Drugs of the Future 2010, 35(4): 307-324

CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.4.1487693

THOMSON REUTERS

REVIEW ARTICLE

RECENT DEVELOPMENTS IN METABOTROPIC GLUTAMATE RECEPTORS AS NOVEL DRUG TARGETS

M.J. O'Neill[1], M.J. Fell[2], K.A. Svensson[2], J.M. Witkin[2] and S.N. Mitchell[1]

[1]Eli Lilly and Co., Ltd., Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey GU20 6PH, UK; [2]Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285-0510, USA

CONTENTS

SUMMARY

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system, activating ionotropic (iGlu) and metabotropic (mGlu) glutamate receptors. Targeting iGlu receptors has proven difficult, as these receptors play such a critical role in fast synaptic transmission. In recent years, there has been a switch in the focus of the pharmaceutical industry to target mGlu receptors, as these receptors have a more modulatory role in the brain. Eight subtypes of the G protein-coupled mGlu receptors have been cloned and classified into three groups according to their second messenger association, sequence homology and agonist selectivity. Group I ($mGlu_1$ and $mGlu_5$) receptors are positively coupled to phosphatidylinositol (PI) hydrolysis, while group II ($mGlu_2$ and $mGlu_3$) and group III ($mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$) receptors are negatively coupled to adenylate cyclase and thought to act as presynaptic autoreceptors, regulating glutamate transmission. There has been rapid progress in understanding the biology of mGlu receptors and their function in the central nervous system (CNS), and the field now has highly potent and selective ligands for many of the mGlu receptor subtypes. Pharmacological tools include both orthosteric and allosteric agonists and antagonists. These molecules have been explored across a range of CNS conditions, the findings of which will be discussed briefly in this review. Recently, some of the most promising molecules have progressed into clinical trials ($mGlu_{2/3}$ receptor agonists for the treatment of anxiety and schizophrenia and $mGlu_5$ receptor antagonists for acute migraine and L-DOPA-induced dyskinesia) and achieved proof of concept. These encouraging results suggest mGlu receptors as novel drug targets with application in a range of psychiatric and neurological conditions.

Correspondence: : Dr. Michael J. O'Neill, Eli Lilly & Co., Ltd., Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey GU20 6PH, UK. E-mail: Oneill_Michael_J@Lilly.com.

INTRODUCTION

Glutamate is the key excitatory amino acid in the brain. Glutamate acts on a number of receptors to control several physiological functions under normal conditions and can contribute to several pathological processes under abnormal or disease situations (Fig. 1). Glutamate has been studied for several decades, and after the "excitotoxicity" hypothesis was proposed, the initial focus of many drug discovery efforts in the 1980s and 1990s was to inhibit ionotropic glutamate (iGlu) receptors (see 1, 2 for review). The major iGlu receptors include NMDA, AMPA and kainate receptors, and these have been reviewed in detail elsewhere (3). Inhibition of NMDA receptors in particular was thought to prevent excitotoxicity and potentially be a treatment for epilepsy, stroke and traumatic brain injury, with additional possible applications in anxiety. Current evidence provides strong support for a role for NMDA receptor antagonists in mood disorders (4, 5). However, as these iGlu receptors play a key role in fast synaptic transmission, many of the earlier compounds also had side effects such as ataxia, psychotomimetic effects and memory impairment. While later drug discovery efforts aimed to target subtypes of the NMDA receptor (NR2B) or use low-affinity compounds (such as memantine) that do not block the ion channel for long periods, the progress in the field has been slow. Conversely, in certain central nervous system (CNS) diseases, there is evidence for reduced glutamate function, and therefore there has also been some focus on trying to enhance glutamatergic neurotransmission in the brain to overcome the deficits. For example, enhancing plasticity with AMPA receptor potentiators has been studied extensively in recent years (6-8).

In addition to its rapid action at iGlu receptors, glutamate also acts on metabotropic glutamate (mGlu) receptors, which are G protein-coupled receptors (GPCRs). This action at mGlu receptors appears to have a modulatory role on various synapses and circuits in the brain (Fig. 1). The discrete localization of these receptors has allowed distinct brain regions to be targeted, which is often an attractive approach for the treatment of CNS diseases. In this review we will

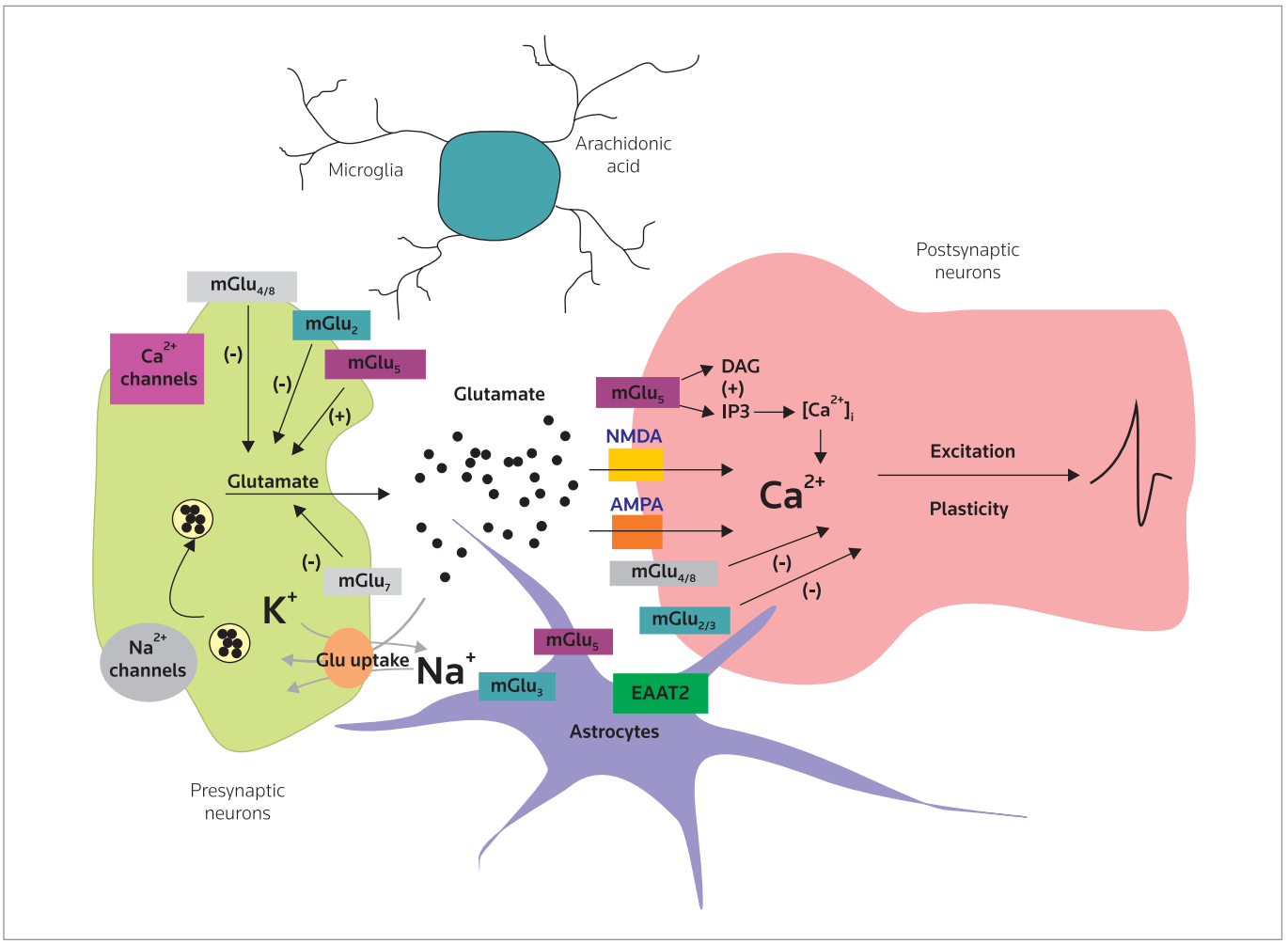


Figure 1. Illustrates some of the localizations and potential sites of action of drugs that modulate mGlu receptors. mGlu receptors are localized presynaptically, postsynaptically and on glial cells. Some are positively (+) or negatively (-) coupled to various intracellular signaling messegers. The specific localizations and signaling pathways allow modulation of mGlu receptors to increase or decrease neurotransmitter release and postsynaptic functions such as excitation or plasticity. In addition, glutamate release and uptake and glial neuronal signaling can be modulated through pharmacological manipulation of various mGlu receptors.

summarize the basic biology of mGlu receptors and illustrate some of the key CNS diseases that might be targeted with mGlu receptor-selective drugs. We will also highlight recent progress in the clinic with $mGlu_5$ receptor antagonists for acute dental anxiety, migraine and dyskinesia, and with $mGlu_{2/3}$ receptor agonists for anxiety and schizophrenia. The specific areas we will cover are summarized in Table I.

BIOLOGY AND BASIC PHARMACOLOGY OF mGLU RECEPTORS

The metabotropic family of glutamate receptors are G protein-linked receptors. In the late 1990s, a number of new ligands for these receptors were described (9, 10), allowing further investigation of the proposed role of mGlu receptors in aspects of CNS function and disease. It is possible that drugs acting on these receptors would be devoid of many of the side effects that plagued iGlu receptor ligands.

To date, eight subtypes of mGlu receptors have been cloned and classified into three groups according to their second messenger association, sequence homology and agonist selectivity (10, 11). Group I ($mGlu_1$ and $mGlu_5$) receptors are positively coupled to phosphatidylinositol (PI) hydrolysis. Group II ($mGlu_2$ and $mGlu_3$) and group III ($mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$) receptors are negatively coupled to adenylate cyclase and thought to act as presynaptic autoreceptors, regulating glutamate transmission (12). Several lines of evidence indicate that $mGlu_3$ receptors are also expressed by astrocytes and glia (13). However, in general, mGlu receptors (of all groups) are expressed to some degree on multiple cell types, such as astrocytes, microglia, oligodendrocytes and some non-CNS cell types (see 14 for review).

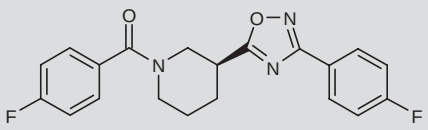
GROUP I mGLU RECEPTORS AS DRUG TARGETS

The predominant area of research to date has focused on the development of selective $mGlu_1$ receptor antagonists for pain (15, 16) and

Table I: *Summary of mGlu receptor subtypes and disease indications covered in this review.*

Group	mGlu subtype	Second messenger coupling	Type of intervention at receptor	Diseases indications covered here	Other disease indications	Pharmacological tools	References
Group I	$mGlu_1$	(+) PI hydrolysis	Blockade	Pain		*$mGlu_1$ antagonists*	
						JNJ-16259685	21, 22
						LY456236	23
						A-841720	36
						JNJ-16567083	38
						FTIDC	194
	$mGlu_5$	(+) PI hydrolysis	Blockade	Depression and anxiety, Parkinson's disease	GERD fragile X, migraine	*$mGlu_5$ antagonists*	
						MPEP	24-26
						MTEP	27-29
						AFQ-056	
			Activation (PAM)	Schizophrenia, CIAS		*$mGlu_5$ PAM*	
						ADX-47273	18
Group II	$mGlu_2$	(–) cAMP	Activation with agonists or PAMs	Schizophrenia	Anxiety, panic	*Mixed $mGlu_{2/3}$ agonists*	
						LY354740	9, 94-97,
						LY379268	105-111, 121
						LY404039	
						$mGlu_2$-selective PAMs	
						LY487379	128, 129
						CBiPES	
						BINA	131, 132
			Blockade	Depression	Cognition	*Mixed $mGlu_{2/3}$ antagonists*	
						LY341495	93, 152
						MGS-0039	153, 154, 159, 161, 164, 171
	$mGlu_3$	(–) cAMP	Activation	Schizophrenia ?	Anxiety	*Mixed $mGlu_{2/3}$ agonists*	
						LY354740	9, 94-97,
						LY379268	105-111, 121
						LY404039	
			Blockade	Depression	Cognition	*Mixed $mGlu_{2/3}$ antagonists*	
						LY341495	93, 152
						MGS-0039	153, 154, 159, 161, 164, 171
Group III	$mGlu_4$	(–) cAMP	Activation	Parkinson's disease	Anxiety	PHCCC	79, 184
						VU-0155041	186
	$mGlu_6$	(–) cAMP					
	$mGlu_7$	(–) cAMP	Activation	Parkinson's disease	Anxiety, depression	AMN-082	178
	$mGlu_8$	(–) cAMP			Anxiety		

PI, phosphatidylinositol; PAM, positive allosteric modulator; CIAS, cognitive impairment associated with schizophrenia; GERD, gastroesophageal reflux disease.



ADX-47273

$mGlu_5$ receptor antagonists for a variety of disease states, including anxiety/depression, migraine and Parkinson's disease (PD) (17). However, more recently, positive allosteric modulators (PAMs) of $mGlu_5$ have been reported, and this area is looking promising for future drug development. For example, **ADX-47273** was recently identified as a potent and selective $mGlu_5$ PAM. In models sensitive to antipsychotic drug treatment, ADX-47273 reduced conditioned avoidance responding of rats and decreased apomorphine-induced climbing in mice, with little effect on stereotypy or catalepsy. Furthermore, ADX-47273 blocked phencyclidine-, apomorphine- and amphetamine-induced increases in locomotor activity in mice and decreased extracellular levels of dopamine in the nucleus accumbens, but not in the striatum, in rats. In cognition models, ADX-47273 increased novel object recognition and reduced impulsivity in the five-choice serial reaction time task in rats (18). More recent studies have reported that ADX-47273 (3 and 10 mg/kg i.p.), the typical antipsychotic haloperidol (0.1 and 0.2 mg/kg i.p.) and the atypical antipsychotics aripiprazole (1.25-5 mg/kg i.p.) and olanzapine (2.5 and 5 mg/kg i.p.) all reduced amphetamine-induced hyperlocomotion in Sprague-Dawley rats (19). Finally, a recent report indicated that ADX-47273 (100 mg/kg) and various clinically used neuroleptics (haloperidol, olanzapine and aripiprazole) attenuated conditioned avoidance responding behavior in rats. However, ADX-47273 and aripiprazole failed to reduce the phencyclidine (PCP)-induced hyperlocomotion (20). Taken together, these effects are consistent with the hypothesis that allosteric potentiation of $mGlu_5$ might provide a novel approach for the development of antipsychotic agents where cognitive deficiencies are currently not well treated, as well as a host of other diseases in which cognitive impairment is not controlled (e.g., depression, Alzheimer's disease).

