbic seizure activity induced by (1*S*,3*R*)-ACPD	Monn et al. (1999)
Sound-induced seizures in mice	0.001–0.3 nmol i.c.v. 1–30 mg/kg i.p.	Dose-dependently reduced score of sound-induced seizure activity	Moldrich et al. (2001)
DHPG-induced seizures in mice	0.0001–1 nmol i.c.v. 10 mg/kg i.p.	Produced a dose-dependent inhibition of DHPG-induced seizures and seizure score	Moldrich et al. (2001)
Sound-induced seizures in GEP rats	0.1–1 mg/kg i.p.	Did not inhibit score-9 seizures at either time-point at any of the doses tested.	Moldrich et al. (2001)
Absence epilepsy in lethargic mice	1 or 10 nmol i.c.v.	Reduced the duration of spike and wave discharge	Moldrich et al. (2001)

Continued.

TABLE 2. Continued

Model	Dose/route	Effects	References
Electrical stimulation of amygdala-kindled rats	10 mg/kg i.p.	The electrically induced seizure score and after-discharge duration was partially inhibited	Moldrich et al. (2001)
6-Hz model of partial seizure in mice	1–200 mg/kg i.p.	Provided dose-dependent protection from 6-Hz seizures	Barton et al. (2003)
Pilocarpine-induced seizure in rats	10 or 100 μM intrahippocampal	Exerted partial protection	Smolders et al. (2004)
Absence epilepsy in WAG/Rij rats	0.33 or 1 mg/kg i.p.	Increased the spike wave discharges	Ngomba et al. (2005)

MPTP:1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD: Parkinson's disease; HD: Huntington's disease; 6-OHDA: 6-hydroxydopamine; (1*S*,3*R*)-ACPD: 1S,3R-1-amino-cyclopentane-1,3-dicarboxylic acid; GEP genetically epilepsyprone-9 rat; and DHPG: (R,S)-3,5-dihydroxyphenylglycine.

biochemical pathways that inhibit programmed cell death, rather than a mechanism that involves a long-lasting induction of other factors (Bond et al. 2000). In contrast, D'Onofrio et al. (2001) showed that LY379268 enhances the expression of $TGF_{ß1}$ in the striatum, whereas 4C3HPG (mixed mGlu1 antagonist/mGlu2/3 receptor agonist) induced $TGF_{ß1}$ in the cerebral cortex but not in the hippocampus. These results raise the possibility that the response of astrocytes to these drugs is region-specific (D'Onofrio et al. 2001).

CHRONIC NEURODEGENERATIVE DISORDERS

Using the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of parkinsonism in mice, Battaglia et al. (2003) demonstrated that LY379268 was protective against MPTPtoxicity which was dependent on the extent of the nigrostriatal lesion. Systemic injection of LY379268 partially reduced the extent of nigrostriatal degeneration induced by high doses of MPTP while LY379268 did not produce a significant neuroprotective effect at lower doses of MPTP. By intracerebroventricular (i.c.v.) administration LY379268 was also shown to alleviate akinesia in the reserpine-treated rat model of Parkinson's disease, whereas systemic LY379268 was ineffective in the same model (Murray et al. 2002). In addition, this report revealed that by chronic treatment LY379268 (10 mg/kg i.p. for 7 days) produced some degree of neuroprotection in animals bearing a near complete or partial lesion of the nigrostriatal tract induced by 6-hydroxy-dopamine (6-OHDA). Similarly, LY379268 exhibited a great potency in depressing excitatory transmission and corticostriatal synapses in slices prepared from 6-OHDA-lesioned animals (Picconi et al. 2002). On the other hand, nigrostriatal degeneration induced by methamphetamine in mice was not attenuated by systemic injection of LY379268 (Battaglia et al. 2002).

To date, there is only one report showing that by chronic treatment LY379268 could increase the survival time in a transgenic mouse model of Huntington's disease (HD). Additionally, LY379268 reduced the early pathological hyperactivity of these HD transgenic mice, although it had no effect on progressive decline in motor coordination and on neuronal intracellular inclusion in the striatum and cortex (Schiefer et al. 2004).

SEIZURE MODELS

LY379268 was originally reported to block dose-dependently limbic seizures produced by intracerebral administration of non-selective mGlu1/2 receptor agonist (Monn et al. 1999). In a comprehensive study (Moldrich et al. 2001), the antiepileptic potential of LY379268 was confirmed using several models of epilepsy (Table 2). In another study comparing the anticonvulsant potential of different mGlu receptor agonists/antagonists, LY379268 was effective in blocking 6-Hz-induced seizure (Barton et al. 2003). In this seizure model, the rank order of potency for the systemically available mGlu receptor modulators was LY379268 > LY389795 > LY456236 {(4-methoxy-phenyl)-(6-methoxy-quinazolin-4-yl)-amine HCl, mGlu1 antagonist)} > MPEP (2-methyl-6-(phenylethynyl) pyridine, mGlu5 antagonist).

LY379268 was, however, ineffective in blocking sound-induced seizures in genetically epilepsyprone-9 (GEP) rats, but was proconvulsant at a low dose (0.1 mg/kg i.p.) following sound stimulus. In DBA/2 mice LY379268 induced intermittent and spontaneous wild running and hindlimb scratching at a dose (3 μmol i.c.v.), which was 1000-fold higher than anticonvulsant doses and as such was most likely toxic due to ''off-target'' effects (Moldrich et al. 2001). As a recent study demonstrated, injection of 1 mg/kg of LY379268 increased the number of spike wave discharges (SWDs) during 3–7 h post-treatment in WAG/Rij rats, which develop spontaneous nonconvulsive seizures after 2–3 months of age (Ngomba et al. 2005). It is worth noticing that, mGlu2/3 receptor signaling was reduced in the somatosensory cortex of 6-month-old WAG/Rij rats. This reduction was measured by the ability of the LY379268 to inhibit forskolin-stimulated cAMP formation, while this brain region showed increase in mGlu2/3 receptor expression (Ngomba et al. 2005). As the cortex has an essential role in the generation of SWDs in WAG/Rij rats, it is possible that LY379268 increases seizures by modulating synaptic activity within the somatosensory cortex. The underlying mechanism of these effects remains to be determined, however.

To date there is only one report that investigated the antiepileptic effects of LY379268 while monitoring the concomitant alterations in the neurotransmitter levels. By intrahippocampal administration LY379268 partially attenuated the pilocarpine-induced seizure which was associated with reduction in pilocarpine-evoked glutamate and GABA release in the hippocampus measured by *in vivo* microdialysis in conscious rat (Smolders et al. 2004). These findings support the hypothesis that mGlu2/3 receptors actively prevent glutamate accumulation during high frequency or evoked events (Cartmell and Schoepp 2000) and that the anticonvulsant effect of LY379268 also involves GABAergic inhibition at least in the hippocampus.

