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Metabotropic Glutamate Receptor Subtype 5 Antagonists MPEP and MTEP

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ABSTRACT

Glutamate regulates the function of central nervous system (CNS), in part, through the cAMP and/or IP3/DAG second messenger-associated metabotropic glutamate receptors (mGluRs). The mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) has been extensively used to elucidate potential physiological and pathophysiological functions of mGluR5. Unfortunately, recent evidence indicates significant non-specific actions of MPEP, including inhibition of NMDA receptors. In contrast, *in vivo* and *in vitro* characterization of the newer mGluR5 antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) indicates that it is more highly selective for mGluR5 over mGluR1, has no effect on other mGluR subtypes, and has fewer off-target effects than MPEP. This article reviews literature on both of these mGluR5 antagonists, which suggests their possible utility in neurodegeneration, addiction, anxiety and pain management.

INTRODUCTION

It is well established that the excitatory neurotransmitter glutamate acts through two classes of receptors — fast ligand-gated ionotropic receptors and slower G-protein coupled receptors (51,58). Because this prevalent amino acid helps maintain homeostasis in the adult brain, pathological alterations in its release, receptors or signaling cascade can mediate temporary and/or permanent effects that disrupt normal function (48,62,72,102, 103,132,150,193,215).

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The ionotropic glutamate receptor class (iGluRs) consists of α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA), kainate (KA) and *N*-methyl-D-aspartate (NMDA) receptors. These ion channels are permeable to both potassium and sodium, and in the case of NMDA receptors and some AMPA receptors, calcium ions. In contrast, the metabotropic glutamate receptor class (mGluRs) consists of three groups classified according to their structure, signal transduction mechanisms and pharmacological sensitivities (51,163). Group I mGluRs (mGluR1 and 5) are positively associated with phospholipase C via G_q proteins and initiate an inositol triphosphate/diacylglycerol (IP3/DAG) second messenger cascade, whereas group II (mGluR2 and 3) and III mGluRs (mGluR4, 6, 7, and 8) are negatively coupled to adenylylcyclase via $G_{i/o}$ proteins (51).

Through the mGluRs, glutamate can modulate excitatory (AMPA and NMDA receptors) and inhibitory (GABA) signaling pathways, in addition to various ion channels, including many specific for potassium and calcium (9,21,46,52,86,100,101,175,179,186, 213). Because these systems are inherently involved in the function and pathophysiology of CNS, drugs that modulate mGluRs can have multiple modulatory/therapeutic effects throughout the CNS.

PHARMACOLOGY

MGluRs and Neuroprotection

Many studies support a role for group I mGluR modulation in both *in vivo* and *in vitro* models of CNS injury (163). In general, non subtype-specific inhibition of group I mGluRs tends to be neuroprotective. In animal models of head injury, NMDA toxicity and global ischemia, as well as *in vitro* models of trauma and ischemia the activation of group I mGluR is neurotoxic (1,6,36,37,63,110,123,188).

Differential effects for the mGluR1 and mGluR5 subtypes have been observed. These may reflect differences in desensitization factors (3,66,136); regulation of intracellular calcium signaling (93); interactions with iGluRs and ion channels via homer; PSD-95 complexes and Shank (30,92,168,199,200); signaling through various heterotrimeric G-protein subunits (45,67); regulation of mGluR mediated responses by regulators of G-protein signaling proteins (161); or expression pattern differences attributable to anatomical location (131,132,169,196), ontogeny (11,23,41,71,155,172,174), injury (64,76,88,117, 119), or disease (4,12,27,43,132,156,175).

Endogenous activation of group I mGluRs induces multifactorial processes underlying neurotoxicity (1,6,36,37,63,110,123,188) including:

1) amplification of neuronal degeneration through iGluR-induced zinc flux and concomitant production of reactive oxygen species (40,42,44,56,72,73,166,168,170,171,191);
2) reduction of the Mg^{2+} block of NMDA receptors (102,103,215);
3) enhancement of glutamate release by decreasing endogenous inhibition (19,35);
4) the release of Ca^{2+} from intracellular stores via IP3 dependent mechanisms (208); and
5) induction of the production of arachidonic acid (61), as well as other mechanisms.