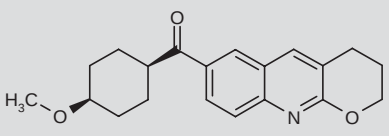
In the present article, we will focus our discussion on group I mGlu receptor antagonists. The rapid progress on the pharmacology of these agents has been greatly helped by the availability of selective and systemically active molecules (see Table I). For example, $mGlu_1$ receptor antagonists such as **JNJ-16259685** (21, 22) and **LY456236** (20), and $mGlu_5$ receptor antagonists such as **MPEP** (24-26) and **MTEP** (27-29) allowed scientists to rapidly elucidate some of the functions of these receptors that might underlie various CNS disorders.

$mGlu_1$ receptor antagonists for pain

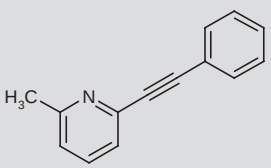
The role of glutamate and various mGlu receptors in pain states has been documented. In particular, group I receptors (15, 16) and $mGlu_1$ receptor antagonists have been studied intensively (30). Glutamate is released from primary afferent neurons and might thereby contribute to the persistent activation of spinal nerves and increased sensitivity to painful stimuli.

$mGlu_1$ receptors are present at several sites (spinal, peripheral) that are known to be involved in nociceptive neurotransmission. Pharmacological studies have shown that $mGlu_1$ receptor agonists can induce spontaneous pain and $mGlu_1$ receptor antagonists can both block these effects of $mGlu_1$ receptor agonists and also prevent pain states elicited by other stimuli (31, 32).

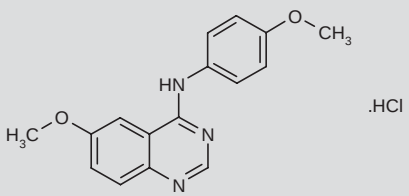
Intrathecal (i.t.) administration of selective $mGlu_1$ receptor antibodies was assessed in a model of persistent pain induced by intrathecal administration of the $mGlu_{1/5}$ receptor agonist dihydroxyphenylglycine (DHPG), as well as in models of heat pain (plantar test), chemical pain (formalin test) and neuropathic pain (constriction injury of the sciatic nerve). DHPG-induced spontaneous nociceptive behavior was significantly attenuated by treatment with either anti-$mGlu_1$ immunoglobulin G (IgG) at 30 µg or anti-$mGlu_5$ IgG (10 and 30 µg). Interestingly, neither antibody (30 µg) significantly reduced formalin pain scores as compared to control IgG. Whether these data reflect differences in the various pain states and models or



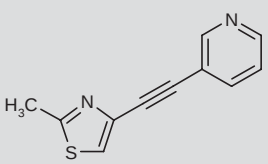
JNJ-16259685



MPEP



LY456236



MTEP

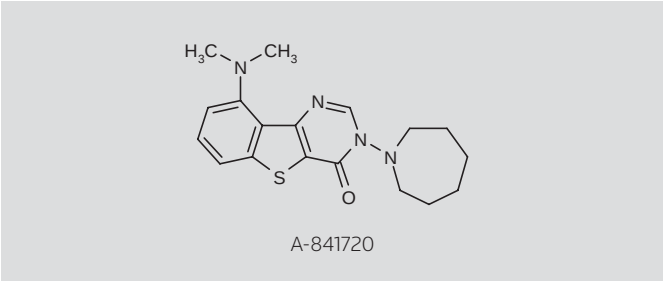
technical differences is unknown. However, i.t. treatment with anti-$mGlu_1$ IgG (30 µg) or anti-$mGlu_5$ IgG (30 µg) significantly reduced cold hypersensitivity exhibited 8 days after constriction injury of the sciatic nerve, supporting the contention that group I mGlu receptors play a role in the development of neuropathic pain. The authors conclude that because these antibodies were effective against neuropathic pain, and not acute heat or chemical noxious stimuli, the results suggest that mGlu receptors are involved in nociceptive processing in chronic pain states rather than signaling acute noxious stimuli, and that DHPG-induced pain may be mediated by similar mechanisms as neuropathic pain (33).

Rats treated with an $mGlu_1$ antisense oligonucleotide reagent delivered continuously to the intrathecal space of the lumbar spinal cord developed marked analgesia, as measured by an increase in the latency to tail flick (55 °C) over a period of 4-7 days. This correlated with a selective reduction in $mGlu_1$, but not $mGlu_5$, immunoreactivity in the superficial dorsal horn compared with untreated control rats (34). Heat-related hyperalgesia and mechanical allodynia following chronic constrictive injury of the sciatic nerve have been reduced using antisense oligonucleotide knockdown of spinal $mGlu_1$ receptors (35).

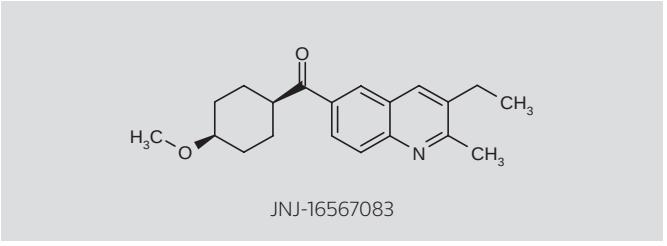
The majority of the evidence cited above and in the literature has supported a role for $mGlu_1$ in inflammatory or neuropathic pain states. However, a recent study from Abbott explored the role of $mGlu_1$ receptors in postoperative pain (36). In this study, the effects of the potent and selective $mGlu_1$ receptor antagonists **A-841720**, A-794282, A-794278 and A-850002 were evaluated in a skin incision-induced postoperative pain model in rats. In this model, all the $mGlu_1$ receptor antagonists induced significant attenuation of spontaneous postoperative pain behaviors (37).

Direct comparisons between various group I antagonists have been carried out in pain models. The systemic administration of the $mGlu_5$ receptor antagonists MPEP and MTEP and the $mGlu_1$ receptor antagonist LY456236 has been shown to reduce hyperalgesia induced by formalin and mechanical allodynia following spinal nerve ligation (37). However, only the $mGlu_1$ receptor antagonist LY456236 completely reversed the allodynia. In another study, the effects of the $mGlu_1$ receptor antagonist **JNJ-16567083** (1.25-5 mg/kg) were compared to MPEP or MTEP (2.5-10 mg/kg) to explore the possible interaction between $mGlu_1$ and $mGlu_5$ receptor antagonists and whether tolerance develops to the analgesic effects of these antagonists after prolonged treatment (38). JNJ-16567083, MTEP and MPEP significantly reduced the manifestation of both phases of the formalin response, but none of these mGlu receptor antagonists affected the withdrawal latencies in a model of acute pain (Hargreaves test), which has a different underlying mechanism than the formalin response. The suppressive effect on formalin-induced pain behavior was much stronger when $mGlu_1$ and $mGlu_5$ receptor antagonists were coinjected compared to administration of a single antagonist. The study also provided the first direct in vivo evidence that prolonged administration of MTEP (5 mg/kg) over 7 days leads to the development of tolerance to its antinociceptive effects.

Despite the consistent reports of efficacy with $mGlu_1$ receptor antagonists in pain states, there have also been several reports of liabilities with $mGlu_1$ receptor antagonists. $mGlu_1$ receptors are highly expressed in the cerebellum, and inhibition can lead to motor impairment and a disruption of balance and coordination. Targeted deletion of the $mGlu_1$ receptor gene can cause defects in development and function in the cerebellum. These effects can be rescued by introduction of the $mGlu_1$ receptor alpha transgene into $mGlu_1$-null mutant (*mGlu1*$^{-/-}$) mice with a Purkinje cell-specific promoter (39). Other reports have suggested that inhibition of $mGlu_1$ can block acquisition of certain cognitive tasks in rodents. For example, one study reported that the analgesic effects of the selective $mGlu_1$ receptor antagonist A-841720 are associated with motor and cognitive (Y-maze and the water maze tests) side effects (40). The authors concluded that the lack of separation between efficacy and side effects in preclinical models indicates that $mGlu_1$ receptor antagonism may not provide an adequate therapeutic window for the development of such antagonists as novel analgesic agents in humans. Taken together, these effects have slowed the progression of $mGlu_1$ receptor antagonists into human pain trials. Several new potent and selective $mGlu_1$ receptor antagonists based on alternative chemical scaffolds have been reported in the patent literature and we will wait to see if these newer molecules will have sufficient margin to take forward into clinical development.



A-841720



JNJ-16567083

$mGlu_5$ receptor antagonists for anxiety/depression

Several pharmaceutical companies (Roche, Lilly, Merck & Co., Novartis, Schering-Plough) and academic labs have consistently reported efficacy with MPEP, MTEP and other novel $mGlu_5$ receptor antagonists in various preclinical models of anxiety. Furthermore, it has also been reported that $mGlu_5$ receptor knockout mice displayed a significant attenuation of the hyperthermic response to stress compared to littermate wild-type control mice (41, 42).

The discovery of the $mGlu_5$ receptor antagonist MPEP (17, 24-26) provided investigators with the tools needed to evalauate the behavioral effects of inhibiting $mGlu_5$ receptors. Early studies from Novartis reported that MPEP had anxiolytic-like actions in animal models (26), and these data were quickly confirmed by other groups

(28, 43). Merck & Co. subsequently reported that a related compound, MTEP, significantly reduced fear-potentiated startle and increased punished responding in a modified Geller–Seifter conflict model, consistent with an anxiolytic-like profile. In both models, the magnitude of the anxiolytic-like response was similar to that seen with diazepam (44, 45). Varty et al. from Schering-Plough (37) compared the effects of $mGlu_5$ and $mGlu_1$ receptor antagonists in the Vogel and conditioned lick suppression models of anxiety. MPEP (3-30 mg/kg), MTEP (3-10 mg/kg) and LY456236 (10-30 mg/kg) produced anxiolytic-like effects similar to the benzodiazepine and chlordiazepoxide (CDP, 6 mg/kg). However, only MPEP and MTEP were able to produce a level of anxiolysis comparable to CDP. In another report from Roche, MPEP had a significant anxiolytic-like effect, comparable in magnitude to diazepam, at 10-30 mg/kg in the two conflict and conditioned emotive response tasks (46).

Fenobam is an atypical anxiolytic agent that has anxiolytic-like activity in rodents and anxiolytic effects in humans (47). Porter and colleagues at Roche (48) reported that fenobam was a selective and potent $mGlu_5$ receptor antagonist acting at an allosteric modulatory site shared with MPEP. Fenobam exhibits anxiolytic-like activity in the stress-induced hyperthermia model, Vogel conflict test, Geller–Seifter conflict test and conditioned emotional response, with a minimum effective dose of 10-30 mg/kg p.o.

There is also evidence that $mGlu_5$ receptor antagonists may have antidepressant-like efficacy. Early studies with MPEP (1-20 mg/kg) reported that the compound shortened the immobility time in the tail suspension test (TST) in mice, although it was inactive in the forced-swim test (FST) in rats (44). Further studies reported antidepressant-like effects for MPEP in olfactory bulbectomized (OB) rats (49). Likewise, MTEP (0.3-3 mg/kg) produced a significant, dose-dependent decrease in the immobility time of mice in the TST; however, at doses of 1 or 10 mg/kg it did not influence the behavior of rats in the FST (50). The lack of response and variability in the early FST studies may have been due to the research protocols employed. Moreover, the repeated administration of MTEP (1 mg/kg) attenuated the OB-related hyperactivity of rats in the open field test, in a manner similar to that seen following chronic (but not acute) treatment with typical antidepressant drugs.

Studies conducted at Lilly reported antidepressant-like activity for MPEP and MTEP in a mouse FST (51). In addition, the authors demonstrated that the antidepressant-like effects were mediated via $mGlu_5$ receptors, since the antidepressant-like effects of MPEP were not observed in $mGlu_5$ receptor knockout mice, whereas comparable effects of the tricyclic antidepressant imipramine persisted in the mutant mice (51). Another recent study reported antidepressant-like effects in behavioral despair tests in rats and mice with both $mGlu_1$ and $mGlu_5$ receptor antagonists (52).

Addex Pharmaceuticals recently completed a proof-of-concept study with a novel $mGlu_5$ antagonist, ADX-10059, in acute dental anxiety. This compound has demonstrated activity in several preclinical models for detecting anxiolytic agents (Vogel test, elevated plus maze, light–dark box). Despite this preclinical evidence, the compound failed to show activity in the acute dental anxiety paradigm (Charlotte Keywood, BPS Meeting, Edinburgh, July 2009). However, it is not known what level of target inhibition (receptor occupancy) was achieved in this proof-of-concept study. There are several PET ligands available for $mGlu_5$ receptors and one of these ligands ($[^{11}C]$-ABP-688) has recently been used in human volunteers (53). It will therefore be possible to use ligands such as this to determine the degree of receptor occupancy achieved by a ligand in future clinical studies. It is also possible that the use of acute dental anxiety might not be the most appropriate clinical paradigm. The neural substrates and downstream biochemical pathways may be quite different between acute dental anxiety and other common anxiety conditions (e.g., generalized anxiety disorder, panic disorder, social anxiety, etc.) and thus further clinical studies in this area are warranted.

$mGlu_5$ receptor antagonists and Parkinson's disease

There has been much interest in the role of $mGlu_5$ receptors in PD for most of the last decade. It was well known that dopaminergic and glutamatergic systems of the basal ganglia are reciprocally involved in the complex circuitry controlling motor behavior (54). Glutamate may play a central role in the disruption of normal basal ganglia function and may be important in driving neurodegeneration in PD (55). Earlier work from Greenamyre and coworkers focused on central infusion or systemic administration of NMDA receptor antagonists (56). However, it was later recognized that $mGlu_5$ receptors are also expressed in key regions of the basal ganglia, such as the subthalamic nucleus (STN) and substantia nigra (SN) zona reticulata, and contribute to glutamatergic transmission in basal ganglia (54, 57). $mGlu_5$ receptors activate directly and indirectly (via potentiation of NMDA currents) neurons in the STN and may contribute to burst firing in the STN, a characteristic of parkinsonian status (58, 59). More recent data indicate that $mGlu_5$ receptor expression is increased in the basal ganglia of monkeys following MPTP treatment (60). In addition, bilateral MPTP-lesioned monkeys showed an increase in $[^3H]$-ABP-688 or $[^3H]$-MPEP in the putamen that was enhanced in dyskinetic animals as opposed to the monkeys which did not develop dyskinesia (60). Therefore, the molecular target appears to be upregulated during the emergence of unwanted motor effects, suggesting that antagonism of $mGlu_5$ receptors could have beneficial effects on motor function. It is also possible that in addition to potential motor benefits, blocking $mGlu_5$ receptors might also help treat the ongoing pathological changes of the disease by inhibiting excitatory drive onto the vulnerable SN pars compacta cells. The availability of tool compounds such as MPEP and MTEP allowed both of these hypotheses to be tested and both symptomatic and neuroprotective effects have been shown in preclinical rodent models of PD.