DRUG ABUSE

Besides dopamine, emerging evidence suggests that glutamate-mediated transmission might also play an important role in regulating the physiological and behavioral actions of drugs of abuse. Glutamate receptor antagonists could decrease the expression of conditioned place preference (Kotlinska and Biala 2000; Popik et al. 2003), behavioral sensitization and conditioned locomotor activity (Hotsenpiller et al. 2001; Jackson et al. 1998), indicating that antagonizing the actions of stimulus-induced glutamate release attenuates the expression of conditioned drug-related behaviors.

Accordingly, systemic LY379268 reversed drug-seeking behaviors (Table 3) evoked by either cocaine (Baptista et al. 2004; Peters and Kalivas 2006) or heroin (Bossert et al. 2004, 2005). In comparison to its effects on drug-related behaviors, LY379268 appeared to be less effective in reducing conditioned behaviors elicited by potent conventional reinforcer, such as sweetened condensed milk (Baptista et al. 2004), food pellets (Peters and Kalivas 2006), or sucrose (Bossert et al. 2006a). These observations indicate that LY379268 may selectively inhibit drug seeking at moderate doses (1 mg/kg) but has nonspecific inhibitory effects on responding for natural rewards at higher doses.

The systemic effect of LY379268 on heroin-seeking behavior was mimicked by local application of LY379268 into the ventral tegmental area (VTA) or into the nucleus accumbens (NAc) shell subregion, whereas intracaudate-putamen or intrasubstantia nigra (SN) infusion of LY379268 was ineffective (Bossert et al. 2004, 2006b). In the heroin relapse model, intra-NAc core injection of LY379268 was effective only at a 10-times higher dose (3.0 μg/site), which might be due to the diffusion into the NAc shell region (Bossert et al. 2006b). Additionally, by local infusion of LY379268 into the NAc core subregion the drug-inhibited cocaine as well as food-seeking behavior (Peters and Kalivas 2006).

These data indicated that one site of action where LY379268 exert effects on drug-seeking behavior is the NAc. The underlying mechanisms in the NAc may involve modulation of both glutamatergic and dopaminergic neurotransmission. *In vivo* microdialysis studies showed that by systemic administration LY379268 decreased the enhanced overflow of dopamine as well as glutamate in the NAc following amphetamine sensitization (Kim et al. 2005). Moreover, by local infusion LY379268 (10 nM to 10 μM) reduced dopamine levels in the NAc shell, but not in the NAc core (Greenslade and Mitchell 2004).

By systemic administration LY379268 was also effective in attenuating alcohol self-administration and cue-induced reinstatement at the dose that reduced spontaneous locomotor activity (Bäckström and Hyytiä 2005). In contrast, the reversal effect of 3 mg/kg LY379268 in the heroin- and cocaine-induced drug seeking behavior cannot be attributable to motor impairment, since this dose did not alter consumption of sweetened milk (Baptista et al. 2004) or have an effect on responding in the extinction context (Bossert et al. 2004). However, it is possible that by repeated administration LY379268 could also alter the alcohol related behavior without motor deficit. Several studies demonstrated that LY379268 had nonspecific motor depressant effects, to which animals developed rapid tolerance following repeated administration, while its therapeutic potential was retained (Cartmell et al. 2000b; Imre et al. 2006). Similarly, Riegel et al. (2003) found that initial injection of LY379268 reduced locomotion, which was diminished by daily treatment for 8–12 days. Following this procedure, LY379268 was still able to reduce dose-dependently the toluene-induced hyperlocomotion, indicating that activation of mGlu2/3 receptors may represent a novel treatment for inhalant addiction (Riegel et al. 2003).

SCHIZOPHRENIA

The NMDA receptor hypofunction model of schizophrenia was developed based on the observation that noncompetitive NMDA receptor antagonists such as PCP, MK801, and ketamine can exacerbate preexisting schizophrenic symptoms and induce a psychotic state in healthy humans (for review see Marino and Conn 2002). In rodents NMDA antagonists induce hyperlocomotion, cognitive deficit, and impairment of sensorimotor gating, which

TABLE 3. In vivo effects of LY379268 on animal models of psychiatric disorders.

Model	Dose/route	Effects	References
Drug abuse			
Locomotor sensitization by AMPH	1 mg/kg i.p.	Blocked the expression of AMPH-induced locomotor sensitization	Kim and Vezina (2002)
Cocaine-related behaviors	0.3–3 mg/kg s.c.	Dose-dependently reversed conditioned reinstatement evoked by cocaine; altered the primary reinforcing effects and reduced self-administration	Baptista et al. (2004)
	0.3, 1, or 3 mg/kg i.p 0.05, 0.5, or 5 nmol/side	Both systemic and intra-NAc core treatment inhibited cocaine-seeking behavior.	Peters and Kalivas (2006)
Heroin-related behaviors	1 or 3 mg/kg i.p. 0.1 or 0.3 μg/site	Both systemic and intra-VTA treatment reduced contextual cue-induced relapse to heroin seeking	Bossert et al. (2004)
	1 or 3 mg/kg i.p.	Reduced contextual discrete tone-light cue-induced relapse to heroin seeking; had no effect on self-administration	Bossert et al. (2005)
	0.3 or 1.0 μg/site	Intra-NAc shell treatment reduced contextual cue-induced relapse to heroin seeking	Bossert et al. (2006b)
Alcohol-related behaviors	0.1, 3, or 5 mg/kg i.p.	Attenuated alcohol self-administration and reinstatement at doses that also decreased spontaneous locomotor activity	Backstrom and Hyytia (2005)
Inhalant addiction	1.5–6 mg/kg i.p.	Attenuated toluene-induced activity	Riegel et al. (2003)
Schizophrenia			
NMDA hypofunction model of psychosis	0.3, 1, or 3 mg/kg s.c.	Effectively reversed PCP-evoked motor activations without gross impairment of the rats' motor abilities	Cartmell et al. (1999)
	0.3, 1, or 3 mg/kg s.c.	Dose-dependently reduced the expression of PCP-induced falling, turning, and back-pedaling in rats	Cartmell et al. (2000a)
	1, 3, or 10 mg/kg s.c.	Suppressed PCP-evoked motor behaviors in rats sensitized to PCP	Clark et al. (2002)
	3 mg/kg s.c.	Blocked PCP-evoked ambulatory activity and fine movements in control and monoamine-depleted rats	Swanson and Schoepp (2002)
	10 mg/kg i.p.	Blocked PCP- and MK801-induced hyperlocomotion in both DA-deficient and control mice.	Chartoff et al. (2005)

Continued.

TABLE 3. Continued.