Because of the direct association between positive modulation of group I mGluRs and the potentiating effects on iGluRs, care must be taken in interpreting results obtained with non-specific group I mGluR modulators, especially compounds that can directly regulate

iGluR activity (135). Moreover, it is important to differentiate the specific contributions of mGluR1 and mGluR5. In relation to cell death phenotype and the pathophysiologically-induced position within the apoptosis/necrosis continuum, this separation is especially important (104). Multiple models of CNS injury, including stroke, brain trauma and spinal cord injury (36,63,110,114,119), suggest that activation of mGluR1 (124) can exacerbate necrosis (1,36,37,63,122,123,135,188). In contrast, the mGluR5 subtype (122) appears to attenuate apoptosis (5,6,52).

2-Methyl-6-(phenylethynyl)pyridine (MPEP)

One of the first mGluR5 subtype specific antagonists used to help separate the effects of mGluR5 from mGluR1 induced by non-specific group I mGluR agonists/antagonists is 2,6-disubstituted pyridine 2-methyl-6-(phenylethynyl)pyridine (MPEP) (68,69,163). MPEP non-competitively inhibits mGluR5 through a novel allosteric site (68,69,141) reducing the efficacy of glutamate-stimulated phosphoinositide (PI) hydrolysis without affecting the Hill coefficient or EC_{50} of glutamate (68,163). MPEP completely inhibits quisqualate-stimulated PI hydrolysis (IC_{50} = 36 nM) (69) and is without effect on human mGluR6 (≤10 μM), mGluR1b (≤30 μM), or mGlu2, -3, -4a, -7b, or -8a (≤100 μM) (69). Similarly, in the rat hippocampus, MPEP (10 mg/kg i.p.) blocks dose-dependent (RS)-2-chloro-5-hydroxyphenylglycine (CHPG)-induced increases in PI hydrolysis (8). It has been proposed that such inhibition results from MPEP stabilizing the inactive conformation of mGluR5 by preventing the association of the transmembrane-6 and -3 helices (111).

In vivo receptor occupancy studies of MPEP (10 mg/kg i.p.) demonstrate significant species variability. For example, in rat brain, MPEP can maintain >75% receptor occupancy for up to 2 h, whereas, in mouse brain >75% receptor occupancy only lasts up to 15 min (7). Binding studies have demonstrated that the mGluR5 antagonist [^{3}H]methoxymethyl-MTEP, which has high affinity (K_d = 20 ± 2.7 nM), is displaced by MPEP with an IC_{50} value of 15 nM (8). In rats, systemic administration of unlabeled MPEP reduced the binding of [^{3}H]methoxymethyl-MTEP with an ID_{50} value of 2 mg/kg i.p. (8).

Over the past several years, MPEP has been used to study the potential role of the mGluR5 subtype in neuroprotection (16,18–20,26,35,38,75,105,114,119,154,158), Parkinson's disease (10,20,31,32,50,60,65,74,91,137,140,158,181,201,205,207,210), Huntington's disease (65,164), epilepsy (2,17,65,106,109,112,113,115,116,120,124,178,187,198), Fragile X syndrome (13,211), addiction (107,145,195,214), anxiety (15,29,33,34,39,49,54,55,81,90,97,98,142,149,151,153,159,165,180,182–185,192,203,209), nociception (22,78,99,108,125,143,144,190,206,216), learning and memory (173), lateral geniculate nucleus relay cell communication (57), thalamic sensory processing (160), signal discrimination in the semicircular canals (82), and others (177).