Symptomatic effects

During the initial behavioral profiling of MPEP, it was shown that the compound increased ipsiversive rotations in unilateral 6-hydroxydopamine (6-OHDA)-lesioned rats (25), and this provided some early evidence that pharmacological manipulation of $mGlu_5$ receptors had effects on the lesioned basal ganglia. Further studies indicated that chronic (not acute) treatment with MPEP at 1.5-6 mg/kg i.p. was able to normalize deficits in a conditional reaction time task model following bilateral 6-OHDA lesion of the rat dorsal striatum (61). In a follow-up study, the same group found that MPEP was also able to provide some reversal of 6-OHDA-induced changes in neu-

roanatomical markers (cytochrome oxidase subunit 1 in STN and glutamate decarboxylase 67 mRNA in SN zona reticulata), which supported the behavioral findings (62).

In order to study the site of action of these effects, Philips et al. examined whether the STN and its output structures mediated such an effect using a unilateral rat model of PD (63). A battery of simple behavioral tests, sensitive to dopamine depletion, was applied consecutively: 1) prior to surgery; 2) 3 weeks following unilateral 6-OHDA lesion of the SN pars compacta; and 3) at 1 h, 24 h and 4 days following a microinjection of MPEP via an indwelling cannula into the STN, entopeduncular nucleus (EP) or SN zona reticulata. Unilaterally dopamine-depleted animals typically had severe motor and sensorimotor asymmetries 3 weeks following surgery. Microinjection of 25 nmol MPEP into the STN of these animals significantly attenuated these asymmetries relative to vehicle. In contrast, microinjection of MPEP into either the EP or SN zona reticulata was without effect. These data suggest that one of the major sites of action of $mGlu_5$ receptor antagonists in 6-OHDA-treated rats is at the level of the STN.

Studies in reserpine-treated rats suggested that there are complex changes in mGlu receptor expression (64). In situ hybridization demonstrated that acute reserpine treatment caused a significant decrease in the expression of $mGlu_5$ receptor mRNA in the rostral and caudal parts of the rat striatum. At the same time, [^{3}H]-MPEP ligand binding experiments detected a significant increase in the total number of $mGlu_5$ receptors in the same region of the motor loop. Therefore, $mGlu_5$ receptor turnover is downregulated in reserpinized rats, due possibly to an imbalance in the rates of synthesis/insertion and internalization/degradation of the receptor.

More recently, several reports have used microPET to study changes in dopamine transporter and $mGlu_5$ receptors in 6-OHDA-lesioned rats (65, 66). These studies have reported enhanced $mGlu_5$ receptor binding in the lesioned striatum and in the ipsilateral hippocampus and cortex, and also that glutamatergic neurotransmission might have a complementary role in dopaminergic degeneration, which can be evaluated by in vivo PET imaging.

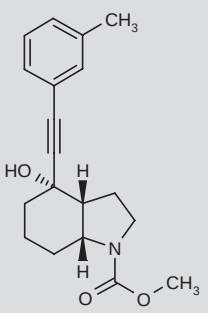
MPEP (67) and MTEP (68, 69) have also been reported to inhibit haloperidol-induced muscle rigidity and catalepsy. Data from a series of studies have shown robust antidyskinetic effects with $mGlu_5$ receptor antagonists (69-71). In many of these studies a unilateral medial forebrain bundle 6-OHDA lesion (90-100% depletion of tyrosine hydroxylase) was used. One study demonstrated that MTEP 5 mg/kg i.p. (at the same time as L-DOPA) for 3 weeks was able to attenuate L-DOPA-mediated abnormal involuntary movements (AIMs) and associated molecular changes (prodynorphin mRNA) in the striatum (70). In another study, MPEP 1.5 mg/kg i.p. (30 min prior to L-DOPA) for 3 weeks blocked L-DOPA-induced AIMs and increased FosB/ΔFosB staining in striatum (71). The addition of molecular markers to these studies suggested that there are clear anatomical substrates underlying the behavioral effects (70, 71). There is also evidence that MPEP and MTEP block L-DOPA-mediated AIMs, with minimal effects on the beneficial motor actions produced by L-DOPA (72). An interesting study from Gravius et al. (73) evaluated if there was tolerance to learning, anxiety and levodopa-induced dyskinesia in rats following subchronic blockade of $mGlu_5$ receptors by MTEP. Results indicated that tolerance does not develop to the anxiolytic-like and antidyskinetic effects of MTEP, at least at the doses and mode of administration used. In addition, there was no tolerance to the memory-impairing effect of MTEP in these studies (73).

A study in MPTP-treated monkeys reported that L-DOPA-induced dyskinesias (LIDs) were associated with an increase of $mGlu_5$ receptor-specific binding in the posterior putamen and pallidum (+41% and +56%, respectively) compared to controls (74). In contrast, prevention of dyskinesias was associated with an important decrease of $mGlu_5$ receptor-specific binding in these areas (–37% and –48%, respectively) compared with dyskinetic animals. Moreover, an upregulation (+34%) of $mGlu_5$ receptor binding was seen in the anterior caudate nucleus of saline-treated MPTP monkeys. This study was the first to provide evidence that enhanced $mGlu_5$ receptor-specific binding in the posterior putamen and pallidum may contribute to the pathogenesis of LIDs in PD.

A more recent study evaluated the dose–response of MPEP and MTEP (1.5-30 mg/kg) administered 15 and 30 min, respectively, prior to L-DOPA in monkeys (75). In general, treatment with $mGlu_5$ receptor antagonists had no effect on the antiparkinsonian activity of L-DOPA. Interestingly, the mean dyskinesia score during the duration of the L-DOPA motor effect, the 1-h peak period dyskinesia scores and the maximal dyskinesia scores were dose-dependently reduced with both drugs, reaching statistical significance at 10 and 30 mg/kg. In 2008, an $mGlu_5$ receptor antagonist from Novartis AG, **AFQ-056**, achieved clinical proof of concept in PD/L-DOPA-induced dyskinesia (http://www.novartis.com/newsroom/media-releases/en/2008/1271207.shtml). This compound was also reported to have antidyskinetic effects in monkeys (Theresa di Paolo et al., MDS Congress, Chicago, 2008).

Neuroprotective effects

Several studies have also reported neuroprotective actions for $mGlu_5$ receptor antagonism in various neurotoxin models of PD. The first studies reported that MPEP (five doses of 5 mg/kg i.p.) when administered prior to methamphetamine (5 x 10 mg/kg s.c. at 2 h) was able to attenuate the decreased levels of dopamine and its metabolites DOPAC (3,4-dihydroxyphenylacetic acid) and HVA (homovanillic acid) (76). Follow-on studies reported that MPEP (30 mg/kg) was able to protect against striatal and nigral degeneration produced by



AFQ-056

MPTP. Of interest, MPEP produced a good level of protection against lower doses of MPTP, but only a mild level of protection against the higher doses of MPTP. These authors also reported that $mGlu_5$ knockout mice were more resistant to MPTP neurotoxicity (77).

Several other studies have reported that MPEP can protect against 6-OHDA-mediated nigrostriatal degeneration (78-80). In some of these published studies, intranigral infusion of MPEP prior to infusion of 6-OHDA provided 20-30% protection, as assessed by the number of TH-positive nigral cells (79, 80). Another study demonstrated that systemic treatment with MPEP (minipump infusion of 1.5 or 3 mg/kg s.c. starting after intrastriatal infusion of 6-OHDA) was able to significantly protect tyrosine hydroxylase-positive SN cells (80). In the same study, MPEP also completely blocked the 6-OHDA-induced increase in metabolic activity in the STN.

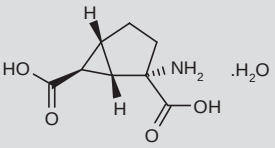
GROUP II mGLU RECEPTORS AS DRUG TARGETS

Group II mGlu receptor agonists for schizophrenia

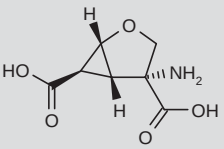
Pathological glutamate release or altered glutamate receptor activity has been implicated in the pathophysiology of many psychiatric conditions, including schizophrenia (81-83). The glutamate hypothesis of schizophrenia is based largely on the observation that the noncompetitive NMDA receptor channel-blocking antagonists, such as PCP, ketamine and MK-801 (84), induce a psychotic state in healthy humans and can exacerbate pre-existing symptoms in patients with schizophrenia (85). Further evidence for a role of glutamate in schizophrenia comes from the finding that noncompetitive NMDA receptor antagonists increase excitability in limbic brain regions such as the prefrontal cortex (as measured by increases in cerebral blood flow and metabolic rates), and these effects are positively correlated to the induction of psychosis (86-88). Accordingly, a drug that can correct or modulate dysfunctional glutamatergic hyperexcitation in limbic cortical regions may have potential in the treatment of schizophrenia (86).

Group II mGlu ($mGlu_2$ and $mGlu_3$) receptors are structurally related and function to modulate glutamate and GABA release as presynaptic autoreceptors on glutamatergic terminals, as presynaptic heteroreceptors (89, 90) or via modulatory actions on glial cells (91, 92). The $mGlu_2$ and $mGlu_3$ receptor subtypes are highly expressed in forebrain and limbic brain areas, including regions which are known to be involved in the pathophysiology of schizophrenia (e.g., prefrontal cortex, dorsal and ventral striatum, thalamus, hippocampus and amygdala) (93). Thus, the anatomical distribution of group II mGlu receptors, combined with their ability to modulate neuronal excitation, and in particular glutamatergic neurotransmission, has led to the concept that group II mGlu receptors may be potential novel targets for therapeutic intervention in schizophrenia. Recent progress in this area of drug discovery has resulted in compounds with promising potential therapeutic efficacy, with the possibility for an improved side effect profile compared to conventional antipsychotic drugs.

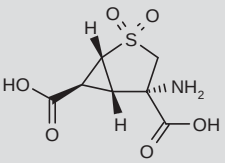
Over the past decade, a series of orthosteric agonists for group II mGlu receptors have been identified (9, 94-98). These conformationally constrained glutamic acid analogues include **LY354740**, **LY379268** and **LY404039**. The compounds are highly selective for



LY354740



LY379268



LY404039

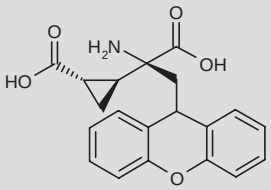
group II mGlu receptors but do not discriminate between the $mGlu_2$ and $mGlu_3$ receptor subtypes (compounds which selectively potentiate $mGlu_2$ receptors have been described and are discussed below). Importantly, orthosteric $mGlu_{2/3}$ receptor agonists have no appreciable affinity for group I or group III mGlu receptors, iGlu receptors, glutamate transporters or monoaminergic receptors such as dopamine or serotonin (5-HT), which are the targets of all current antipsychotic medications (99). To date, the actions of multiple $mGlu_{2/3}$ receptor agonists have been explored in a variety of animal models predictive of antipsychotic efficacy. Notably, selective $mGlu_{2/3}$ receptor agonists attenuate many of the behavioral and neurochemical effects of the major psychotomimetic drugs used to model psychosis. The effects of $mGlu_{2/3}$ receptor agonists in these models and evidence for antipsychotic efficacy are discussed in subsequent sections.

In rodents, subanesthetic doses of NMDA receptor antagonists selectively increase brain excitation in limbic brain regions (medial prefrontal cortex [mPFC], hippocampus, cingulate cortex) and areas directly connected to them (thalamus, nucleus accumbens) (100). Behaviorally, these actions manifest as increases in locomotor activity and stereotypies (101, 102), and impairments in cognitive function and attentional behaviors (103, 104). Like atypical antipsychotic drugs, $mGlu_{2/3}$ receptor agonists (LY379268, LY354740 and LY404039) block many of these behaviors (105-111). NMDA receptor antagonists also increase the efflux of various neurotransmitters in limbic brain regions and this can be attenuated by the administration of $mGlu_{2/3}$ receptor agonists. For example, the $mGlu_{2/3}$ agonists LY379268 and LY354740 attenuate PCP- or ketamine-evoked increases in glutamate efflux in the mPFC (105). $mGlu_{2/3}$ receptor agonists also attenuate NMDA receptor antagonist-evoked increases in dopamine and norepinephrine efflux in the nucleus accumbens and hippocampus, respectively (110, 112, 113), and LY379268 attenu-

ates ketamine-induced increases in dialysate histamine levels in the mPFC, ventral hippocampus and nucleus accumbens shell (114). Thus, it appears that antipsychotic-like actions of $mGlu_{2/3}$ receptor agonists involve not only reductions in glutamatergic neurotransmission, but may also indirectly involve the modulation of monoaminergic transmission including dopamine, norepinephrine and histamine. LY354740 also blocks PCP-induced increases in brain activation, as measured by pharmacomagnetic resonance imaging (phMRI) (115). It should be noted, however, that this $mGlu_{2/3}$ receptor agonist does not block all the effects of NMDA receptor antagonists. For example, LY-354740 had no effect on PCP-induced disruption of prepulse inhibition (PPI) (116), nor did it attenuate the discriminative stimulus effects of PCP in rats (117).

Amphetamine-induced motor activation is commonly used to model acute psychosis or the positive symptoms of schizophrenia, and the behavioral effects of amphetamine have been attributed to increased dopaminergic and noradrenergic activity in mesolimbic brain regions, including the nucleus accumbens (118). All clinically effective antipsychotics reverse the locomotor-stimulating effects of amphetamine, and this property has been ascribed to their antagonism of mesolimbic dopamine receptors (119). When administered to rodents, $mGlu_{2/3}$ receptor agonists also attenuate certain behaviors (increase in ambulations and rearing behavior but not fine movements) induced by amphetamines (106, 120). As in the PCP model, these effects of $mGlu_{2/3}$ receptor agonists are reversed by pretreatment with the selective $mGlu_{2/3}$ receptor antagonist **LY341495** in a dose-related manner (106). The mechanisms which underlie these effects of $mGlu_{2/3}$ receptor agonists on amphetamine-induced hyperactivity are not clear, but could include decreases in the release of glutamate and other neurotransmitters. In contrast to typical dopamine receptors (121), glutamatergic neurons are, however, important regulators of dopaminergic tone in the nucleus accumbens (122). Thus, $mGlu_{2/3}$ receptor agonists may reduce glutamate release in the nucleus accumbens and thereby indirectly modulate dopamine neurotransmission.