Model	Dose/route	Effects	References
NMDA hypofunction model of psychosis	3 mg/kg i.p.	Reduced PCP-evoked hyperlocomotion in mice without affecting PPI deficit	Galici et al. (2005)
	1 or 10 μM	Intra-NAc shell administration reduced the PCP-evoked DA release	Greenslade and Mitchell (2004)
	0.3–10 mg/kg s.c.	In rats dose-dependently inhibited ketamine-induced hyperactivity and NE release in the ventral hippocampus	Lorrain et al. (2003b)
	3 mg/kg s.c. 1 μM	Both systemic and intra-mPFC administration in rats blocked ketamine-evoked Glu, but not DA, release in the mPFC	Lorrain et al. (2003a)
	1–3 mg/kg i.p.	Dose-dependently reduced ketamine-induced hyperactivity in rats, but had no effect on PPI deficit	Imre et al. (2006)
AMPH model of psychosis	1 mg/kg s.c.	Attenuated AMPH-induced ambulations and rearing but did not alter fine motor movements in rats	Cartmell et al. (2000c)
	3 mg/kg i.p.	Reduced AMPH-evoked hyperlocomotion in mice without affecting PPI deficit	Galici et al. (2005)
Serotonergic drug-related model	0.125–2.5 mg/kg i.p.	Inhibited DOI-induced head twitches in mice in a dose-dependent manner	Klodzinska et al. (2002)
	15 mg/kg i.p. 0.01–1.0 μM.	Reduced DOI-induced cell activity in the mPFC measured by c-fos expression and electrophysiologically in rats	Zhai et al. (2003)
	0.3–10 mg/kg i.p.	Significantly diminished stimulus control by LSD in rats	Winter et al. (2004)
Anxiety and stress			
Stress-induced hyperprolactinemia	10 mg/kg s.c.	Reduced immobilization stress-induced hyperprolactinemia in rats	Johnson et al. (2002)
Stress-evoked norepinephrine levels	1, 3, or 10 mg/kg p.o.	Attenuated the elevated platform stress-evoked increase in extracellular NE in the rat mPFC	Lorrain et al. (2005)
Despair test	1 mg/kg i.p.	Did not affect corticosterone levels in either control or stressed mice	Scaccianoce et al. (2003)

AMPH = amphetamine; NAc = nucleus accumbens; VTA = ventral tegmental area; NMDA = *N*-methyl-D-aspartate; PCP = phencyclidine; MK801 = disocilpine; NE = norepinephrine; mPFC = medial prefrontal cortex; Glu = glutamate; DA = dopamine; PPI = prepulse inhibition; DOI = ((±)1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane); and LSD = lysergic acid diethylamide.

is associated with an excessive glutamate release in limbic regions (Imre et al. 2006; Jentsch and Roth 1999; Lorrain et al. 2003a; Moghaddam et al. 1997).

Using this model, Cartmell et al. (1999, 2000a,b) demonstrated first that LY379268 reversed PCP-evoked hyperlocomotion and nonambulatory fine movements (e.g., turning, head weaving, and back-pedaling) with the relative potency order of haloperidol > LY379268 > clozapine > LY354740. Additionally, LY379268 was effective in reversing enhanced locomotor effect of repeated (10 days) PCP administration (Clark et al. 2002). Moreover, microdialysis studies performed by the same group demonstrated that LY379268 shared common neurochemical characteristics with atypical antipsyhotics. Similar to clozapine and risperidone, LY379268 increased the dupaminergic and serotonergic neurotransmission in the PFC (Cartmell and Schoepp 2000; Cartmell et al. 2000d,e, 2001). These findings implied initially that LY379268 possesses potential antipsychotic activity (Table 3).

Other studies extended these results showing that systemic LY379268 was also able to prevent ketamine-induced hyperlocomotion that was linked to reduction in ketamine-evoked glutamate, but not dopamine, release in the PFC (Imre et al. 2006; Lorrain et al. 2003a,b). Similarly, Moghaddam and Adams (1998) reported that systemic LY354740 could attenuate both PCP-induced motor impairments and increase in glutamate release without influencing increased dopamine release in the PFC. Together, these data suggested that mGlu2/3 receptor agonists may block NMDA antagonist-mediated behaviors via a novel mechanism (reduction in evoked glutamate release), which, unlike with typical and atypical antipsychotic drugs, might be independent of the dopaminergic neurotransmission in the PFC. Such a hypothesis is supported by evidence that LY379268 was effective in suppressing NMDA antagonist-induced hyperlocomotion in dopamine- and 5-HT-deficient rodents (Swanson and Schoepp 2002; Chartoff et al. 2005).

It should be noted that LY379268 also suppressed baseline locomotor activity at the dose range (1–10 mg/kg), which is effective in reducing NMDA antagonist-evoked hyperactivity. Nevertheless, at these doses of LY379268, the animals' motor abilities were not impaired, as they did not display ataxia and performed normally on the rotorod (Cartmell et al. 1999, 2000a,b). At acute doses higher than 10 mg/kg p.o., LY379268 produced motor impairment in the rotorod test, but this effect was tolerated following 4 days of subchronic treatment (Cartmell et al. 2000b). Importantly, this tolerance to motor impairment induced by the higher doses of LY379268 was not associated with changes in LY379268 potency in reversing PCP-evoked motor activities. On the other hand, repeated administration of LY379268 alongside with PCP could not prevent the development of PCP sensitization (Clark et al. 2002).

In addition to the effectiveness of LY379268 in the NMDA antagonistsevoked hyperlocomotion, this compound was effective in blocking amphetamine-induced hyperlocomotion and rearing, but not fine motor movements (Cartmell et al. 1999, 2000c). It has been suggested that inhibition of amphetamine-evoked stereotypy can be predictive of the occurrence of extrapyramidal side effects in the clinic. Thus, the lack of effect of LY379268 on the increase in fine motor movements produced by amphetamine suggests that this compound, similar to clozapine, may have a low risk of extrapyramidal side effects (Cartmell et al. 1999, 2000c). In another pharmacological model of schizophrenia, LY379268 could reduce the 5-HT_{2A} agonist DOI-induced head twitches (Klodzinska et al. 2002) and the DOI-induced cell activity in the PFC measured by c-Fos expression (Zhai et al. 2003). Consistent with these observations, LY379268 was also shown to attenuate stimulus control by LSD

(Winter et al. 2004). These data indicated that mGlu2/3 receptor agonists may counteract the psychotomimetic effects of hallucinogenic drugs (Table 3).

In contrast to the overwhelming literature regarding the effects of LY379268 on locomotor abnormalities in schizophrenic models, there are only two studies that investigated the effects of LY379268 on psychotomimetic drugsevoked sensorimotor gating deficit. Both reports showed that by systemic administration LY379268 was not able to prevent amphetamine- or NMDA antagonist-induced prepulse inhibition impairment (PPI), a measure of sensorimotor gating function (Galici et al. 2005, Imre et al. 2006). Since atypical antipsychotics are generally effective in the PPI model, these results cast doubt on the proposed antipsychotic properties of LY379268.