Unfortunately, in addition to acting as an mGluR5 specific antagonist. MPEP has been reported to have electrophysiological effects on human NMDA1A/2B (10 μM), NMDA1A/2A (100 μM) and kainate Glu6-(IYQ) (100 μM) receptor subtypes. In addition, effects on rat AMPA Glu3-(flop) (100 μM) expressed in *Xenopus laevis* oocytes (69) and on rat NMDA receptors in rat primary cortical neurons (20 μM) have been observed (135). See Table 1 for actions and selectivity of MPEP and MTEP.

TABLE 1. MPEP and MTEP: Meachanism(s) of action and selectivity

Name	Mechanism(s) of action	Off-site effects
MPEP, 2-methyl-6-(phenyl-ethynyl)pyridine	1) Non-competitive mGluR5 antagonist	1) mGluR1d, IC_{50} > 10 μM
	2) Allosteric modulator	2) NR2B IC_{50} = 18 μM
	3) Inhibits PLC/IP3/DAG	3) MAOA, IC_{50} = 8 μM
MTEP, 3-[(2-methyl-1,3-thi-azol-4-yl)ethynyl]pyridine	1) Non-competitive mGluR5 antagonist	1) mGluR1d, IC_{50} > 10 μM
	2) Inhibits PLC/IP3/DAG	2) NR2B IC_{50} > 300 μM
		3) MAOA, IC_{50} = 30 μM

MPEP and MTEP are mGluR5 specific antagonists that inhibit the PLC/Gq/IP3/DAG second messenger cascade (7,8,53,54,68,69,163). Although both compounds have off-site effects (54), MTEP is better suited for paradigms in which NMDA receptors play a significant role.

3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP)

The recently developed MTEP was expected to have less non-specific effects than MPEP. Initial characterization of MTEP in an *in vitro* Ca^{2+} flux assay provided an IC_{50} of 5 nM and a K_i of 16 nM (54). Furthermore, MTEP has a log *D* value of 2.1 compared with 3.5 for MPEP (54) indicating better solubility and CNS penetrability. *In vivo* and *in vitro* characterization of MTEP (7,8,53) indicates that it is highly selective for mGluR5 and has no significant effect on other mGluR subtypes. Moreover, MTEP has fewer off-target effects than MPEP, such as minimal inhibition of NMDA/glycine-evoked increases in recombinant human NR1A/2B receptor-mediated intracellular calcium (MTEP: 19% at 300 μM; MPEP: IC_{50} = 18 μM) (53,54). Taken together, these results suggest that MTEP has greater selectivity at mGluR5 than other known antagonists (53).

In vivo and *in vitro* studies indicate that the cytochrome P450 (CYP) isoforms CYP1A1/2, CYP2C6 and CYP2C11 are primarily responsible for the metabolism of MTEP (77). The major oxidative metabolites of MTEP are a hydroxymethyl metabolite, two oxides, a thiazole-ring opened metabolite and CO_2 (212). Metabolism of MTEP (1 μM) in dog, monkey and human hepatic microsomes was similar (approximately 65%) (77). Metabolic stability studies accurately predicted the *in vivo* clearance for MTEP (2 mg/kg, i.v. and 10 mg/kg p.o.) in rats; (Clp = 28.5 ± 2.3 mL/min/kg; VDss = 8.4 ± ± 1.4 L/kg; terminal $t_{1/2}$ = 8.3 ± 0.9 h; 16% bioavailability) (77). Administration of MTEP (1 mg/kg, i.v.) to rhesus monkeys resulted in a Clp of ~42 mL/min/kg (77).

Similar to MPEP, *in vivo* receptor occupancy studies of MTEP (3 mg/kg i.p.) demonstrate significant species variability. In rat brain, MTEP also maintains >75% receptor occupancy for 2 h, whereas, in mouse brain >75% occupancy lasts for only 30 and 15 min (7).