Atypical antipsychotics such as clozapine and olanzapine block 5-HT_{2A} receptors and this action has been linked to improvements in the control of negative and cognitive symptoms (123). Although $mGlu_{2/3}$ receptor agonists do not directly interact with 5-HT receptors, in electrophysiological experiments $mGlu_{2/3}$ receptor agonists (LY354740, LY379268 and LY404039) block both 5-HT_{2A} receptor-mediated and electrically evoked excitatory postsynaptic currents in the prefrontal cortex of rats (99, 124). These actions of $mGlu_{2/3}$ receptor agonists are blocked by the $mGlu_{2/3}$ receptor antagonist LY341495. The administration of $mGlu_{2/3}$ receptor agonists also blocks behavioral (headshakes) and neurochemical effects (increased mPFC c-fos expression) of serotonergic psychotogens which act through 5-HT_{2A} receptor activation (e.g., 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane, or DOI) (125, 126). Interestingly, these findings suggest a common mechanism of action shared by clinically effective atypical antipsychotic drugs and $mGlu_{2/3}$ receptor agonists.

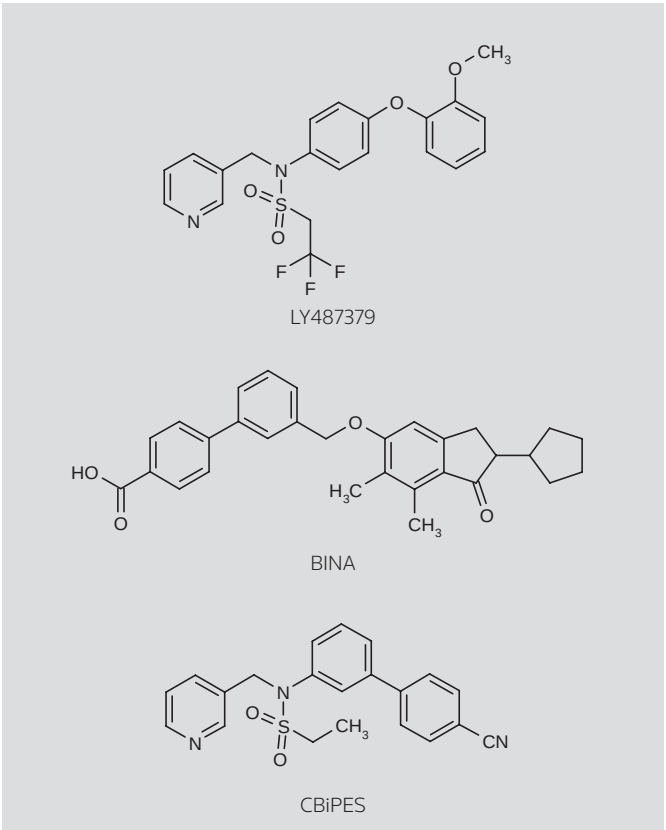


LY341495

In addition to effects in psychostimulant models of psychosis, a number of other behavioral and neurochemical effects of $mGlu_{2/3}$ receptor agonists suggest their antipsychotic potential. For instance, the $mGlu_{2/3}$ receptor agonist LY379268 significantly increases extracellular levels of dopamine, 5-HT and their major metabolites (DOPAC, HVA and 5-HIAA [5-hydroxyindoleacetic acid]) in the prefrontal cortex (111, 127). Increases in central monoamine levels in this brain area have been suggested to underlie the beneficial effects of atypical antipsychotics on the negative and cognitive symptoms of schizophrenia (125). Furthermore, the $mGlu_{2/3}$ receptor agonist LY404039 has been shown to block conditioned avoidance responding without altering escape responses (a model predictive of antipsychotic efficacy) and to produce minimal disruption of rotarod behavior (111). Thus, $mGlu_{2/3}$ receptor agonists show similar efficacy as therapeutically used antipsychotic drugs in these preclinical screens, but with evidence of a lower liability for motor side effects.

In addition to orthosteric $mGlu_{2/3}$ receptor agonists, several allosteric potentiators of $mGlu_2$ receptors have been described. In contrast to $mGlu_{2/3}$ receptor agonists which act directly at the glutamate (orthosteric) site, these allosteric modulators act at a site within the seven-transmembrane domain and induce a leftward shift in the glutamate concentration–response curve. Unlike orthosteric $mGlu_{2/3}$ receptor agonists, these PAMs are selective for $mGlu_2$ and do not potentiate responses to the activation of $mGlu_3$ or other mGlu receptor subtypes. A number of structural classes have been published during the past years and are typified by **LY487379** (128, 129) and **BINA** (130, 131). Many of these $mGlu_2$ PAMs have been shown to have efficacy in animal models predictive of antipsychotic efficacy. For example, **CBiPES** and LY487379 reverse PCP-induced hyperlocomotor activity in mice. Similarly, BINA also blocks PCP- (but not amphetamine) induced hyperlocomotor activity and disruptions in PPI in mice (132). A recent study also suggests that BINA can reverse the increase in BOLD functional MRI (fMRI) signal in the rat brain induced by PCP (133). Together these data demonstrate that, like orthosteric agonists of $mGlu_{2/3}$ receptors, selective PAMs of $mGlu_2$ receptors have efficacy in animal models of psychosis and may be useful as a novel approach for the treatment of schizophrenia. In addition, the mechanism of allosteric modulation could potentially offer advantages in terms of improved tolerability without the development of tolerance when compared to classical orthosteric agonists.

Although $mGlu_{2/3}$ receptor agonists demonstrate activity in preclinical models in which atypical antipsychotics are also effective, recent evidence suggests that the antipsychotic-like effects of $mGlu_{2/3}$ receptor agonists are mechanistically distinct from current antipsychotic medications, which primarily target dopaminergic and 5-HT receptor subtypes. For example, studies carried out in transgenic mice reveal that the antipsychotic actions of the $mGlu_{2/3}$ receptor agonists LY404039, LY379268 and LY314582 in the PCP and



amphetamine hyperlocomotor models are lost in mice with selective deletions of $mGlu_2$ and $mGlu_{2/3}$ receptors, but not $mGlu_3$ receptors (132-136). In marked contrast, the ability of atypical antipsychotics (e.g., clozapine, risperidone and olanzapine) to prevent psychostimulant-evoked increases in locomotor activity are unaffected by the loss of $mGlu_{2/3}$ receptors. Additionally, the effects of $mGlu_{2/3}$ receptor agonists in animal models are readily blocked by pretreatment with the $mGlu_{2/3}$ receptor antagonist LY341495 (106, 111). A dominant role for $mGlu_2$ receptors in the antipsychotic-like effects of $mGlu_{2/3}$ receptor agonists is further supported by the finding that the effects of orthosteric $mGlu_{2/3}$ receptor agonists can be mimicked by selective allosteric potentiators of $mGlu_2$ receptors. Together with the studies described previously, these data suggest that orthosteric $mGlu_{2/3}$ receptor agonists and/or selective $mGlu_2$ receptor potentiators may provide a novel approach to the treatment of schizophrenia that is mechanistically distinct from current antipsychotic medications.

Consistent with the predictions from preclinical animal studies, a recent 4-week phase II proof-of-concept study in patients with schizophrenia demonstrated antipsychotic activity with LY2140023 monohydrate, the oral prodrug of the $mGlu_{2/3}$ receptor agonist LY404039 (137). LY2140023-treated patients showed statistically significant improvements in the Positive and Negative Symptom Scale (PANSS) total scores by the end of the first week of treatment compared to placebo, and similar improvements were observed in the Clinical Global Impression-Severity (CGI-S), PANSS negative and PANSS positive subscores. Unlike currently available antipsychotic medications, adverse events such as dyskinesia, akathisia, parkinsonism or increased serum prolactin were not reported in patients receiving the $mGlu_{2/3}$ receptor agonist. Encouragingly, in contrast to some antipsychotic medications which may have negative metabolic side effects, LY2140023 treatment resulted in a mean 0.51-kg weight reduction. This initial proof-of-concept study by Patil et al. provides evidence that the activation of $mGlu_{2/3}$ receptors might be an effective novel approach for treating both the positive and negative symptoms of schizophrenia. Another recent clinical trial to replicate the findings failed to meet the primary endpoint, as there was a large placebo response in the study (the active comparator olanzapine also failed to separate from placebo in this trial). Therefore, additional trials will be required to determine the safety of these mGlu compounds after long-term treatment, as well as efficacy in other symptom domains such as cognitive function, which remains a major unmet therapeutic need in schizophrenia.

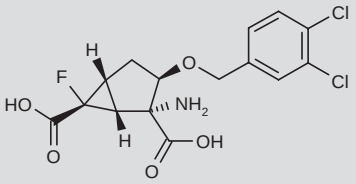
Dampening of glutamatergic tone with group II mGlu receptor agonists may also be a useful approach for the treatment of anxiety/stress disorders. Indeed, clinical proof of concept for $mGlu_{2/3}$ receptor agonists in the treatment of affective disorders has also been achieved (138, 139).

Group II mGlu receptor antagonists as potential antidepressant agents

Evidence supporting a prominent role for pathophysiological regulation of glutamate in major depressive disorders is accumulating (140-143). A major hypothesis derived from convergent preclinical and clinical findings, put simplistically, is that an upregulation of glutamate neurotransmission through AMPA receptor signaling (143, 144) and a downregulation of NMDA receptor function (4, 145) is the driving force of the machinery necessary for homeostatic mood functioning. There are a host of biological targets that can be engaged by small molecules to modify this system, including direct interaction of molecules with AMPA or NMDA receptors, regulatory sites for glutamate release that include transporters, other neurotransmitter regulators (e.g., GABA, dopamine) and the mGlu receptors. Three groups of mGlu receptors have been defined and all have been associated to a greater or lesser extent with the regulation of mood. The present brief overview and discussion will focus on the group II receptors, which include $mGlu_2$ and $mGlu_3$ receptors (142, 145, 146).

Evidence supporting a role for blockade of $mGlu_2$ and/or $mGlu_3$ receptors as a potential novel antidepressant strategy comes from a number of sources: 1) receptor localization; 2) receptor physiology; 3) antidepressant-like behavioral effects of $mGlu_{2/3}$ receptor antagonists; 4) antidepressant-like biochemical effects of $mGlu_{2/3}$ receptor antagonists; 5) impact of $mGlu_{2/3}$ receptor antagonists on AMPA receptor function; and 6) commonalities in the antidepressant efficacy of ketamine and conventional antidepressants (e.g., fluoxetine, desipramine) in humans to the mechanisms underlying effects of $mGlu_{2/3}$ receptor antagonists. In summary, convergent evidence provides a cogent reason to anticipate that $mGlu_{2/3}$ receptor blockade in humans could deliver an antidepressant effect.

$mGlu_2$ and $mGlu_3$ receptors are well positioned both anatomically and physiologically to regulate glutamate and other neurotransmitters within the CNS in the control of mood. High levels of expression



MGS-0039

of $mGlu_2$ mRNA are identified in neurons of the accessory and external regions of the anterior olfactory bulb, pyramidal neurons in the entorhinal and parasubicular cortical regions, and granule cells of the dentate gyrus (147). $mGlu_3$ mRNA is highly expressed in neuronal cells of the cerebral cortex and the caudate putamen, and in granule cells of the dentate gyrus (148). Unlike other mGlu receptors, $mGlu_3$ mRNA is highly expressed in glial cells throughout the brain (149), where recent focus in relation to mood disorders has been placed (150). $mGlu_2$ receptors are mainly localized presynaptically as an autoreceptor or heteroreceptor, and are found in preterminal rather than terminal portions of axons (150). $mGlu_3$ receptors have a prominent localization at postsynaptic sites, as well as on glial cells (151).

Understanding the role of $mGlu_{2/3}$ receptors in mood disorders has been aided by the discovery of selective pharmacological tools. LY341495 diplays nanomolar affinity for $mGlu_2$ and $mGlu_3$ receptors, with $mGlu_8$ receptors as the closest selectivity target (> 100-fold) (152). A glutamate analogue, **MGS-0039**, has recently been reported to have nanomolar affinity at $mGlu_2$ and $mGlu_3$ receptors, but the affinity at $mGlu_5$ and $mGlu_8$ receptors has not yet been reported (153, 154). Due to the limited oral bioavailability of MGS-0039, ester prodrugs have been constructed that are designed to deliver MGS-0039 after oral dosing through hydrolytic release of the parent compound, and oral activity has been disclosed (155, 156). In addition to these two molecules that act at the orthosteric (glutamate) site of the $mGlu_{2/3}$ receptors, negative allosteric modulators of $mGlu_{2/3}$ receptors have also been identified and characterized to some extent (157, 158).

$mGlu_{2/3}$ receptors also influence the release and synaptic availability of glutamate and other neurotransmitters known to regulate mood, such as GABA and monoamine neurotransmitters (89, 90). MGS-0039 and LY341495 increased firing rates of the serotonergic dorsal raphe neurons (159), and MGS-0039 increased 5-HT levels in extracellular compartments of the mPFC (160; see 146 for comparable findings with LY341495). MGS-0039 has also been shown to modulate dopaminergic tone (160), a finding that has been linked to $mGlu_2$ receptors, as defined by mice lacking $mGlu_2$ receptors (161). Hippocampal neurogenesis is one of the mechanisms associated with antidepressant activity (see 162-164 for review). Subchronic dosing with MGS-0039 (14 days) increased progenitor cell proliferation in the dentate gyrus (165).

Robust antidepressant-like behavioral effects have been reported for MGS-0039 and LY341495. Efficacy has been observed in the FST in both mice and rats, in the TST in mice (144, 153, 166) and in the learned helplessness test (167). LY341495 attenuated reward deficits observed in nicotine-dependent rats, as evaluated by intracranial self-stimulation (168), indicating that blockade of $mGlu_{2/3}$ receptors opposes anhedonic effects. The AMPA receptor antagonist NBQX precipitated withdrawal-like elevations in threshold in nicotine-treated rats (168), showing an involvement of AMPA receptors. In addition to models predictive of efficacy in mood disorders, MGS-0039 showed anxiolytic-like effects in some anxiety models (142).

Although full examination of this issue is not possible here, it is important to mention that $mGlu_{2/3}$ receptor agonists have also been reported to help accelerate the biochemical processing of antidepressant-like effects. Chronic imipramine administration decreased the abililty of $mGlu_{2/3}$ receptor agonists to inhibit forskolin-stimulated cAMP formation, although there was an increase in the group II mGlu receptor-mediated phosphoinositol responses (169, 170).