PAIN

While a number of recent studies have focused on Group I mGlu receptors in pain (for review see Fundytus 2001), less is known about the specific role of Group II mGlu receptors in pain processing. The first reports on the involvement of mGluR2/3 in nociceptive processing relied on a relatively nonselective mGluR2/3 agonist (Fisher and Coderre 1996), whereas only few studies used systemically active, selective ligands such as LY379268.

Electrophysiological spinal administration of mGlu2/3 receptor agonists, including LY379268, attenuated capsaicin-induced central sensitization of spinothalamic tract neurons in primates while having no effect under normal control conditions (Neugebauer et al. 2000).

In testing the drug in rats as an analgesic, systemic LY379268 did not affect withdrawal latencies to either mechanical or thermal acute noxious stimuli in normal rats, but delayed hyperalgesia produced by the intraplantar administration of carrageenan in rats, and also reduced capsaicin-induced hyperalgesia in a warm water tail withdrawal test (Sharpe et al. 2002). In this study, rotorod test showed that LY379268 did not produce motor impairment at the antihyperalgesic doses.

Simmons et al. (2002) demonstrated that the mGlu2/3 receptor agonists LY354740, LY379268, and LY389795 attenuated late-phase pawlicking pain behavior in the formalin model of persistent pain with a potency order of LY389795 > LY379268 > LY354740. These effects occurred without overt motor impairment as measured by rotorod test. In the L5/L6 spinal nerve ligation model of neuropathic pain in rats, LY379268 also significantly reversed mechanical allodynia in a dose-dependent manner (Simmons et al. 2002). In contrast, LY379268 had no effect in acute nociceptive pain models including the tail flick reflex test and paw withdrawal latency test (Simmons et al. 2002).

These results indicated that mGlu2/3 receptors might be involved in persistent pain mechanisms but not in acute pain processing. A recent report partly confirmed this hypothesis showing that LY379268 was effective in persistent pain models such as formalin test, carrageenaan-induced thermal hyperalgesia, and capsaicin-induced mechanical allodynia (Jones et al. 2005). In acute pain models, LY379268 could also increase response latencies in the hot plate test, but had no effect in the tail flick test. It should be noted, however, that LY379268 was effective only at does (3 and 10 mg/kg s.c.) that also produced motor impairment as measured by the invert screen test. Moreover, this study demonstrated that upon repeated dosing (4 days), a tolerance developed against the analgesic effects of LY379268.

ANXIETY AND STRESS

While a growing body of preclinical and clinical evidence suggested that activation of mGlu2/3 receptors may represent a novel treatment for anxiety- and stress-related disorders (Swanson et al. 2005), only few reports evaluated the anxiolytic properties of LY379268 (Table 3). Johnson and Chamberlain (2002) demonstrated that LY379268 could prevent immobilization stress- and cathecholamines depletion-induced hyperprolactinemia in male rats without effect on basal prolactin plasma level. Additionally, both acute and repeated administration of LY379268 could prevent the increase in norepinephrine level in the PFC, which was induced by exposure of rats to an open and elevated platform (Lorrain et al. 2005).

These data might be indicative of anxiolytic properties of LY379268. However, such a hypothesis has not yet been tested in an adequate animal model of anxiety. In fact, at 3 mg/kg, LY379268 appeared to be anxiogenic, as it increased startle reflex magnitude, which is considered to be a sign of anxiety (Imre et al. 2006). At a lower dose (1 mg/kg) such an effect was no longer observed, but animals exhibited reduced exploratory behavior in the open field. Although this latter effect was attributed to anxiolytic action of LY379268, it can also be a consequence of the suppressant effects of this compound on locomotion. Thus, further behavioral studies are needed to clarify how LY379268 can influence anxiety stage using different animal models of anxiety.

With regard to neuroendocrine functions associated with stress responses, it was initially suggested that hypothalamic–pituitary–adrenal (HPA) axis is predominantly under the control of group $^1/_2$ mGlu receptors, whereas mGlu2/3 receptors play a minor, if any, role (Johnson et al. 2001). Blockade of mGlu2/3 receptors in mice resulted, however, in an increased plasma corticosterone level and release of corticotropin releasing hormone (CRH) in isolated mouse hypothalami (Scaccianoce et al. 2003). This latter effect was prevented by co-administration of LY379268, while this drug per se did not affect either basal and stress-induced corticosterone levels or CRH release (Scaccianoce et al. 2003). Consistent with this, systemic LY379268 did not change either basal or ketamine-evoked plasma corticosterone levels in rats (Imre et al. 2006). Based on these findings it was concluded that endogenous activation of mGlu2/3 receptors tonically inhibit the HPA axis by controlling CRH release at the hypothalamic level.

Matrisciano et al. (2005) demonstrated that chronic imipramine treatment upregulated the expression of mGlu2/3 receptors in hippocampus, cortex, and nucleus accumbens and resulted in neuroadaptive changes in function of mGlu2/3 receptors as indicated by the reduced ability of LY379268 to inhibit forskolin-stimulated cAMP formation. In a recent study performed by the same authors, LY379268 was shown to shorten the latency for the development of chronic imipramine-induced downregulation of β-adrenoceptors (a prototypical marker of neuroadaptation to antidepressant medication) in the hippocampus (Matrisciano et al. 2005). These data raise the possibility that mGlu2/3-receptor activation combined with classical antidepressants may shorten the time required for the relief of depressive symptoms.

CONCLUSION

LY379268 represents a novel generation of the mGlu2/3 receptor agonists with high affinity and bioavailability. Accordingly, preclinical studies have indicated the effectiveness

of LY379268 in treating several neurodegenerative and psychiatric disorders, which are generally associated with excessive glutamate neurotransmission.

Both *in vitro* and *in vivo* data have demonstrated the neuroprotective properties of LY379268, with the exception of focal ischemia. The underlying mechanisms of its neuroprotectant effects may combine blockade of presynaptic glutamate release via mGlu2 receptors and induction of neurotrophic factors (such as TGF-β) via mGlu3 receptors located on astrocytes. The latter mechanism suggests a broad application for this drug in neurodegenerative disorders and may allow circumvention of the major limitation associated with the peripheral administration of neurotrophic factors, that is, their poor penetration across the blood–brain barrier.

In a variety of seizure models LY379268 has shown different degrees of anticonvulsant activity with comparable therapeutic index to clinical antiepileptic drugs (Moldrich et al. 2001). LY379268 appeared to be proconvulsive only at doses that were 1000-fold higher than anticonvulsant doses. Additionally, LY379268 may have usefulness in treating drug addiction, since it was effective in reducing heroin- and cocaine-induced drug seeking behavior and cocaine self-administration.

Using pharmacological models of schizophrenia, LY379268 has been suggested to have antipsychotic properties, as it was able to reverse specific motor deficits evoked by different psychomimetic drugs. Moreover, microdialysis studies demonstrated that LY379268 shares common neurochemical characteristics with atypical antipsychotics such as clozapine and risperidone. However, LY379268 failed to reverse sensorimotor gaiting deficits, a key symptom of schizophrenia, which may question its antypsychotic activity.