The Role of mGluR5 in Neurodegeneration

As mentioned above *in vivo* and *in vitro* studies suggest that activation of the mGluR5 subtype is neuroprotective through its ability to attenuate apoptosis (5,6,52,121), and does not appear to modulate necrosis. This concept is supported by multiple studies. For ex-

ample, use of antisense oligonucleotides against group I mGluR revealed that inhibition of mGluR1, but not mGluR5 is neuroprotective (123) in an *in vitro* necrotic injury model. In a model of global ischemia, 10 pmol MPEP (2× i.c.v.) or 10 mg/kg MPEP (2× i.p.) had no effect on CA1 pyramidal cell death (114). Similarly, *in vitro*, MPEP (0.1–1 μM) had no effect on oxygen and glucose deprivation-induced neuronal damage (114). Further support was provided by studies in which the group I mGluR agonist (S)-3,5-dihydroxyphenylglycine (DHPG) or the mGluR5 selective agonist, (RS)-2-chloro-5-hydroxyphenylglycine (CHPG) decreased apoptotic cell death induced by either the non-specific protein kinase C (PKC) inhibitor staurosporine or the topoisomerase II inhibitor etoposide (6). The DHPG effects were blocked by MPEP but not by a mGluR1 antagonist (6).

Nevertheless, it has been reported that MPEP is neuroprotective (16,19,20,38,154). For example, in a model of parkinsonism, MPEP (4 × 5 mg/kg, i.p. injections, 30 min before each MPTP injection) was protective against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; 80 mg/kg) toxicity (20). In another study, pretreatment with MPEP improved cognitive and motor functions and reduced lesion volume following lateral fluid percussion injury (FPI) (122). In a rat intraluminal filament model of temporary middle cerebral artery occlusion, a model for focal cerebral ischemia, MPEP also appears to be neuroprotective (16). Combined, these studies suggest that perhaps in certain *in vivo* models, mGluR5 activation exacerbates injury. However, in the latter study above, activation of mGluR5 with CHPG after focal cerebral ischemia, also reduced 24 h infarct volume in a dose-dependent manner (16). Hence, in the temporary middle cerebral artery occlusion model, both CHPG and MPEP were neuroprotective. It is important to note that even though early (15 min) post-injury treatment with optimal dose MPEP provided neuroprotection, delayed (135 min post-injury) treatment was not effective (16). These conflicting data can be explained by experiments which show the ability of MPEP to inhibit NMDA receptor activity, in addition to acting as an mGluR5 antagonist (16,123). Moreover, the ability of CHPG to provide neuroprotection can potentially be explained by its anti-apoptotic activity (6).

To address the important question as to whether mGluR5 antagonists provide neuroprotection, in part, through their ability to directly modulate NMDA receptor activity, the effects of MTEP or MPEP were tested in cultured cortical neurons derived from rat and either wild-type (WT) or mGluR5(–/–) mice exposed to NMDA- or glutamate-induced toxicity (105). These two well-established *in vitro* models of neuronal injury produce significant cell death within 24 h (122,135). The mGluR5 knockout mouse cortical cultures were used to address whether MPEP-mediated neuroprotection against NMDA-induced neurotoxicity occurs independent of mGluR5. Pretreatment with MPEP (20 μM and higher) showed significant neuroprotection as revealed by either LDH release or calcein AM assays. In contrast, pretreatment with MTEP (2 to 100 μM) had no effect (105). Both MPEP and MTEP at 200 μM decreased NMDA-induced cell death in cortical cultures from mGluR5-knockouts. Thus, blockade of neuronal mGluR5 is not protective against glutamate receptor mediated cell death, and the use of mGluR5 antagonists at high concentrations can lead to neuroprotection through mechanisms not associated with mGluR5 modulation.

In summary, multiple lines of evidence indicate the necessity to distinguish between the group I mGluR subtypes 1 and 5. With regard to neuroprotection, mGluR1 activation appears to exacerbate necrosis, whereas mGluR5 activation protects against apoptosis.

Although the mGluR5 specific antagonist MPEP has been used extensively to determine the role of mGluR5 in CNS function and pathology, its non-specific effects, such as inhibition of NMDA receptors, may make it difficult to assign specific physiological roles for mGluR5 using this compound. Unlike MPEP, the newer mGluR5 antagonist MTEP does not provide neuroprotection at doses that are both optimal for mGluR5 blockade, in part, because it does not have direct effects upon NMDA receptor activity.