The mechanisms underlying the biochemical and behavioral effects of $mGlu_{2/3}$ receptor antagonists have been shown to be related to the functional amplification of AMPA receptor function. Increased 5-HT release in the mPFC by MGS-0039 was attenuated by NBQX, an AMPA receptor antagonist. NBQX also prevented the antidepressant-like effects of MGS-0039 in the TST (171). The downstream action of $mGlu_{2/3}$ receptor antagonism on AMPA receptors is compelling, given data implicating AMPA receptor enhancements as a core mechanism involved in the action of antidepressants; indeed, AMPA receptor potentiators have been suggested as putative antidepressants (6, 143, 144, 145, 172, 173).

If $mGlu_{2/3}$ receptor antagonists are antidepressant in humans, the question remains whether such novel antidepressants would provide value beyond that of conventional or monoamine-based antidepressants. Furthermore, what side effect liabilities might be anticipated with this mechanism? As for the efficacy question, additional impact upon cognition and fatigue/wake states is anticipated (142). As for the question of side effects, the potential for reduced sexual dysfunction and treatment-emergent weight gain is not anticipated given this is a non-selective serotonin reuptake inhibitor (SSRI) mechanism of action.

GROUP III mGLU RECEPTORS AS DRUG TARGETS

There has also been a huge increase of interest in the role of the various group III mGlu receptors in CNS disorders. The area has been hampered by poor pharmacological tools. However, recently some newer molecules have emerged. In particular, $mGlu_4$ and $mGlu_7$ agonists and PAMs have been reported (174-176). Although much of the focus with $mGlu_7$ and $mGlu_8$ (primarily receptor knockout data) receptors has been on their role in anxiety and depression (91, 145, 177, 178), in this review we will focus on the role of $mGlu_4$ and $mGlu_7$ receptors in PD, where the science has been most advanced.

$mGlu_4$ and $mGlu_7$ receptor agonists or PAMs for PD

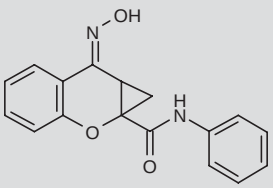
The group III mGlu receptors ($mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$) are coupled to $G_{i/o}$ proteins and are predominantly expressed presynaptically, where they regulate the release of both glutamate and GABA (91). It is well established that group III mGlu receptors are localized in the basal ganglia (179, 180), a group of interconnected subcortical nuclei involved in the control of motor function. In particular, group

III mGlu receptors are localized presynaptically on a number of projecton pathways within the basal ganglia, including striatopallidal, striatonigral and subthalamonigral projections, and consequently are potential targets for the treatment of neurodegenerative diseases like PD.

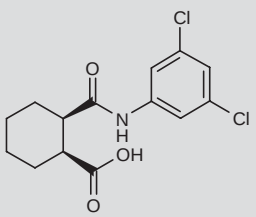
In PD, degeneration of the nigrostriatal dopaminergic system leads to an imbalance between dopaminergic and glutamatergic transmission in the basal ganglia and this excessive activity in the basal ganglia disrupts motor control. Moreover, alterations in the activity of the basal ganglia, in particular hyperactivity of subthalamic nucleus output pathways, have been hypothesized to contribute towards degeneration of the nigrostriatal system through pathological increases in glutamate release at the subthalamonigral synapse (181). Consequently, administration of group III mGlu receptor agonists may ameliorate some of the motor symptoms associated with PD, but also interfere with the ongoing neurodegenerative processes underlying the progressive loss of nigral neurons.

A potential role for group III mGlu receptors in the control of motor function relevant to PD was first shown by the ability of the nonselective group III agonists L-(+)-2-amino-4-phosphonobutyric acid (L-AP4) or L-serine-*O*-phosphate (L-SOP), when administered directly into the globus pallidus, substantia nigra or by the intracerebroventricular route, to relieve motor symptoms in animal models of parkinsonism, including haloperidol-induced catalepsy (182) and reserpine-induced akinesia (183). Moreover, L-AP4 was found to be as effective as L-DOPA in decreasing forelimb asymmetry in rats unilaterally lesioned with 6-OHDA (182). The action of group III mGlu receptor agonists on reserpine-induced akinesia was also mimicked by administration of **PHCCC**, which behaves as a selective allosteric potentiator of $mGlu_4$ receptors (184, 185), and more recently, on both reserpine-induced akinesia and haloperidol-induced catalepsy by **VU-0155041**, a more potent $mGlu_4$ receptor allosteric modulator than PHCCC (186).

The symptomatic activity of L-AP4 and PHCCC is thought to be mediated by activation of presynaptic $mGlu_4$ receptors localized on GABAergic fibers projecting from the neostriatum to the external globus pallidus. Support for this hypothesis emanates from the fact that, within the basal ganglia, the highest level of $mGlu_4$ receptor immunoreactivity is found in the globus pallidus (179), and activation of $mGlu_4$ receptors in this region mimics the action of dopamine in reducing GABA release (182, 187). Electrophysiological investigations using rat brain slices have revealed that activation of group III mGlu receptors with L-AP4 inhibits striatal-evoked $GABA_A$-mediated inhibitory postsynaptic currents in the globus pallidus (182, 187). Importantly, the response to L-AP4 was absent in $mGlu_4$ receptor knockout mice and enhanced by administration of PHCCC (182), confirming the role of $mGlu_4$ receptors in the regulation of striatopallidal transmission and suggesting that the resulting $mGlu_4$ receptor-mediated disinhibition of thalamocortical neurons may result in an improvement in parkinsonian symptoms.



PHCCC



VU-0155041

As mentioned previously, loss of dopaminergic transmission in the nigrostriatal system produces a shift in the balance in activity of the basal ganglia from the direct to the indirect pathway, with the resulting hyperactivity of the subthalamic nucleus and consequent hypokinesia. In addition, hyperactivity of subthalamic nucleus output pathways may also contribute towards degeneration of the nigrostriatal system (181). A role for $mGlu_4$ receptors in the control of excitatory transmission in the SN pars compacta has emerged from in vitro studies showing that activation of group III mGlu receptors with L-AP4 inhibited evoked excitatory postsynaptic currents (188, 189) and that these effects were potentiated by coadministration of PHCCC (189). In addition, both L-AP4 and PHCCC have also been shown to be neuroprotective in experimental models of PD in vivo. In studies utilizing intranigral administration of 6-OHDA, L-AP4 produced significant protection of the nigrostriatal system following nigral administration (79, 190), while systemic administration of PHCCC, or administration directly into the external globus pallidus, also prevented MPTP-induced deficits in the dopamine system (191). Furthermore, the failure of PHCCC to prevent MPTP-induced toxicity in $mGlu_4$ receptor knockout mice supported a role for $mGlu_4$ receptors in the degeneration of the nigrostriatal system in experimental PD, and as a potential target for the treatment of PD.

The preclinical evaluation of $mGlu_4$ receptor ligands –including orthosteric agonists and PAMs– has been hampered by their poor solubility, lack of selectivity (over other group II mGlu receptors) or deficient brain penetration. More recently, a number of groups have developed new tools that may address some of these issues (174, 192, 193). In particular, Buerrier et al. described a selective and brain-penetrant orthosteric agonist that modulates basal ganglia transmission in vitro and reverses haloperidol-induced catalepsy when given systemically (193), reinforcing the potential role of the $mGlu_4$ receptor as a therapeutic target for the treatment of PD.

CONCLUSIONS

There has been huge progress in our understanding of mGlu receptors and their role in CNS diseases. There are now good preclinical data supporting that certain subtypes of these receptors may be important in pain, schizophrenia, depression, anxiety and PD. Several pharmaceutical companies are actively working in the area and we expect to see new compounds entering clinical trials in the coming years.

DISCLOSURES

All the authors are employees of Eli Lilly & Co.

REFERENCES

1. O'Neill, M.J., Lees, K.R. *Ionotropic glutamate receptors as therapeutic targets*. In: Therapeutic Potential of Ionotropic Glutamate Receptor Antagonists and Modulators, Chapter 13, Stroke. W. Danysz, D. Lodge, C.G. Parsons (Eds.). F.P. Graham Publishing Co., 2002, 403-47.
2. O'Neill, M.J., McCulloch, J., Lodge, D. *Stroke: Mechanisms of excitotoxicity and approaches for therapy.* In: Handbook of Contemporary Neuropharmacology. D.R. Sibley, I. Hannin, M. Kuhar, P. Skolnick (Eds.). John Wiley and Sons: New York, 2007.
3. Bowie, D. *Ionotropic glutamate receptors & CNS disorders.* CNS Neurol Disord Drug Targets 2008, 7(2): 129-43.
4. Paul, I.A., Skolnick, P. *Glutamate and depression: Clinical and preclinical studies.* Ann N Y Acad Sci 2003, 1003: 250-72.
5. Pittenger, C., Sanacora, G., Krystal, J.H. *The NMDA receptor as a therapeutic target in major depressive disorder.* CNS Neurol Disord Drug Targets 2007, 6(2): 101-15.
6. O'Neill, M.J., Bleakman, D., Zimmerman, D.M., Nisenbaum, E.S. *AMPA receptor potentiators for the treatment of CNS disorders.* Curr Drug Targets CNS Neurol Disord 2004, 3(3): 181-94.
7. Lynch, G. *Glutamate-based therapeutic approaches: Ampakines.* Curr Opin Pharmacol 2006, 6(1): 82-8.
8. Lynch, G., Gall, C.M. *Ampakines and the threefold path to cognitive enhancement.* Trends Neurosci 2006, 29(10): 554-62.
9. Schoepp, D.D., Jane, D.E., Monn, J.A. *Pharmacological agents acting at subtypes of metabotropic glutamate receptors*. Neuropharmacology 1999, 38(10): 1431-76.
10. Pin, J.-P., De Colle, C., Bessis, A.-S., Acher, F. *New perspectives for the development of selective metabotropic glutamate receptor ligands*. Eur J Pharmacol 1999, 375(1-3): 277-94.
11. Pin, J.-P., Duvoisin, R. *The metabotropic glutamate receptors: Structure and function.* Neuropharmacology 1995, 34(1): 1-26.
12. Shigemoto, R., Wada, E., Ohishi, H., Takada, M., Mizuno, M., Roberts, J.D.B., Somogyi, P. *Differential presynaptic localization of metabotropic glutamate receptor subtypes, mGluR2/3 and mGluR7 in the hippocampus*. Soc Neurosci Abst 1995, 21: Abst 338.20.
13. Petralia, R.S., Wang, W.-X., Niedzielski, A.S., Wenthold, R.J. *The metabotropic glutamate receptors, mGluR2 and mGluR3, show unique postsynaptic, presynaptic and glial localizations.* Neuroscience 1996, 71(4): 949-76.
14. Ferraguti, F., Shigemoto, R. *Metabotropic glutamate receptors.* Cell Tissue Res 2006, 326(2): 483-504.
15. Bhave, G., Karim, F., Carlton, S.M., Gereau, R.W. 4th. *Peripheral group I metabotropic glutamate receptors modulate nociception in mice.* Nat Neurosci 2001, 4(4): 417-23.
16. Karim, F., Wang, C.C., Gereau, R.W. 4th. *Metabotropic glutamate receptor subtypes 1 and 5 are activators of extracellular signal-regulated kinase signaling required for inflammatory pain in mice.* J Neurosci 2001, 21(11): 3771-9.
17. Gasparini, F., Bilbe, G, Gomez-Mancilla, B., Spooren, W. *mGluR5 antagonists: Discovery, characterization and drug development.* Curr Opin Drug Discov Devel 2008, 11(5): 655-65.
18. Liu, F., Grauer, S., Kelley, C. et al. *ADX47273 [S-(4-fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]-oxadiazol-5-yl]-piperidin-1-yl}-methanone]: A novel metabotropic glutamate receptor 5-selective positive allosteric modulator with preclinical antipsychotic-like and procognitive activities.* J Pharmacol Exp Ther 2008, 327(3): 827-39.
19. Schlumberger, C., Pietraszek, M., Gravius, A., Klein, K.U., Greco, S., Morè, L., Danysz, W. *Comparison of the mGlu(5) receptor positive allosteric modulator ADX47273 and the mGlu(2/3) receptor agonist LY354740 in tests for antipsychotic-like activity.* Eur J Pharmacol 2009, 623(1-3): 73-83.
20. Schlumberger, C., Pietraszek, M., Gravius, A., Danysz, W. *Effects of a positive allosteric modulator of mGluR5 ADX47273 on conditioned avoidance response and PCP-induced hyperlocomotion in the rat as models for schizophrenia.* Pharmacol Biochem Behav 2010, 95(1): 23-30.
21. Steckler, T., Lavreysen, H., Oliveira, A.M. et al. *Effects of mGlu1 receptor blockade on anxiety-related behaviour in the rat lick suppression test.* Psychopharmacology (Berl) 2005, 179(1): 198-206.
22. Steckler, T., Oliveira, A.F., Van Dyck, C. et al. *Metabotropic glutamate receptor 1 blockade impairs acquisition and retention in a spatial water maze task.* Behav Brain Res 2005, 164(1): 52-60.
23. Shannon, H.E., Peters, S.C., Kingston, A.E. *Anticonvulsant effects of LY456236, a selective mGlu1 receptor antagonist.* Neuropharmacology 2005, 49(Suppl. 1): 188-95.
24. Gasparini, F., Lingenhöhl K., Stoehr, N. et al. *2-Methyl-6-(phenylethynyl)-pyridine (MPEP), a potent, selective and systemically active mGlu5 receptor antagonist.* Neuropharmacology 1999, 38(10): 1493-503.
25. Spooren, W.P., Gasparini, F., Bergmann, R., Kuhn, R. *Effects of the prototypical mGlu(5) receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine on rotarod, locomotor activity and rotational responses in unilateral 6-OHDA-lesioned rats.* Eur J Pharmacol 2000, 406(3): 403-10.
26. Spooren, W.P., Vassout, A., Neijt, H.C. et al. *Anxiolytic-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine in rodents.* J Pharmacol Exp Ther 2000, 295(3): 1267-75.
27. Anderson, J.J., Rao, S.P., Rowe, B. et al. *[3H]Methoxymethyl-3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine binding to metabotropic glutamate receptor subtype 5 in rodent brain: In vitro and in vivo characterization.* J Pharmacol Exp Ther 2002, 303(3): 1044-51.
28. Cosford, N.D., Tehrani, L., Roppe, J. et al. *3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]-pyridine: A potent and highly selective metabotropic glutamate subtype 5 receptor antagonist with anxiolytic activity.* J Med Chem 2003, 46(2): 204-6.
29. Cosford, N.D., Roppe, J., Tehrani, L. et al. *[3H]-Methoxymethyl-MTEP and [3H]-methoxy-PEPy: Potent and selective radioligands for the metabotropic glutamate subtype 5 (mGlu5) receptor.* Bioorg Med Chem Lett 2003, 13(3): 351-4.
30. Schkeryantz, J.M., Kingston, A.E., Johnson, M.P. *Prospects for metabotropic glutamate 1 receptor antagonists in the treatment of neuropathic pain*. J Med Chem 2007, 50(11): 2563-8.
31. Hofmann, H.A., Siegling, A., Denzer, D., Spreyer, P., De Vry, J. *Metabotropic glutamate mGlu1 receptor mRNA expression in dorsal root ganglia of rats after peripheral nerve injury.* Eur J Pharmacol 2001, 429(1-3): 135-8.
32. Zhou, S., Komak, S., Du, J., Carlton, S.M. *Metabotropic glutamate 1alpha receptors on peripheral primary afferent fibers: Their role in nociception.* Brain Res 2001, 913(1): 18-26.
33. Fundytus, M.E., Fischer, K., Dray, A., Henry, J.L., Coderre, T.J. *In vivo antinociceptive activity of anti-rat mGluR1 and mGluR5 antibodies in rats*. Neuroreport 1998, 9(4): 731-5.
34. Young, M.R., Blackburn-Munro, G., Dickinson, T., Johnson, M.J., Anderson, H., Nakalembe, I., Fleetwood-Walker, S.M. *Antisense ablation of type I metabotropic glutamate receptor mGluR1 inhibits spinal nociceptive transmission.* J Neurosci 1998, 18(23): 10180-8.
35. Fundytus, M.E., Osborne, M.G., Henry, J.L., Coderre, T.J., Dray, A. *Antisense oligonucleotide knockdown of mGluR1 alleviates hyperalgesia*

and allodynia associated with chronic inflammation. Pharmacol Biochem Behav 2002, 73(2): 401-10.