As an analgesic, LY379268 appeared to be effective in persistent pain but not in acute pain models. However, the latest results indicated that the analgesic effects may be attributable to the locomotion suppressant effects of LY379268 that is often observed after acute administration. Although by repeated administration LY379268 could produce tolerance against this motor impairment, it also resulted in loss of analgesic effect. In contrast, repeated dosing of LY379268 did not diminish its ability to reduce psychostimulant- or inhalant-induced activity (Cartmell et al. 2000b; Riegel et al. 2003).

At present, only limited information is available on the effects of LY379268 in anxiety- and stress-related animal models, while its less potent analog LY354740 has proved to be anxiolytic in both animals and humans (Swanson et al. 2005). Furthermore, there are no data concerning the ability of LY379268 to influence cognition under either normal or pathological conditions, which would be crucial for determination of its therapeutic potential.

In conclusion, LY379268 possesses a broad spectrum of activity with limited side effects in disorders associated with excessive glutamate neurotransmission. LY379268 and related compounds can be considered to be promising targets for pharmacological interventions.

REFERENCES

Aghajanian GK, Marek GJ (1999) Serotonin, via 5-HT_{2A} receptors, increases EPSCs in layer V pyramidal cells of prefrontal cortex by an asynchronous mode of glutamate release. *Brain Res 825*:161-171.

Anwyl R (1999) Metabotropic glutamate receptors: Electrophysiological properties and role in plasticity. *Brain Res Rev 29*:83-120.

Bäckström P, Hyytiä P (2005) Suppression of alcohol self-administration and cue-induced reinstatement of alcohol seeking by the mGlu2/3 receptor agonist LY379268 and the mGlu8 receptor agonist (S)-3,4-DCPG. *Eur J Pharmacol 528*:110-118.

Baptista MA, Martin-Fardon R, Weiss F (2004) Preferential effects of the metabotropic glutamate 2/3 receptor agonist LY379268 on conditioned reinstatement versus primary reinforcement: Comparison between cocaine and a potent conventional reinforcer. *J Neurosci 24*:4723-4727.

Barton ME, Peters SC, Shannon HE (2003) Comparison of the effect of glutamate receptor modulators in the 6 Hz and maximal electroshock seizure models. *Epilepsy Res 56*:17-26.

Battaglia G, Fornai F, Busceti CL, Aloisi G, Cerrito F, De Blasi A, Melchiorri D, Nicoletti F (2002) Selective blockade of mGlu5 metabotropic glutamate receptors is protective against methamphetamine neurotoxicity. *J Neurosci 22*:2135-2141.

Battaglia G, Busceti CL, Pontarelli F, Biagioni F, Fornai F, Paparelli A, Bruno V, Ruggieri S, Nicoletti F (2003) Protective role of group-II metabotropic glutamate receptors against nigro-striatal degeneration induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice. *Neuropharmacology 45*:155-166.

Behrens MM, Strasser U, Heidinger V, Lobner D, Yu SP, McDonald JW, Won M, Choi DW (1999) Selective activation of group II mGluRs with LY354740 does not prevent neuronal excitotoxicity. *Neuropharmacology 38*:1621-1630.

Bond A, Ragumoorthy N, Monn JA, Hicks CA, Ward MA, Lodge D, O'Neill MJ (1999) LY379268, a potent and selective group II metabotropic glutamate receptor agonist, is neuroprotective in gerbil global, but not focal, cerebral ischaemia. *Neurosci Lett 273*:191-194.

Bond A, Jones NM, Hicks CA, Whiffin GM, Ward MA, O'Neill MF, Kingston AE, Monn JA, Ornstein PL, Schoepp DD, et al. (2000) Neuroprotective effects of LY379268, a selective mGlu2/3 receptor agonist: Investigations into possible mechanism of action in vivo. *J Pharmacol Exp Ther 294*:800-809.

Bossert JM, Liu SY, Lu L, Shaham Y (2004) A role of ventral tegmental area glutamate in contextual cue-induced relapse to heroin seeking. *J Neurosci 24*:10726-10730.

Bossert JM, Busch RF, Gray SM (2005) The novel mGluR2/3 agonist LY379268 attenuates cue-induced reinstatement of heroin seeking. *Neuroreport 16*:1013-1016.

Bossert JM, Poles GC, Sheffler-Collins SI, Ghitza UE (2006a) The mGluR2/3 agonist LY379268 attenuates context- and discrete cue-induced reinstatement of sucrose seeking but not sucrose self-administration in rats. *Behav Brain Res 173*:148-152.

Bossert JM, Gray SM, Lu L, Shaham Y (2006b) Activation of group II metabotropic glutamate receptors in the nucleus accumbens shell attenuates context-induced relapse to heroin seeking. *Neuropsychopharmacology 31*:2197-2209.

Bruno V, Battaglia G, Casabona G, Copani A, Caciagli F, Nicoletti F (1998) Neuroprotection by glial metabotropic glutamate receptors is mediated by transforming growth factor-beta. *J Neurosci 18*:9594-9600.

Bruno V, Sureda FX, Storto M, Casabona G, Caruso A, Knöpfel T, Kuhn R, Nicoletti F (1997) The neuroprotective activity of group-II metabotropic glutamate receptors requires new protein synthesis and involves a glial-neuronal signaling. *J Neurosci 17*:1891-1897.

Cai Z, Xiao F, Fratkin JD, Rhodes PG (1999) Protection of neonatal rat brain from hypoxic-ischemic injury by LY379268, a group II metabotropic glutamate receptor agonist. *Neuroreport 10*:3927-3931.

Carter K, Dickerson J, Schoepp DD, Reilly M, Herring N, Williams J, Sallee FR, Sharp JW, Sharp FR (2004) The mGlu2/3 receptor agonist LY379268 injected into cortex or thalamus decreases neuronal injury in retrosplenial cortex produced by NMDA receptor antagonist MK-801: Possible implications for psychosis. *Neuropharmacology 47*:1135-1145.

Cartmell J, Schoepp DD (2000) Regulation of neurotransmitter release by metabotropic glutamate receptors. *J Neurochem 75*:889-907.

Cartmell J, Monn JA, Schoepp DD (1999) The metabotropic glutamate 2/3 receptor agonists LY354740 and LY379268 selectively attenuate phencyclidine versus d-amphetamine motor behaviors in rats. *J Pharmacol Exp Ther 291*:161-170.

Cartmell J, Monn JA, Schoepp DD (2000a) Attenuation of specific PCP-evoked behaviors by the potent mGlu2/3 receptor agonist, LY379268 and comparison with the atypical antipsychotic, clozapine. *Psychopharmacology (Berl) 48*:423-429.

Cartmell J, Monn JA, Schoepp DD (2000b) Tolerance to the motor impairment, but not to the reversal of PCP-induced motor activities by oral administration of the mGlu2/3 receptor agonist, LY379268. *Naunyn Schmiedeberg's Arch Pharmacol 361*:39-46.