A Role for mGluR5 in Addiction and Pain

Addiction

In addition to its role in neurodegeneration, mGluR5 studies using MPEP and/or MTEP suggest that mGluR5 contributes to the processes underlying addiction. Drug cues can recruit responses in the amygdala, anterior cingulate, orbital prefrontal and dorsolateral prefrontal cortex, and nucleus accumbens (89). Moreover, the ventral tegmental area-nucleus accumbens pathway appears to be the central regulator of reward signals induced by drugs of abuse (126). It has been proposed that addiction, in part, involves certain molecular mechanisms that underlie learning and memory (89,126). Because many of these addiction-associated regions participate in learning and memory, and because both iGluRs and mGluRs are intimately involved in such processes, it is not surprising that glutamate receptors appear, in part, to underlie mechanisms associated with addiction.

Both iGluRs and mGluRs are implicated in the behavioral effects of psychostimulants (96,191,205). For example, acute cocaine treatment significantly reduces the mRNA level for GluR3, GluR4, and NMDAR1 subunits in the nucleus accumbens, and NMDAR1 mRNA levels in dorsolateral striatum and the ventral tegmental area (70). Moreover, repeated cocaine administration significantly increases levels of GluR2 mRNA in prefrontal cortex and mGluR5 mRNA levels in the nucleus accumbens and dorsolateral striatum (70). Additional studies using mGlu5 (–/–) mice also support a role for mGluR5 in cocaine self-administration and cocaine-induced locomotor sensitization (47).

Studies using MPEP or MTEP have also implicated mGluR5 in effects caused by psychostimulants (83,84,94,107,145,148), nicotine (80,94,146,147,195,214), or ethanol (14, 55,85,135,164). MPEP dose-dependently (1–9 mg/kg) decreases nicotine (rats: 0.01 or 0.03 mg/kg/infusion; mice: 0.048 mg/infusion) or cocaine (0.25 mg/infusion) self-administration, but does not appear to alter acute nicotine (0.25 mg) or cocaine (10 mg/kg)-induced facilitation of brain reward function in rats (94). MPEP (50 mg/kg) also blocks expression of context-conditioned morphine (10 mg/kg) or amphetamine but not cocaine (10 mg/kg) or 3,4-methylenedioxymethamphetamine (MDMA) reward in the rat (83,84). In addition, MPEP (5 mg/kg i.p.) significantly enhances the locomotor activity increased by PCP (phencyclidine; 2.5 mg/kg s.c.) (148), but inhibits amphetamine (1 mg/kg s.c.)-induced hyperactivity (148).

In squirrel monkeys, MPEP attenuated cocaine self-administration, cocaine-induced reinstatement of drug seeking and the discriminative stimulus effects of cocaine at doses that did not markedly impair motor function or operant behavior in the context of drug discrimination (107). Although MPEP exhibits some selectivity for mGluR5 receptors *in vitro* and *in vivo* (69,197), it also has the ability to directly reduce NMDA receptor activity (134) and to interact functionally with NMDA receptors in rats (87,152). Thus, the ability of MPEP to elicit cocaine-attenuating effects may reflect, at least in part, modulation of

NMDA receptor activity. Moreover, although these findings suggest that mGluR5 antagonists may be a valuable tool against addiction, chronic use of MPEP is potentially problematic due to its effects on the NMDA receptor.

To date, relatively few studies have used MTEP to examine the role of mGluR5 in addiction. In a naloxone-precipitated morphine withdrawal model, MTEP (1–10 mg/kg) dose-dependently inhibited naloxone-induced symptoms of morphine withdrawal, without effects on locomotor activity (145). In another study, MTEP was effective in models of ethanol addiction (85). Together, the experimental studies with MPEP or MTEP suggest that blocking mGlu5 receptors may provide a novel and effective pharmacotherapeutic approach for the treatment of certain types of drug dependence and addiction.