36. Zhu, C.Z., Baker, S., El-Kouhen, O. et al. *Analgesic activity of metabotropic glutamate receptor 1 antagonists on spontaneous post-operative pain in rats.* Eur J Pharmacol 2008, 580(3): 314-21.
37. Varty, G.B., Grilli, M., Forlani, A. et al. *The antinociceptive and anxiolytic-like effects of the metabotropic glutamate receptor 5 (mGluR5) antagonists, MPEP and MTEP, and the mGluR1 antagonist, LY456236, in rodents: a comparison of efficacy and side-effect profiles.* Psychopharmacology (Berl) 2005, 179(1): 207-17.
38. Sevostianova, N., Danysz, W. *Analgesic effects of mGlu1 and mGlu5 receptor antagonists in the rat formalin test.* Neuropharmacology 2006, 51(3): 623-30.
39. Ichise, T., Kano, M., Hashimoto, K. et al. *mGluR1 in cerebellar Purkinje cells essential for long-term depression, synapse elimination, and motor coordination.* Science 2000, 288(5472): 1832-5.
40. El-Kouhen, O., Lehto, S.G., Pan, J.B. et al. *Blockade of mGluR1 receptor results in analgesia and disruption of motor and cognitive performances: Effects of A-841720, a novel non-competitive mGluR1 receptor antagonist.* Br J Pharmacol 2006, 149(6): 761-74.
41. Brodkin, J., Bradbury, M., Busse, C., Warren, N., Bristow, L.J., Varney, M.A. *Reduced stress-induced hyperthermia in mGluR5 knockout mice.* Eur J Neurosci 2002, (11): 2241-4.
42. Brodkin, J., Busse, C., Sukoff, S.J., Varney, M.A. *Anxiolytic-like activity of the mGluR5 antagonist MPEP a comparison with diazepam and buspirone.* Pharmacol Biochem Behav 2002, 73(2): 359-66.
43. Tatarczynska, E., Klodzinska, A., Chojnacka-Wójcik, E., Palucha, A., Gasparini, F., Kuhn, R., Pilc, A. *Potential anxiolytic- and antidepressant-like effects of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist.* Br J Pharmacol 2001, 132(7): 1423-30.
44. Roppe, J.R., Wang, B., Huang, D. et al. *5-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]-2,3'-bipyridine: A highly potent, orally active metabotropic glutamate subtype 5 (mGlu5) receptor antagonist with anxiolytic activity.* Bioorg Med Chem Lett 2004, 14(15): 3993-6.
45. Busse, C.S., Brodkin, J., Tattersall, D. et al. *The behavioral profile of the potent and selective mGlu5 receptor antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) in rodent models of anxiety.* Neuropsychopharmacology 2004, 29(11): 1971-9.
46. Ballard, T.M., Woolley, M.L., Prinssen, E., Huwyler, J., Porter, R., Spooren, W. *The effect of the mGlu5 receptor antagonist MPEP in rodent tests of anxiety and cognition: A comparison.* Psychopharmacology (Berl) 2005, 179(1): 218-29.
47. Pecknold, J.C., McClure, D.J., Appeltauer, L., Wrzesinski, L., Allan. T. *Treatment of anxiety using fenobam (a nonbenzodiazepine) in a double-blind standard (diazepam) placebo-controlled study.* J Clin Psychopharmacol 1982, 2(2): 129-33.
48. Porter, R.H., Jaeschke, G., Spooren, W. et al. *Fenobam: A clinically validated nonbenzodiazepine anxiolytic is a potent, selective, and noncompetitive mGlu5 receptor antagonist with inverse agonist activity.* J Pharmacol Exp Ther 2005, 315(2): 711-21.
49. Wieronska, J.M., Szewczyk, B., Branski, P., Palucha, A., Pilc, A. *Antidepressant-like effect of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist in the olfactory bulbectomized rats.* Amino Acids 2002, 23(1-3): 213-6.
50. Palucha, A., Branski, P., Szewczyk, B., Wieronska, J.M., Klak, K., Pilc, A. *Potential antidepressant-like effect of MTEP, a potent and highly selective mGluR5 antagonist.* Pharmacol Biochem Behav 2005, 81(4): 901-6.
51. Li, X., Need, A.B., Baez, M., Witkin, J.M. *Metabotropic glutamate 5 receptor antagonism is associated with antidepressant-like effects in mice.* J Pharmacol Exp Ther 2006, 319(1): 254-9.
52. Belozertseva, I.V., Kos, T., Popik, P., Danysz, W., Bespalov, A.Y. *Antidepressant-like effects of mGluR1 and mGluR5 antagonists in the rat forced swim and the mouse tail suspension tests.* Eur Neuropsychopharmacol 2007, 17(3): 172-9.
53. Treyer, V., Streffer, J., Ametamey, S.M. et al. *Radiation dosimetry and biodistribution of 11C-ABP688 measured in healthy volunteers.* Eur J Nucl Med Mol Imaging 2008, 35(4): 766-70.
54. Conn, P.J., Battaglia, G., Marino, M.J., Nicoletti, F. *Metabotropic glutamate receptors in the basal ganglia motor circuit.* Nat Rev Neurosci 2005, 6(10): 787-98.
55. Blandini, F., Greenamyre, J.T. *Prospects of glutamate antagonists in the therapy of Parkinson's disease.* Fundam Clin Pharmacol 1998, 12(1): 4-12.
56. Greenamyre, J.T., Eller, R.V., Zhang, Z., Ovadia, A., Kurlan, R., Gash, D.M. *Antiparkinsonian effects of remacemide hydrochloride, a glutamate antagonist, in rodent and primate models of Parkinson's disease.* Ann Neurol 1994, 35(6): 655-61.
57. Testa, C.M., Standaert, D.G., Young, A.B., Penney, J.B. Jr. *Metabotropic glutamate receptor mRNA expression in the basal ganglia of the rat.* J Neurosci 1994, 14(5, Pt. 2): 3005-18.
58. Awad, H., Hubert, G.W., Smith, Y., Levey, A.I., Conn, P.J. *Activation of metabotropic glutamate receptor 5 has direct excitatory effects and potentiates NMDA receptor currents in neurons of the subthalamic nucleus.* J Neurosci 2000, 20(21): 7871-9.
59. Marino, M.J., Wittmann, M., Bradley, S.R., Hubert, G.W., Smith, Y., Conn, P.J. *Activation of group I metabotropic glutamate receptors produces a direct excitation and disinhibition of GABAergic projection neurons in the substantia nigra pars reticulata.* J Neurosci 2001, 21(18): 7001-12.
60. Sanchez-Pernaute, R., Wang, J.Q., Kuruppu, D. et al. *Enhanced binding of metabotropic glutamate receptor type 5 (mGluR5) PET tracers in the brain of parkinsonian primates.* Neuroimage 2008, 42(1): 248-51.
61. Breysse, N., Baunez, C., Spooren, W., Gasparini, F., Amalric, M. *Chronic but not acute treatment with a metabotropic glutamate 5 receptor antagonist reverses the akinetic deficits in a rat model of parkinsonism.* J Neurosci 2002, 22(13): 5669-78.
62. Breysse, N., Amalric, M., Salin, P. *Metabotropic glutamate 5 receptor blockade alleviates akinesia by normalizing activity of selective basal-ganglia structures in parkinsonian rats.* J Neurosci 2003, 23(23): 8302-9.
63. Phillips, J.M., Lam, H.A., Ackerson, L.C., Maidment, N.T. *Blockade of mGluR glutamate receptors in the subthalamic nucleus ameliorates motor asymmetry in an animal model of Parkinson's disease.* Eur J Neurosci 2006, 23(1): 151-60.
64. Ismayilova, N., Verkhratsky, A., Dascombe, M.J. *Changes in mGlu5 receptor expression in the basal ganglia of reserpinised rats.* Eur J Pharmacol 2006, 545(2-3): 134-41.
65. Pellegrino, D., Cicchetti, F., Wang, X., Zhu, A., Yu, M., Saint-Pierre, M., Brownell, A.L. *Modulation of dopaminergic and glutamatergic brain function: PET studies on parkinsonian rats.* J Nucl Med 2007, 48(7): 1147-53.
66. Zhu, A., Wang, X., Yu, M., Wang, J.Q., Brownell, A.L. *Evaluation of four pyridine analogs to characterize 6-OHDA-induced modulation of mGluR5 function in rat brain using microPET studies.* J Cereb Blood Flow Metab 2007, 27(9): 1623-31.
67. Ossowska, K., Konieczny, J., Wolfarth, S., Wieronska, J., Pilc, A. *Blockade of the metabotropic glutamate receptor subtype 5 (mGluR5) produces antiparkinsonian-like effects in rats.* Neuropharmacology 2001, 41(4): 413-20.
68. Ossowska, K., Konieczny, J., Wolfarth, S., Pilc, A. *MTEP, a new selective antagonist of the metabotropic glutamate receptor subtype 5 (mGluR5), produces antiparkinsonian-like effects in rats.* Neuropharmacology 2005, 49(4): 447-55.