Cartmell J, Monn JA, Schoepp DD (2000c) The mGlu2/3 receptor agonist LY379268 selectively blocks amphetamine ambulations and rearing. *Eur J Pharmacol 400*: 221-224.

Cartmell J, Perry KW, Salhoff CR, Monn JA, Schoepp DD (2000d) The potent, selective mGlu2/3 receptor agonist LY379268 increases extracellular levels of dopamine, 3,4-dihydroxyphenylacetic acid, homovanillic acid,

and 5-hydroxyindole-3-acetic acid in the medial prefrontal cortex of the freely moving rat. *J Neurochem 75*:1147-1154.

Cartmell J, Salhoff CR, Perry KW, Monn JA, Schoepp DD (2000e) Dopamine and 5-HT turnover are increased by the mGlu2/3 receptor agonist LY379268 in rat medial prefrontal cortex, nucleus accumbens and striatum. *Brain Res 887*:378-384.

Cartmell J, Perry KW, Salhoff CR, Monn JA, Schoepp DD (2001) Acute increases in monoamine release in the rat prefrontal cortex by the mGlu2/3 agonist LY379268 are similar in profile to risperidone, not locally mediated, and can be elicited in the presence of uptake blockade. *Neuropharmacology 40*:847-855.

Chartoff EH, Heusner CL, Palmiter RD (2005) Dopamine is not required for the hyperlocomotor response to NMDA receptor antagonists. *Neuropsychopharmacology 30*:1324-1333.

Chen YL, Huang CC, Hsu KS (2001) Time-dependent reversal of long-term potentiation by low frequency stimulation at the hippocampal mossy fiber-CA3 synapses. *J Neurosci 21*:3705-3714.

Clark M, Johnson BG, Wright RA, Monn JA, Schoepp DD (2002) Effects of the mGlu2/3 receptor agonist LY379268 on motor activity in phencyclidine-sensitized rats. *Pharmacol Biochem Behav 73*:339-346.

Conn PJ, Pin JP (1997) Pharmacology and functions of metabotropic glutamate receptors. *Annu Rev Pharmacol Toxicol 37*:205-237.

Danbolt NC (2001) Glutamate uptake. *Prog Neurobiol 65*:1-105.

D'Onofrio M, Cuomo L, Battaglia G, Ngomba RT, Storto M, Kingston AE, Orzi F, De Blasi A, Di Iorio P, Nicoletti F, et al. (2001) Neuroprotection mediated by glial group-II metabotropic glutamate receptors requires the activation of the MAP kinase and the phosphatidylinositol-3-kinase pathways. *J Neurochem 78*:435-445.

Eng DL, Lee YL, Lal PG (1997) Expression of glutamate uptake transporters after dibutyryl cyclic AMP differentiation and traumatic injury in cultured astrocytes. *Brain Res 778*:215-221.

Fisher K, Coderre TJ (1996) The contribution of metabotropic glutamate receptors (mGluRs) to formalin-induced nociception. *Pain 68*:255-263.

Fundytus ME (2001) Glutamate receptors and nociception. Implications for the drug treatment of pain. *CNS Drugs 15*:29-58.

Galici R, Echemendia NG, Rodriguez AL, Conn PJ (2005) A selective allosteric potentiator of metabotropic glutamate (mGlu) 2 receptor has effects similar to an orthosteric mGlu2/3 receptor agonist in mouse models predictive of antipsychotic activity. *J Pharmacol Exp Ther 315*:1181-1187.

Greenslade RG, Mitchell SN (2004) Selective action of (–)-2-oxa-4-aminobicyclo[3.1.0]hexane-4, 6-dicarboxylate (LY379268), a group II metabotropic glutamate receptor agonist, on basal and phencyclidine-induced dopamine release in the nucleus accumbens shell. *Neuropharmacology 47*:1-8.

Hotsenpiller G, Giorgetti M, Wolf ME (2001) Alterations in behaviour and glutamate transmission following presentation of stimuli previously associated with cocaine exposure. *Eur J Neurosci 14*:1843-1855.

Huang LQ, Rowan MJ, Anwyl R (1997) mGluR II agonist inhibition of LTP induction, and mGluR II antagonist inhibition of LTD induction, in the dentate gyrus in vitro. *Neuroreport 8*:687-693.

Imre G, Salomons A, Jongsma M, Fokkema DS, Den Boer JA, Ter Horst GJ (2006) Effects of the mGluR2/3 agonist LY379268 on ketamine evoked behaviours and neurochemical changes in the dentate gyrus of the rat. *Pharmacol Biochem Behav 84*:392-399.

Jackson A, Mead AN, Rocha BA, Stephens DN (1998) AMPA receptors and motivation for drug: Effect of the selective antagonist NBQX on behavioural sensitization and on self-administration in mice. *Behav Pharmacol 9*:457-467.

Jentsch JD, Roth RH (1999) The neuropsychopharmacology of phencyclidine: From NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology 20*:201-225.

Johnson MP, Chamberlain M. (2002) Modulation of stress-induced and stimulated hyperprolactinemia with the group II metabotropic glutamate receptor selective agonist, LY379268. *Neuropharmacology 43*:799-808.

Johnson MP, Kelly G, Chamberlain M (2001) Changes in rat serum corticosterone after treatment with metabotropic glutamate receptor agonists or antagonists. *J Neuroendocrinol 13*:670-677.

Jones CK, Eberle EL, Peters SC, Monn JA, Shannon HA (2005) Analgesic effects of the selective group II (mGlu2/3) metabotropic glutamate receptor agonists LY379268 and LY389795 in persistent and inflammatory pain models after acute and repeated dosing. *Neuropharmacology 49*:206-218.

Kew JN, Ducarre JM, Pflimlin MC, Mutel V, Kemp JA (2001) Activity-dependent presynaptic autoinhibition by group II metabotropic glutamate receptors at the perforant path inputs to the dentate gyrus and CA1. *Neuropharmacology 40*:20-27.

Kim JH, Vezina P (2002) The mGlu2/3 receptor agonist LY379268 blocks the expression of locomotor sensitization by amphetamine. *Pharmacol Biochem Behav 73*:333-337.

Kim JH, Austin JD, Tanabe L, Creekmore E, Vezina P (2005) Activation of group II mGlu receptors blocks the enhanced drug taking induced by previous exposure to amphetamine. *Eur J Neurosci 21*:295-300.

Kingston AE, O'Neill MJ, Lam A, Bales KR, Monn JA, Schoepp DD (1999a) Neuroprotection by metabotropic glutamate receptor glutamate receptor agonists: LY354740, LY379268 and LY389795. *Eur J Pharmacol 377*:155-165.