Nociception

A role for group I mGluRs, including mGluR5, in nociception has been well established by functional studies (95,127,129,157,202). Nociceptive responses of thalamic neurons are mediated in part by mGlu5 receptors (25). In a model of cannabinoid-induced anti-nociception in the periaqueductal grey (PAG) matter of rats, MPEP prevented the ability of the cannabinoid receptor agonist (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate (WIN 55,212-2) to increase nociceptive reaction latency in the plantar test. Moreover, studies indicate that mGlu5 receptors may modulate nociception in the periaqueductal grey (PAG) matter of rats (144) and that antihyperalgesic effects of WIN 55,212-2 are mediated through interactions with spinal metabotropic glutamate-5 receptors (79). MPEP (50 nmol) also blocked increases in nociceptive reaction induced by intra-periaqueductal grey matter microinjections of capsaicin (1–3–6 nmol/rat) (143).

A role for mGluR5 in nociception is further supported by studies showing that in response to noxious stimuli, there are changes in mGluR5 expression (59,88,118). Such changes can lead to altered gene expression (24) and synaptic plasticity (128) within the sensory elements of the nociceptive pathways. For example, nerve injury-induced increases in mGluR5 in lumbar DRG A-fiber somata correlated with the ability of MPEP to dose-dependently reverse thermal hyperalgesia following L5 spinal nerve ligation. Such results led these authors to suggest that after L5 spinal nerve injury, mGluR5 expression on A-fibers may be essential for the development of thermal hyperalgesia (88).

It is also suggested that mGluR5 can modulate pain due to inflammation and neuropathy (95). For example, in multiple rodent models (218), MPEP (3–30 mg/kg, i.p.) produced a dose-dependent reversal of thermal and mechanical hyperalgesia following complete Freund's adjuvant (CFA)-induced inflammatory hypersensitivity. In addition, MPEP decreased thermal hyperalgesia observed in carrageenan-induced inflammatory hypersensitivity without affecting paw edema. Moreover, MPEP abolished acetic acid-induced writhing activity in mice, and was shown to reduce mechanical allodynia and thermal hyperalgesia observed in a model of post-operative hypersensitivity and formalin-induced spontaneous pain. At 30 mg/kg, i.p., MPEP also significantly attenuated mechanical allodynia observed in three neuropathic pain models: spinal nerve ligation, sciatic nerve constriction and vincristine-induced neuropathic pain. Similar to MPEP, MTEP (3–30 mg/kg, i.p.) also reduced complete CFA-induced thermal hyperalgesia. At 100 mg/kg, i.p., however, both MPEP and MTEP showed CNS side effects as measured by rotarod performance and exploratory locomotor activity (218).

Both MPEP and MTEP were also tested in the mouse formalin and rat spinal nerve ligation (SNL) pain models, as well as in anxiety models including the Vogel conflict and conditioned lick suppression (CLS) tests for anxiety (203). Systemic administration of MPEP and MTEP reduced hyperalgesia induced by formalin and mechanical allodynia following SNL and showed anxiolytic effects (203).

Additional studies in rats showed that MPEP, in a dose-dependent and reversible manner, blocked pressure-induced responses to contralateral hindpaw nociceptive neurons within the ventroposterolateral thalamus (28). In a spinal cord *in vitro* model, MPEP (30 μM, 60 min) attenuated ventral root potentials following single shock electrical stimulation of the dorsal root and inhibited responses evoked by repetitive stimulation (28).

Finally, it has also been suggested that both peripheral and central mGluR5 receptors may play a role in nociceptive transmission observed during post-operative pain in rats (217). In this model, MPEP (ED_{50} = 15 mg/kg, i.p.) showed dose-dependent effects. Overall, experimental pain studies using both MPEP and MTEP support a role for mGluR5 in nociceptive processes and suggest that selective modulation of mGlu5 receptors may provide a new pharmacotherapeutic approach for certain types of pain.