69. Dekundy, A., Pietraszek, M., Schaefer, D., Cenci, M.A., Danysz, W. *Effects of group I metabotropic glutamate receptors blockade in experimental models of Parkinson's disease.* Brain Res Bull 2006, 69(3): 318-26.
70. Mela, F., Marti, M., Dekundy, A., Danysz, W., Morari, M., Cenci, M.A. *Antagonism of metabotropic glutamate receptor type 5 attenuates l-DOPA-induced dyskinesia and its molecular and neurochemical correlates in a rat model of Parkinson's disease.* J Neurochem 2007, 101(2): 483-97.
71. Levandis, G., Bazzini, E., Armentero, M.T., Nappi, G., Blandini, F. *Systemic administration of an mGluR5 antagonist, but not unilateral subthalamic lesion, counteracts l-DOPA-induced dyskinesias in a rodent model of Parkinson's disease.* Neurobiol Dis 2008, 29(1): 161-8.
72. Rylander, D., Recchia, A., Mela, F., Dekundy, A., Danysz, W., Cenci, M.A. *Pharmacological modulation of glutamate transmission in a rat model of L-DOPA-induced dyskinesia: Effects on motor behavior and striatal nuclear signaling.* J Pharmacol Exp Ther 2009, 330(1): 227-35.
73. Gravius, A., Dekundy, A., Nagel, J., Morè, L., Pietraszek, M., Danysz, W. *Investigation on tolerance development to subchronic blockade of mGluR5 in models of learning, anxiety, and levodopa-induced dyskinesia in rats.* J Neural Transm 2008, 115(12): 1609-19.
74. Samadi, P., Grégoire, L., Morissette, M. et al. *mGluR5 metabotropic glutamate receptors and dyskinesias in MPTP monkeys.* Neurobiol Aging 2008, 29(7): 1040-51.
75. Morin, N., Grégoire, L., Gomez-Mancilla, B., Gasparini, F., Di Paolo, T. *Effect of the metabotropic glutamate receptor type 5 antagonists MPEP and MTEP in parkinsonian monkeys*. Neuropharmacology 2010, 58(7): 981-6.
76. Golembiowska, K., Konieczny, J., Wolfarth, S., Ossowska, K. *Neuroprotective action of MPEP, a selective mGluR5 antagonist, in methamphetamine-induced dopaminergic neurotoxicity is associated with a decrease in dopamine outflow and inhibition of hyperthermia in rats.* Neuropharmacology 2003, 45(4): 484-92.
77. Battaglia, G., Busceti, C.L, Molinaro, G. et al. *Endogenous activation of mGlu5 metabotropic glutamate receptors contributes to the development of nigro-striatal damage induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice.* J Neurosci 2004, 24(4): 828-35.
78. Armentero, M.T., Fancellu, R., Nappi, G., Bramanti, P., Blandini, F. *Prolonged blockade of NMDA or mGluR5 glutamate receptors reduces nigrostriatal degeneration while inducing selective metabolic changes in the basal ganglia circuitry in a rodent model of Parkinson's disease.* Neurobiol Dis 2006, 22(1): 1-9.
79. Vernon, A.C., Palmer, S., Datla, K.P., Zbarsky, V., Croucher, M.J., Dexter, D.T. *Neuroprotective effects of metabotropic glutamate receptor ligands in a 6-hydroxydopamine rodent model of Parkinson's disease.* Eur J Neurosci 2005, 22(7): 1799-806.
80. Vernon, A.C., Zbarsky, V., Datla, K.P., Croucher, M.J., Dexter, D.T. *Subtype selective antagonism of substantia nigra pars compacta group I metabotropic glutamate receptors protects the nigrostriatal system against 6-hydroxydopamine toxicity in vivo.* J Neurochem 2007, 103(3): 1075-91.
81. Olney, J.W., Farber, N.B. *Glutamate receptor dysfunction and schizophrenia*. Arch Gen Psychiatry 1995, 52(12): 998-1007.
82. Olney, J.W., Newcomer, J.W., Farber, N.B. *NMDA receptor hypofunction model of schizophrenia.* J Psychiatr Res 1999, 33(6): 523-33.
83. Weinberger, D.R. *Schizophrenia drug says goodbye to dopamine*. Nat Med 2007, 13(9): 1018-9.
84. Andine, P., Widermark, N., Axelsson, R., Nyberg, G., Olofsson, U., Martensson, E., Sandberg, M. *Characterization of MK-801-induced behavior as a putative rat model of psychosis*. J Pharmacol Exp Ther 1999, 290(3): 1393-408.
85. Javitt, D.C., Zukin, S.R. *Recent advances in the phencyclidine model of schizophrenia*. Am J Psychiatry 1991, 148(10): 1301-8.
86. Krystal, J.H., Belger, A., D'Souza, C., Anand, A., Charney, D.S., Aghajanian, G.K., Moghaddam, B. *Therapeutic implications of the hyperglutamatergic effects of NMDA antagonists*. Neuropsychopharmacology 1999, 21: S143-7.
87. Lahti, A.C., Holcomb, H.H., Gao, X.M., Tamminga, C.A. *NMDA-sensitive glutamate antagonism: A human model of psychosis.* Neuropsychopharmacology 1999, 22: S158-69.
88. Holcomb, H.H., Lahti, A.C., Medoff, D.R., Cullen, T., Tamminga, C.A. *Effects of noncompetitive NMDA receptor blockade on anterior cingulate cerebral blood flow in volunteers with schizophrenia*. Neuropsychopharmacology 2005, 30: 2275-82.
89. Cartmell, J., Schoepp, D.D. *Regulation of neurotransmitter release by metabotropic glutamate receptors.* J Neurochem 2000, 75(3): 889-907.
90. Schoepp, D.D. *Unveiling the functions of presynaptic metabotropic glutamate receptors in the central nervous system*. J Pharmacol Exp Ther 2001, 299(1): 12-20.
91. Conn, P.J. , Pin, J.P. *Pharmacology and functions of metabotropic glutamate receptors.* Annu Rev Pharmacol Toxicol 1997, 37: 205-37.
92. Bruno, V., Battaglia, G., Casabona, G., Copani, A., Caciagli, F., Nicoletti, F. *Neuroprotection by glial metabotropic glutamate receptors is mediated by transforming growth factor-beta*. J Neurosci 1998, 18(23): 9594-600.
93. Wright, R.A., Arnold, M.B., Wheeler, W.J., Ornstein, P.L, Schoepp, D.D. *[3H]LY341495 binding to group II metabotropic glutamate receptors in rat brain*. J Pharmacol Exp Ther 2001, 298(2): 453-60.
94. Monn, J.A., Valli, M.J., Johnson, B.G. et al. *Synthesis of the four isomers of 4-aminopyrrolidine-2,4-dicarboxylate: Identification of a potent, highly selective, and systemically-active agonist for metabotropic glutamate receptors negatively coupled to adenylate cyclase*. J Med Chem 1996, 39(15): 2990-3000.
95. Monn, J.A., Valli, M.J., Massey, S.M. et al. *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 1999, 42(6): 1027-40.
96. Monn, J.A., Valli, M.J., Massey, S.M. et al. *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 1997, 40(4): 528-37.
97. Monn, J.A., Massey, S.M., Valli, M.J. et al. *Synthesis and metabotropic glutamate receptor activity of S-oxidized variants of (-)-4-amino-2-thiabicyclo-[3.1.0]hexane-4,6-dicarboxylate: Identification of potent, selective, and orally bioavailable agonists for mGlu2/3 receptors.* J Med Chem 2007, 50(2): 233-40.
98. Nakazato, A., Kumagai, T., Sakagami, K. et al. *Synthesis, SARs, and pharmacological characterization of 2-amino-3 or 6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as potent, selective, and orally active group II metabotropic glutamate receptor agonists.* J Med Chem 2000, 43(25): 4893-909.
99. Rorick-Kehn, L.M., Johnson, B.G., Burkey, J.L. et al. *Pharmacological and pharmacokinetic properties of a structurally novel, potent, and selective metabotropic glutamate 2/3 receptor agonist: In vitro characterization of agonist (-)-(1R,4S,5S,6S)-4-amino-2-sulfonylbicyclo[3.1.0]-hexane-4,6-dicarboxylic acid (LY404039).* J Pharmacol Exp Ther 2007, 321(1): 308-17.
100. Nakki, R., Sharp, F.R., Sagar, S.M., Honkaniemi, J. *Effects of phencyclidine on immediate early gene expression in the brain.* J Neurosci Res 1996, 45(1): 13-27.

101. Danysz, W., Essmann, U., Bresink, I., Wilke, R. *Glutamate antagonists have different effects on spontaneous locomotor activity in rats*. Pharmacol Biochem Behav 1994, 48(1): 111-8.

102. Moghaddam, B., Adams, B., Verma, A., Daly, D. *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 1997, 17(8): 2921-7.

103. Danysz, W., Wroblewski, J.T., Costa, E. *Learning impairment in rats by N-methyl-D-aspartate receptor antagonists.* Neuropharmacology 1988, 27(6): 653-6.

104. Parada-Turska, J., Turski, W.A. *Excitatory amino acid antagonists and memory: Effect of drugs acting at N-methyl-D-aspartate receptors in learning and memory tasks.* Neuropharmacology 1990, 29(12): 1111-6.

105. Moghaddam, B., Adams, B.W. *Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats*. Science 1998, 281: 1349-52.

106. Cartmell, J., Monn, J.A., Schoepp, D.D. *The metabotropic glutamate 2/3 receptor agonists LY354740 and LY379268 selectively attenuate phencyclidine versus d-amphetamine motor behaviors in rats*. J Pharmacol Exp Ther 1999, 291(1): 161-70.

107. Cartmell, J., Monn, J.A., Schoepp, D.D. *Attenuation of specific PCP-evoked behaviors by the potent mGlu2/3 receptor agonist, LY379268 and comparison with the atypical antipsychotic, clozapine*. Psychopharmacology (Berl) 2000, 148(4): 423-9.

108. Cartmell, J., Monn, J.A., Schoepp, D.D. *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 Schmiedebergs Arch Pharmacol 2000, 361(1): 39-46.

109. Swanson, C.J., Schoepp, D.D. *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 2002, 303(3): 919-27.

110. Swanson, C.J., Schoepp, D.D. *A role for noradrenergic transmission in the actions of phencyclidine and the antipsychotic and antistress effects of mGlu2/3 receptor agonists.* Ann N Y Acad Sci 2003, 1003: 309-17.

111. Rorick-Kehn, L.M., Johnson, B.G., Knitowski, K.M. et al. *In vivo pharmacological characterization of the structurally novel, potent, selective mGlu2/3 receptor agonist LY404039 in animal models of psychiatric disorders*. Psychopharmacology (Berl) 2007, 193(1): 121-36.

112. Lorrain, D.S., Baccei, C.S., Bristow, L.J., Anderson, J.J., Varney, M.A. *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 2003, 117(3): 697-706.

113. Greenslade, R.G., Mitchell, S.N. *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 2004, 47(1): 1-8.

114. Fell, M.J., Katner, J.S., Johnson, B.G., Perry, K.W., Svensson, K.A. *Differential effects of the mGlu2/3 receptor agonist LY379268 and clozapine on ketamine evoked locomotor activity and neurotransmitter release in the rat brain*. Neuropharmacology 2008, 55(4): 595.

115. Gozzi, A., Large, C.H., Schwarz, A., Bertani, S., Crestan, V., Bifone, A. *Differential effects of antipsychotic and glutamatergic agents on the phMRI response to phencyclidine.* Neuropsychopharmacology 2008, 33(7): 1690-703.

116. Schreiber, R., Lowe, D., Voerste, A., De Vry, J. *LY354740 affects startle responding but not sensorimotor gating or discriminative effects of phencyclidine*. Eur J Pharmacol 2000, 388(2): R3-4.

117. Ossowska, K., Pietraszek, M., Wardas, J., Nowak, G., Zajaczkowski, W., Wolfarth, S., Pilc, A. *The role of glutamate receptors in antipsychotic drug action*. Amino Acids 2000, 19(1): 87-94.

118. Auclair, A., Cotecchia, S., Glowinski, J., Tassin, J.P. *D-Amphetamine fails to increase extracellular dopamine levels in mice lacking alpha 1b-adrenergic receptors: Relationship between functional and nonfunctional dopamine release.* J Neurosci 2002, 22(21): 9150-4.

119. Ellenbroek, B.A. *Treatment of schizophrenia: A clinical and preclinical evaluation of neuroleptic drugs*. Pharmacol Ther 1993, 57(1): 1-78.

120. Cartmell, J., Monn, J.A., Schoepp, D.D. *The mGlu(2/3) receptor agonist LY379268 selectively blocks amphetamine ambulations and rearing*. Eur J Pharmacol 2000, 400(2-3): 221-4.

121. Fell, M.J., Perry, K.W., Falcone, J.F. et al. *In vitro and in vivo evidence for a lack of interaction with dopamine D2 receptors by the metabotropic glutamate 2/3 receptor agonists 1S,2S,5R,6S-2-aminobicyclo[3.1.0]hexane-2,6-bicarboxylate monohydrate (LY354740) and (-)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY379268).* J Pharmacol Exp Ther 2009, 331(3): 1126-36.

122. Taber, M.T., Fibiger, H.C. *Electrical stimulation of the prefrontal cortex increases dopamine release in the nucleus accumbens of the rat: Modulation by metabotropic glutamate receptors.* J Neurosci 1995, 15(5, Pt. 2): 3896-904.

123. Meltzer, H.Y. *Mechanism of action of atypical antipsychotic drugs*. In: Neuropsychopharmacology: The Fifth Generation of Progress. K.L. Davis, D. Charney, J.T. Coyle, C. Nemeroff (Eds.). Lippincott Williams & Wilkins, 2002, 819-31.

124. Marek, G.J., Wright, R.A., Schoepp, D.D., Monn, J.A., Aghajanian, G.K. *Physiological antagonism between 5-hydroxytryptamine(2A) and group II metabotropic glutamate receptors in prefrontal cortex*. J Pharmacol Exp Ther 2000, 292(1): 76-87.

125. Gewirtz, J.C., Marek, G.J. *Behavioral evidence for interactions between a hallucinogenic drug and group II metabotropic glutamate receptors*. Neuropsychopharmacology 2000, 23(5): 569-76.

126. Zhai, Y., George, C.A., Zhai, J., Nisenbaum, E.S., Johnson, M.P., Nisenbaum, L.K. *Group II metabotropic glutamate receptor modulation of DOI-induced c-fos mRNA and excitatory responses in the cerebral cortex*. Neuropsychopharmacology 2003, 28(1): 45-52.

127. Cartmell, J., Perry, K.W., Salhoff, C.R., Monn, J.A., Schoepp, D.D. *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 2000, 75(3): 1147-54.

128. Johnson, M.P., Baez, M., Jagdmann, G.E. Jr. et al. *Discovery of allosteric potentiators for the metabotropic glutamate 2 receptor: Synthesis and subtype selectivity of N-(4-(2-methoxyphenoxy)phenyl)-N-(2,2,2-trifluoroethylsulfonyl)pyrid-3-ylmethylamine*. J Med Chem 2003, 46(15): 3189-92.

129. Schaffhauser, H., Rowe, B.A., Morales, S. et al. *Pharmacological characterization and identification of amino acids involved in the positive modulation of metabotropic glutamate receptor subtype 2.* Mol Pharmacol 2003, 64(4): 798-810.

130. Pinkerton, A.B., Vernier, J.M., Schaffhauser, H. et al. *Phenyl-tetrazolyl acetophenones: Discovery of positive allosteric potentiatiors for the metabotropic glutamate 2 receptor.* J Med Chem 2004, 47(18): 4595-9.

131. Bonnefous, C., Vernier, J.M., Hutchinson, J.H. et al. *Biphenyl-indanones: Allosteric potentiators of the metabotropic glutamate subtype 2 receptor*. Bioorg Med Chem Lett 2005, 15(19): 4354-8.

132. Galici, R., Jones, C.K., Hemstapat, K. et al. *Biphenyl-indanone A, a positive allosteric modulator of the metabotropic glutamate receptor subtype*

2, has antipsychotic- and anxiolytic-like effects in mice. J Pharmacol Exp Ther 2006, 318(1): 173-85.