Kingston AE, O'Neill MJ, Bond A, Bruno V, Battaglia G, Nicoletti F, Harris JR, Clark BP, Monn JA, Lodge D, et al. (1999b) Neuroprotective actions of novel and potent ligands of group I and group II metabotropic glutamate receptors. *Ann N Y Acad Sci 890*:438-449.

Klodzinska A, Bijak M, Tokarski K, Pilc A (2002) Group II mGlu receptor agonists inhibit behavioural and electrophysiological effects of DOI in mice. *Pharmacol Biochem Behavior 73*:327-332.

Kotlinska J, Biala G (2000) Memantine and ACPC affect conditioned place preference induced by cocaine in rats. *Pol J Pharmacol 52*:179-185.

Lam AG, Soriano MA, Monn JA, Schoepp DD, Lodge D, McCulloch J (1998) Effects of the selective metabotropic glutamate agonist LY354740 in a rat model of permanent ischaemia. *Neurosci Lett 254*:121-123.

Lam AGM, Monn JA, Schoepp DD, Lodge D, McCulloch J (1999) Group II selective metabotropic glutamate receptor agonists and local cerebral glucose use in the rat. *J Cereb Blood Flow Metab 19*:1083-1091.

Laurie DJ, Schoeffter P, Wiederhold KH, Sommer B (1997) Cloning, distribution and functional expression of the human mGlu6 metabotropic glutamate receptor. *Neuropharmacology 36*:145-152.

Liu XB, Munoz A, Jones EG (1998) Changes in subcellular localization of metabotropic glutamate receptor subtypes during postnatal development of mouse thalamus. *J Comp Neurol 395*:450-465.

Lorrain DS, Baccei CS, Bristow LJ, Anderson JJ, Varney MA (2003a) Effects of ketamine and N-methyl-D-aspartate on glutamate and dopamine release in the rat prefrontal cortex: Modulation by a group II selective metabotropic glutamate receptor agonist LY379268. *Neuroscience 117*:697-706.

Lorrain DS, Schaffhauser H, Campbell UC, Baccei CS, Correa LD, Rowe B, Rodriguez DE, Anderson JJ, Varney MA, Pinkerton AB, et al. (2003b) Group II mGlu receptor activation suppresses norepinephrine release in the ventral hippocampus and locomotor responses to acute ketamine challenge. *Neuropsychopharmacology 28*:1622-1632.

Lorrain DS, Baccei CS, Correa LD, Bristow LJ (2005) Comparison of the effects of diazepam, the CRF1 antagonist CP-154,526 and the group II mGlu receptor agonist LY379268 on stress-evoked extracellular norepinephrine levels. *Neuropharmacology 48*:927-935.

Marek GJ, Wright RA, Schoepp DD, Monn JA, Aghajanian GK (2000) Physiological antagonism between 5 hydroxytryptamine(2A) and group II metabotropic glutamate receptors in prefrontal cortex. *J Pharmacol Exp Ther 292*:76-87.

Marino MJ, Conn PJ (2002) Direct and indirect modulation of the N-methyl D-aspartate receptor: Potential for the development of novel antipsychotic therapies. *Current Drug Targets 1*:1-16.

Matrisciano F, Storto M, Ngomba RT, Cappuccio I, Caricasole A, Scaccianoce S, Riozzi B, Melchiorri D, Nicoletti F (2002) Imipramine treatment up-regulates the expression and function of mGlu2/3 metabotropic glutamate receptors in the rat hippocampus. *Neuropharmacology 42*:1008-1015.

Matrisciano F, Scaccianoce S, Del Bianco P, Panaccione I, Canudas AM, Battaglia G, Riozzi B, Ngomba RT, Molinaro G, Tatarelli R, et al. (2005) Metabotropic glutamate receptors and neuroadaptation to antidepressants: Imipramine-induced down-regulation of β-adrenergic receptors in mice treated with metabotropic glutamate 2/3 receptor ligands. *J Neurochem 93*:1345-1352.

Mineff E, Valtschanoff J (1999) Metabotropic glutamate receptors 2 and 3 expressed by astrocytes in rat ventrobasal thalamus. *Neurosci Lett 270*:95-98.

Moghaddam B, Adams BW (1998) Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. *Science 281*:1349-1352.

Moghaddam B, Adams B, Verma A, Daly D (1997) Activation of glutamatergic neurotransmission by ketamine: A novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci 17*:2921-2927.

Moldrich RX, Jerey M, Talebi A, Beart PM, Chapman AG, Meldrum BS (2001) Antiepileptic activity of group II metabotropic glutamate receptor agonists (-)-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). *Neuropharmacology 41*:8-18.

Moldrich RX, Aprico K, Diwakarla S, O'Shea RD, Beart PM (2002) Astrocyte mGlu2/3-mediated cAMP potentiation is calcium sensitive: Studies in murine neuronal and astrocyte cultures. *Neuropharmacology 43*:189-203.

Monn JA, Valli MJ, Massey SM, Wright RA, Salhoff CR, Johnson BG, Howe T, Alt CA, Rhodes GA, Robey RL, et al. (1997) Design, synthesis, and pharmacological characterization of (+)-2 aminobicyclo [3.1.0] hexane-2,6-dicarboxylic acid (LY354740): A potent, selective, and orally active group 2 metabotropic glutamate receptor agonist possessing anticonvulsant and anxiolytic properties. *J Med Chem 40*:528-537.

Monn JA, Valli MJ, Massey SM, Hansen MM, Kress TJ, Wepsiec JP, Harkness AR, Grutsch JL Jr, Wright RA, Johnson BG, et al. (1999) Synthesis, pharmacological characterization, and molecular modeling of heterobicyclic amino acids related to (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740): Identification of two new potent, selective, and systemically active agonists for group II metabotropic glutamate receptors. *J Med Chem 42*:1027-1040.

Murray TK, Messenger MJ, Ward MA, Woodhouse S, Osborne DJ, Duty S, O'Neill MJ (2002) Evaluation of the mGluR2/3 agonist LY379268 in rodent models of Parkinson's disease. *Pharmacol Biochem Behav 73*:455-466.

Neugebauer V, Chen PS, Willis WD (2000) Groups II and III metabotropic glutamate receptors differentially modulate brief and prolonged nociception in primate STT cells. *J Neurophysiol 84*:2998-3009.

Ngomba RT, Biagioni F, Casciato S, Willems-van Bree E, Battaglia G, Bruno V, Nicoletti F, van Luijtelaar ELJM (2005) The preferential mGlu2/3 receptor antagonist, LY341495, reduces the frequency of spike-wave discharges in the WAG/Rij rat model of absence epilepsy. *Neuropharmacology 49*:89-103.

Ohishi H, Shigemoto R, Nakanishi S, Mizuno N (1993a) Distribution of the messenger RNA for a metabotropic glutamate receptor, mGluR2, in the central nervous system of the rat. *Neuroscience 53*:1009-1018.