SUMMARY

Multiple studies using the mGluR5 antagonists MPEP and MTEP suggest that the mGluR5 receptor may be involved in physiological or pathophysiological responses associated with neurodegeneration, addiction, pain and anxiety. However, given non-specific effects of MPEP, studies in which this compound alone was used to infer a role for mGluR5 actions should be re-assessed with more selective compounds such as MTEP or by using receptor knockout animals.

Conflict of Interest Statement. Dr. Lea is employed by New Health Sciences, Inc (NHSi). NHSi is not developing MPEP or MTEP for clinical use.

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REFERENCES

1. Agrawal SK, Theriault E, Fehlings MG. Role of group I metabotropic glutamate receptors in traumatic spinal cord white matter injury. *J Neurotrauma* 1998;15:929–941.
2. Akbas SH, Yegin A, Ozben T. Effect of pentylenetetrazol-induced epileptic seizure on the antioxidant enzyme activities, glutathione and lipid peroxidation levels in rat erythrocytes and liver tissues. *Clin Biochem* 2005;38:1009–1014.
3. Alagarsamy S, Marino MJ, Rouse ST, Gereau RWt, Heinemann SF, Conn PJ. Activation of NMDA receptors reverses desensitization of mGluR5 in native and recombinant systems. *Nat Neurosci* 1999;2: 234–240.
4. Al-Ghoul WM, Meeker RB, Greenwood RS. Kindled seizures increase metabotropic glutamate receptor expression and function in the rat supraoptic nucleus. *J Neurosci Res* 1998;54:412–423.

5. Allen JW, Eldadah BA, Faden AI. Beta-amyloid-induced apoptosis of cerebellar granule cells and cortical neurons: exacerbation by selective inhibition of group I metabotropic glutamate receptors. *Neuropharmacology* 1999;38:1243–1252.
6. Allen JW, Knoblach SM, Faden AI. Activation of group I metabotropic glutamate receptors reduces neuronal apoptosis but increases necrotic cell death *in vitro*. *Cell Death Differ* 2000;7:470–476.
7. Anderson JJ, Bradbury MJ, Giracello DR, et al. *In vivo* receptor occupancy of mGlu5 receptor antagonists using the novel radioligand [^{3}H]3-methoxy-5-(pyridin-2-ylethynyl)pyridine). *Eur J Pharmacol* 2003;473: 35–40.
8. Anderson JJ, Rao SP, Rowe B, et al. [^{3}H]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;303:1044–1051.
9. Anwyl R. Metabotropic glutamate receptors: Electrophysiological properties and role in plasticity. *Brain Res Brain Res Rev* 1999;29:83–120.
10. Armentero MT, 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* 2005;22:1–9.
11. Aronica E, Dell'Albani P, Condorelli DF, Nicoletti F, Hack N, Balazs R. Mechanisms underlying developmental changes in the expression of metabotropic glutamate receptors in cultured cerebellar granule cells: Homologous desensitization and interactive effects involving *N*-methyl-D-aspartate receptors. *Mol Pharmacol* 1993;44:981–989.
12. Aronica EM, Gorter JA, Paupard MC, Grooms SY, Bennett MV, Zukin RS. Status epilepticus-induced alterations in metabotropic glutamate receptor expression in young and adult rats. *J Neurosci* 1997;17: 8588–8595.
13. Aschrafi A, Cunningham BA, Edelman GM, Vanderklish PW. The fragile X mental retardation protein and group I metabotropic glutamate receptors regulate levels of mRNA granules in brain. *Proc Natl Acad Sci USA* 2005;102:2180–2185.
14. Backstrom P, Bachteler D, Koch S, Hyytia P, Spanagel R. mGluR5 antagonist MPEP reduces ethanol-seeking and relapse behavior. *Neuropsychopharmacology* 2004;29:921–928.
15. Ballard TM, Woolley ML, 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; 179:218–229.
16. Bao WL, Williams AJ, Faden AI, Tortella FC. Selective mGluR5 receptor antagonist or agonist provides neuroprotection in a rat model of focal cerebral ischemia. *Brain Res* 2001;922:173–179.
17. Barton ME, Peters SC, Shannon HE. Comparison of the effect of glutamate receptor modulators in the 6 Hz and maximal electroshock seizure models. *Epilepsy Res* 2003;56:17–26.
18. Baskys A, Bayazitov I, Fang L, Blaabjerg M, Poulsen FR, Zimmer J. Group I metabotropic glutamate receptors reduce excitotoxic injury and may facilitate neurogenesis. *Neuropharmacology* 2005;49(Suppl 1): 146–156.
19. Battaglia G, Bruno V, Pisani A, et al. Selective blockade of type-1 metabotropic glutamate receptors induces neuroprotection by enhancing gabaergic transmission. *Mol Cell Neurosci* 2001;17:1071–1083.
20. Battaglia G, Busceti CL, 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;24:828–835.
21. Bayer KU, De Koninck P, Leonard AS, Hell JW, Schulman H. Interaction with the NMDA receptor locks CaMKII in an active conformation. *Nature* 2001;411:801–805.
22. Berrino L, Oliva P, Rossi F, Palazzo E, Nobili B, Maione S. Interaction between metabotropic and NMDA glutamate receptors in the periaqueductal grey pain modulatory system. *Naunyn Schmiedeberg's Arch Pharmacol* 2001;364:437–443.
23. Berthele A, Boxall SJ, Urban A, et al. Distribution and developmental changes in metabotropic glutamate receptor messenger RNA expression in the rat lumbar spinal cord. *Brain Res Dev Brain Res* 1999;112: 39–53.
24. Bianchi R, Rezzani R, Borsani E, Rodella L. mGlu5 receptor antagonist decreases Fos expression in spinal neurons after noxious visceral stimulation. *Brain Res* 2003;960:263–266.
25. Binns KE, Salt TE. Actions of the systemically active metabotropic glutamate antagonist MPEP on sensory responses of thalamic neurones. *Neuropharmacology* 2001;40:639–644.