133. Jones, C.K., Xiang, Z., Jones, P.J. et al. *Novel allosteric modulators of metabotropic glutamate receptors subtypes 2 and 5 for the treatment of schizophrenia*. Neuropharmacology 2008, 55(4): 603.
134. Spooren, W.P.J.M., Gasparini, F., van der Putten, H., Koller, M., Nakanishi, S., Kuhn, R. *Lack of effect of LY314582 (a group 2 metabotropic glutamate receptor agonist) on phencyclidine-induced locomotor activity in metabotropic glutamate receptor 2 knockout mice.* Eur J Pharmacol 2000, 397(1): R1-2.
135. Fell, M.J., Svensson, K.A., Johnson, B.G., Schoepp, D.D. *Evidence for the role of mGlu2 not mGlu3 receptors in the pre-clinical antipsychotic pharmacology of the mGlu2/3 receptor agonist (-)-(1R,4S,5S,6S)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY404039).* J Pharmacol Exp Ther 2008, 326(1): 209-17.
136. Woolley, M.L., Pemberton, D.J., Bate, S., Corti, C., Jones. D.N. *The mGlu2 but not the mGlu3 receptor mediates the actions of the mGluR2/3 agonist, LY379268, in mouse models predictive of antipsychotic activity*. Psychopharmacology (Berl) 2008, 196(3): 431-40.
137. Patil, S.T., Zhang, L., Martenyi, F. et al. *Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: A randomized phase 2 clinical trial*. Nat Med 2007, 1(9): 1102-7.
138. Schoepp, D.D., Wright, R., Levine, L.R., Gaydos, B., Potter, W.Z. *LY354740, an mGlu2/3 receptor agonist as a novel approach to treat anxiety/stress.* Stress 2003, 6(3): 189-97.
139. Swanson, C.J., Bures, M., Johnson, M.P., Linden, A.M., Monn, J.A., Schoepp, D.D. Metabotropic glutamate receptors as novel targets for anxiety and stress disorders. Nat Rev Drug Discov 2005, 4(2): 131-44.
140. Zarate, C.A. Jr., Singh, J.B., Carlson, P.J. et al. *A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression*. Arch Gen Psychiatry 2006, 63(8): 856-64.
141. Valentine, G.W., Sanacora, G. *Targeting glial physiology and glutamate cycling in the treatment of depression.* Biochem Pharmacol 2009, 78(5): 431-9.
142. Witkin, J.M., Eiler, W.J.A. *Antagonism of metabotropic glutamate group II receptors in the potential treatment of neurological and neuropsychiatric disorder*s. Drug Dev Res 2006, 67: 757-69.
143. Alt, A., Nisenbaum, E.S., Bleakman, D., Witkin, J.M. *A role for AMPA receptors in mood disorders*. Biochem Pharmacol 2006, 71(9): 1273-88.
144. Skolnick, P. *AMPA receptors: A target for novel antidepressants?* Biol Psychiatry 2008, 63(4): 347-8.
145. Pilc, A., Chaki, S., Nowak, G., Witkin, J.M. *Mood disorders: Regulation by metabotropic glutamate receptors.* Biochem Pharmacol 2008, 75(5): 997-1006.
146. Witkin, J.M., Marek, G.J., Johnson, B.G., Schoepp, D.D. *Metabotropic glutamate receptors in the control of mood disorders.* CNS Neurol Disord Drug Targets 2007, 6(2): 87-100.
147. Ohishi, H., Shigemoto, R., Nakanishi, S., Mizuno, N. *Distribution of the messenger RNA for a metabotropic glutamate receptor, mGluR2, in the central nervous system of the rat.* Neuroscience 1993, 53(4): 1009-18.
148. Tanabe, Y., Nomura, A., Masu, M., Shigemoto, R., Mizuno, N., Nakanishi, S. *Signal transduction, pharmacological properties, and expression patterns of two rat metabotropic glutamate receptors, mGluR3 and mGluR4.* J Neurosci 1993, 13(4): 1372-8.
149. Banasr, M., Chowdhury, G.M., Terwilliger, R., Newton, S.S., Duman, R.S., Behar, K.L., Sanacora, G. *Glial pathology in an animal model of depression: Reversal of stress-induced cellular, metabolic and behavioral deficits by the glutamate-modulating drug riluzole.* Mol Psychiatry 2008, Epub ahead of print.
150. Shigemoto, R., Kinoshita, A., Wada, E. et al. *Differential presynaptic localization of metabotropic glutamate receptor subtypes in the rat hippocampus.* J Neurosci 1997, 17(19): 7503-22.
151. Ohishi, H., Shigemoto, R., Nakanishi, S., Mizuno, N. *Distribution of the mRNA for a metabotropic glutamate receptor (mGluR3) in the rat brain: An in situ hybridization study.* J Comp Neurol 1993, 335(2): 252-66.
152. Kingston, A.E., Ornstein, P.L., Wright, R.A. et al. *LY341495 is a nanomolar potent and selective antagonist of group II metabotropic glutamate receptors.* Neuropharmacology 1998, 37(1): 1-12.
153. Chaki, S., Yoshikawa, R., Hirota, S. et al. *MGS0039: A potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity*. Neuropharmacology 2004 46(4): 457-67.
154. Nakazato, A., Sakagami, K., Yasuhara, A. et al. *Synthesis, in vitro pharmacology, structure-activity relationships, and pharmacokinetics of 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as potent and selective group II metabotropic glutamate receptor antagonists.* J Med Chem 2004, 47(18): 4570-87.
155. Nakamura, M., Kawakita, Y., Yasuhara, A., Fukasawa, Y., Yoshida, K., Sakagami, K., Nakazato, A. *In vitro and in vivo evaluation of the metabolism and bioavailability of esterprodrugs of MGS0039 (3-(3,4-dichlorobenzyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid), a potent metabotropic glutamate receptor antagonist.* Drug Metab Dispos 2006, 34(3): 369-74.
156. Yasuhara, A., Nakamura, M., Sakagami, K. et al. *Prodrugs of 3-(3,4-dichlorobenzyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (MGS0039): A potent and orally active group II mGluR antagonist with antidepressant-like potential.* Bioorg Med Chem 2006, 14(12): 4193-207.
157. Hemstapat, K., Da Costa, H., Nong, Y. et al. *A novel family of potent negative allosteric modulators of group II metabotropic glutamate receptors.* J Pharmacol Exp Ther 2007, 322(1): 254-64.
158. Woltering, T.J., Wichmann, J., Goetschi, E. et al. *Synthesis and characterization of 1,3-dihydro-benzo[b][1,4]diazepin-2-one derivatives: Part 3. New potent non-competitive metabotropic glutamate receptor 2/3 antagonists.* Bioorg Med Chem Lett 2008, 18(8): 2725-9.
159. Kawashima, N., Karasawa, J., Shimazaki, T., Chaki, S., Okuyama, S., Yasuhara, A., Nakazato, A. *Neuropharmacological profiles of antagonists of group II metabotropic glutamate receptors*. Neurosci Lett 2005, 378(3): 131-4.
160. Karasawa, J., Yoshimizu, T., Chaki, S. *A metabotropic glutamate 2/3 receptor antagonist, MGS0039, increases extracellular dopamine levels in the nucleus accumbens shell*. Neurosci Lett 2006, 393(2-3): 127-30.
161. Morishima, Y., Miyakawa, T., Furuyashiki, T., Tanaka, Y., Mizuma, H., Nakanishi, S. *Enhanced cocaine responsiveness and impaired motor coordination in metabotropic glutamate receptor subtype 2 knockout mice*. Proc Natl Acad Sci U S A 2005, 102(11): 4170-5.
162. Santarelli, L., Saxe, M., Gross, C. et al. *Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants*. Science 2003, 301(5634): 805-9.
163. Alt, A., Witkin, J.M., Bleakman, D. *AMPA receptor potentiators as novel antidepressants.* Curr Pharm Des 2005, 11(12): 1511-27.
164. Duman, R.S., Nakagawa, S., Malberg, J. *Regulation of adult neurogenesis by antidepressant treatment.* Neuropsychopharmacology 2001, 25(6): 836-44.
165. Yoshimizu, T., Chaki, S. *Increased cell proliferation in the adult mouse hippocampus following chronic administration of group II metabotropic glutamate receptor antagonist, MGS0039.* Biochem Biophys Res Commun 2004, 315(2): 493-6.

166. Bespalov, A.Y., van Gaalen, M.M., Sukhotina, I.A., Wicke, K., Mezler, M., Schoemaker, H., Gross, G. *Behavioral characterization of the mGlu group II/III receptor antagonist, LY-341495, in animal models of anxiety and depression*. Eur J Pharmacol 2008, 592(1-3): 96-102.

167. Yoshimizu, T., Shimazaki, T., Ito, A., Chaki, S. *An mGluR2/3 antagonist, MGS0039, exerts antidepressant and anxiolytic effects in behavioral models in rats*. Psychopharmacology (Berl) 2006, 186(4): 587-93.

168. Kenny, P.J., Gasparini, F., Markou, A. *Group II metabotropic and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)/kainate glutamate receptors regulate the deficit in brain reward function associated with nicotine withdrawal in rats*. J Pharmacol Exp Ther 2003, 306(3): 1068-76.

169. Matrisciano, F., Storto, M., Ngomba, R.T. *Imipramine treatment up-regulates the expression and function of mGlu2/3 metabotropic glutamate receptors in the rat hippocampus.* Neuropharmacology 2002, 42(8): 1008-15.

170. Matrisciano, F., Scaccianoce, S., Del Bianco, P. *Metabotropic glutamate receptors and neuroadaptation to antidepressants: Imipramine-induced down-regulation of beta-adrenergic receptors in mice treated with metabotropic glutamate 2/3 receptor ligands.* J Neurochem 2005, 93(5): 1345-52.

171. Karasawa, J., Shimazaki, T., Kawashima, N., Chaki, S. *AMPA receptor stimulation mediates the antidepressant-like effect of a group II metabotropic glutamate receptor antagonist*. Brain Res 2005, 1042(1): 92-8.

172. Bleakman, D., Alt, A., Witkin, J.M. *AMPA receptors in the therapeutic management of depression.* CNS Neurol Disord Drug Targets 2007, 6(2): 117-26.

173. Zarate. C.A. Jr., Manji, H.K. *The role of AMPA receptor modulation in the treatment of neuropsychiatric diseases*. Exp Neurol 2008, 211(1): 7-10.

174. Engers, D.W., Niswender, C.M., Weaver, C.D. et al. *Synthesis and evaluation of a series of heterobiarylamides that are centrally penetrant metabotropic glutamate receptor 4 (mGluR4) positive allosteric modulators (PAMs).* J Med Chem 2009, 52(14): 4115-8.

175. Williams, R., Niswender, C.M., Luo, Q., Le, U., Conn, P.J., Lindsley, C.W. *Positive allosteric modulators of the metabotropic glutamate receptor subtype 4 (mGluR4). Part II: Challenges in hit-to-lead.* Bioorg Med Chem Lett 2009, 19(3): 962-6.

176. Niswender, C.M., Lebois, E.P., Luo, Q. et al. *Positive allosteric modulators of the metabotropic glutamate receptor subtype 4 (mGluR4): Part I. Discovery of pyrazolo[3,4-d]pyrimidines as novel mGluR4 positive allosteric modulators*. Bioorg Med Chem Lett 2008, 18(20): 5626-30.

177. Cryan, J.F., Kelly, P.H., Neijt, H.C., Sansig, G., Flor, P.J., van Der Putten, H. *Antidepressant and anxiolytic-like effects in mice lacking the group III metabotropic glutamate receptor mGluR7.* Eur J Neurosci 2003, (11): 2409-17.

178. Mitsukawa, K., Yamamoto, R., Ofner, S. et al. *A selective metabotropic glutamate receptor 7 agonist: Activation of receptor signaling via an allosteric site modulates stress parameters in vivo.* Proc Natl Acad Sci U S A 2005, 102(51): 18712-7.

179. Bradley, S.R., Standaert, D.G., Rhodes, K.J., Rees, H.D., Testa, C.M., Levey, A.I., Conn, P.J. *Immunohistochemical localization of subtype 4a metabotropic glutamate receptors in the rat and mouse basal ganglia.* J Comp Neurol 1999, 407(1): 33-46.

180. Messenger, M.J., Dawson, L.G., Duty, S. *Changes in metabotropic receptor 1-8 gene expression in the rodent basal ganglia motor loop following lesion of the nigrostriatal tract.* Neuropharmacology 2002, 43(2): 261-71.

181. Rodriguez, M.C., Obeso, J.A., Olanow, C.W. *Subthalamic nucleus-mediated excitotoxicity in Parkinson's disease: A target for neuroprotection*. Ann Neurol 1998, 44(3, Suppl. 1): S175-88.

182. Valenti, O., Marino, M.J., Wittman, M., Lis, E., DiLella, A.G., Kinney, G.G., Conn, P.J. *Group III metabotropic glutamate receptor-mediated modulation of the striatopallidal synapse*. J Neurosci 2003, 23(18): 7218-26.

183. MacInnes, N., Messenger, M.J., Duty, S. *Activation of group III metabotropic glutamate receptors in selected regions of the basal ganglia alleviates akinesia in the reserpine-treated rat.* Br J Pharmacol 2004, 141(1): 15-22.

184. Maj, M., Bruno, V., Dragic, Z. et al. *(-)-PHCCC, a positive allosteric modulator of mGluR4: Characterization, mechanism of action, and neuroprotection*. Neuropharmacology 2003, 45(7): 895-906.

185. Marino, M.J., Williams, D.L. Jr., O'Brien, J.A. et al. *Allosteric modulation of group III metabotropic glutamate receptor 4: A potential approach to Parkinson's disease treatment*. Proc Natl Acad Sci U S A 2003, 100(23): 13668-73.

186. Niswender, C.M., Johnson, K.A., Weaver, C.D. et al. *Discovery, characterization and antiparkinsonian effect of novel positive allosteric modulators of metabotropic glutamate receptor 4*. Mol Pharmacol 2008, 74(5): 1345-58.

187. Matsui, T., Kita, H. *Activation of group III metabotropic glutamate receptors presynaptically reduces both GABAergic and glutamatergic transmission in the rat globus pallidus.* Neuroscience 2003, 122(3): 727-37.

188. Wigmore, M.A., Lacey, M.G. *Metabotropic glutamate receptors depress glutamate-mediated synaptic input to rat midbrain dopamine neurones in vitro.* Br J Pharmacol 1998, 123(4): 667-74.

189. Valenti, O., Mannaioni, G., Seabrook, G.R., Conn, P.J., Marino, M.J. *Group III metabotropic glutamate-receptro-mediated modulation of excitatory transmission in rodent substantia nigra pars compacta dopamine neurons.* J Pharmacol Exp Ther 2005, 313(3): 1296-304.

190. Vernon, A.C., Zbarsky, V., Datla, K.P., Dexter, D.T., Croucher, M.J. *Selective activation of group III metabotropic glutamate receptors by L-(+)-2-amino-4-phosphonobutyric acid protects the nigrostriatal system against 6-hydroxydopamine toxicity in vivo.* J Pharmacol Exp Ther 2007, 320(1): 397-409.

191. Battaglia, G., Busceti, C.L., Molinaro, G., Biagioni, F., Traficante, A., Nicoletti, F., Bruno, V. *Pharmacological activation of mGlu4 metabotropic glutamate receptors reduces nigrostriatal degeneration in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.* J Neurosci 2006, 26(27): 7222-9.

192. Cuomo, D., Martella, G., Barabino, E. et al. *Metabotropic glutamate receptor subtype 4 selectively modulates both glutamate and GABA transmission in the striatum: Implications for Parkinson's disease treatment.* J Neurochem 2009, 109(4): 1096-105.

193. Beurrier, C., Lopez, S., Révy, D. et al. *Electrophysiological and behavioral evidence that modulation of metabotropic glutamate receptor 4 with a new agonist reverses experimental parkinsonism.* FASEB J 2009, 23(10): 3619-28.

194. Suzuki, G., Kimura, T., Satow, A. et al. *Pharmacological characterization of a new, orally active and potent allosteric metabotropic glutamate receptor 1 antagonist, 4-[1-(2-fluoropyridin-3-yl)-5-methyl-1H-1,2,3-triazol-4-yl]-N-isopropyl-N-methyl-3,6-dihydropyridine-1(2H)-carboxamide (FTIDC).* J Pharmacol Exp Ther 2007, 321(3): 1144-53.