Ohishi H, Shigemoto R, Nakanishi S, Mizuno N (1993b) Distribution of the mRNA for a metabotropic glutamate receptor (mGluR3) in the rat brain: An in situ hybridization study. *J Comp Neurol 335*:252-266.

Ohishi H, Neki A, Mizuno N (1998) Distribution of a metabotropic glutamate receptor, mGluR2, in the central nervous system of the rat and mouse: An immunohistochemical study with a monoclonal antibody. *Neurosci Res 30*:65-82.

Peters J, Kalivas PW (2006) The group II metabotropic glutamate receptor agonist, LY379268, inhibits both cocaine- and food-seeking behavior in rats. *Psychopharmacology 186*:143-149.

Petralia RS, Wang YX, Niedzielski AS, Wenthold RJ (1996) The metabotropic glutamate receptors, mGluR2 and mGluR3, show unique postsynaptic, presynaptic and glial localizations. *Neuroscience 71*:949-976.

Picconi B, Pisani A, Centonze D, Battaglia G, Storto M, Nicoletti F, Bernardi G, Calabresi P (2002) Striatal metabotropic glutamate receptor function following experimental parkinsonism and chronic levodopa treatment. *Brain 125*:2635-2645.

Poli A, Beraudi A, Villani L, Storto M, Battaglia G, Di Giorgi Gerevini V, Cappuccio I, Caricasole A, D'Onofrio M, Nicoletti F (2003) Group II metabotropic glutamate receptors regulate the vulnerability to hypoxic brain damage. *J Neurosci 23*:6023-6029.

Popik P, Wrobel M, Rygula R, Bisaga A, Bespalov AY (2003) Effects of memantine, an NMDA receptor antagonist, on place preference conditioned with drug and nondrug reinforcers in mice. *Behav Pharmacol 14*:237-244.

Riegel AC, Ali SF, French ED (2003) Toluene-induced locomotor activity is blocked by 6-hydroxydopamine lesions of the nucleus accumbens and the mGluR2/3 agonist LY379268. *Neuropsychopharmacology 28*:1440-1447.

Scaccianoce S, Matrisciano F, Del Bianco P, Caricasole A, Gerevini VD, Cappuccio I, Melchiorri D, Battaglia G, Nicoletti F (2003) Endogenous activation of group-II metabotropic glutamate receptors inhibits the hypothalamic-pituitary-adrenocortical axis. *Neuropharmacology 44*:555-561.

Scanziani M, Salin PA, Vogt KE, Malenka RC, Nicoll RA (1997) Use-dependent increases in glutamate concentration activates presynaptic metabotropic glutamate receptors. *Nature 385*:630-634.

Schiefer J, Sprünken A, Puls C, Lüesse H, Milkereit A, Milkereit E, Johann V, Kosinski CM (2004) The metabotropic glutamate receptor 5 antagonist MPEP and the mGluR2 agonist LY379268 modify disease progression in a transgenic mouse model of Huntington's disease. *Brain Res 1019*:246-254.

Schlag BD, Vondrasek JR, Munir M, Kalandadze A, Zelenaia OA, Rothstein JD, Robinson MB (1998) Regulation of the glial Na^+-dependent glutamate transporters by cyclic AMP analogs and neurons. *Mol Pharmacol 53*:355-369.

Schoepp DD (2001) Unveiling the functions of presynaptic metabotropic glutamate receptors in the central nervous system. *J Pharmacol Exp Ther 299*:12-20.

Schoepp DD, Jane DE, Monn JA (1999) Pharmacological agents acting at subtypes of metabotropic glutamate receptors. *Neuropharmacology 38*:1431-1476.

Schoepp DD, Cartmell J, Johnson BG, Salhoff CR, Wright RA, Tizzano JP, Monn JA (2001) Excitatory amino acids: Ten years later, manaus 98. In: *Biomedical and Health Research*, vol. 45. Amsterdam: IOS Press, 207-216.

Schubert P, Ogata T, Ferroni S, McRae A, Nakamura Y, Rudolphi K (1996) Modulation of glial cell signaling by adenosine and pharmacological reinforcement. A neuroprotective strategy? *Mol Chem Neuropathol 28*:185-190.

Sharpe EF, Kingston AE, Lodge D, Monn JA, Headley PM (2002) Systemic pre-treatment with a group II mGlu agonist, LY379268, reduces hyperalgesia in vivo. *Br J Pharmacol 135*:1255-1262.

Shigemoto R, Kinoshita A, Wada E, Nomura S, Ohishi H, Takada M, Flor PJ, Neki A, Abe T, Nakanishi S, et al. (1997) Differential presynaptic localization of metabotropic glutamate receptor subtypes in the rat hippocampus. *J Neurosci 17*:7503-7522.

Simmons RMA, Webster AA, Kalra AB, Iyengar S (2002) Group II mGluR receptor agonists are effective in persistent and neuropathic pain models in rats. *Pharmacol Biochem Behav 73*:419-427.

Smolders I, Lindekens H, Clinckers R, Meurs A, O'Neill MJ, Lodge D, Ebinger G, Michotte Y (2004) In vivo modulation of extracellular hippocampal glutamate and GABA levels and limbic seizures by group I and II metabotropic glutamate receptor ligands. *J Neurochem 88*:1068-1077.

Swanson CJ, Schoepp DD (2002) The group II metabotropic glutamate receptor agonist (-)-2-oxa-4-aminobicyclo[3.1.0.]hexane-4,6-dicarboxylate (LY379268) and clozapine reverse phencyclidine-induced behaviors in monoamine-depleted rats. *J Pharmacol Exp Ther 303*:919-927.

Spooren W, Ballard T, Gasparini F, Amalric M, Mutel V, Schreiber R (2003) Insight into the function of Group I and Group II metabotropic glutamate (mGlu) receptors: Behavioural characterization and implications for the treatment of CNS disorders. *Behav Pharmacol 14*:257-277.

Swanson CJ, Bures M, Johnson MP, Linden AM, Monn JA, Schoepp DD (2005) Metabotropic glutamate receptors as novel targets for anxiety and stress disorders. *Nat Rev Drug Discov 4*:131-144.

Watkins JC (2000) L-glutamate as a central neurotransmitter: Looking back. *Biochem Soc Trans 28*(4):297-309.

Winder DG, Conn PJ (1996) Roles of metabotropic glutamate receptors in glial function and glial neuronal communication. *J Neurosci Res 46*:131-137.

Winter JC, Eckler JR, Rabin RA (2004) Serotonergic/glutamatergic interactions: The effects of mGlu2/3 receptor ligands in rats trained with LSD and PCP as discriminative stimuli. *Psychopharmacology 172*:233-240.

Zhai Y, George CA, Zhai J, Nisenbaum ES, Johnson MP, Nisenbaum LK (2003) Group II metabotropic glutamate receptor modulation of DOI-induced c-fos mRNA and excitatory responses in the cerebral cortex. *Neuropsychopharmacology 28*:45-52.