26. Blaabjerg M, Fang L, Zimmer J, Baskys A. Neuroprotection against NMDA excitotoxicity by group I metabotropic glutamate receptors is associated with reduction of NMDA stimulated currents. *Exp Neurol* 2003; 183:573–580.
27. Blumcke I, Becker AJ, Klein C, et al. Temporal lobe epilepsy associated up-regulation of metabotropic glutamate receptors: Correlated changes in mGluR1 mRNA and protein expression in experimental animals and human patients. *J Neuropathol Exp Neurol* 2000;59:1–10.
28. Bordi F, Ugolini A. Involvement of mGluR(5) on acute nociceptive transmission. *Brain Res* 2000;871: 223–233.
29. Bradbury MJ, Giracello DR, Chapman DF, et al. Metabotropic glutamate receptor 5 antagonist-induced stimulation of hypothalamic-pituitary-adrenal axis activity: Interaction with serotonergic systems. *Neuropharmacology* 2003;44:562–572.
30. Brakeman PR, Lanahan AA, O'Brien R, et al. Homer: A protein that selectively binds metabotropic glutamate receptors [see comments]. *Nature* 1997;386:284–288.
31. 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;23:8302–8309.
32. 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;22:5669–5678.
33. Brodkin J, Bradbury M, Busse C, Warren N, Bristow LJ, Varney MA. Reduced stress-induced hyperthermia in mGluR5 knockout mice. *Eur J Neurosci* 2002;16:2241–2244.
34. Brodkin J, Busse C, Sukoff SJ, Varney MA. Anxiolytic-like activity of the mGluR5 antagonist MPEP a comparison with diazepam and buspirone. *Pharmacol Biochem Behav* 2002;73:359–366.
35. Bruno V, Battaglia G, Copani A, et al. Metabotropic glutamate receptor subtypes as targets for neuroprotective drugs. *J Cereb Blood Flow Metab* 2001;21:1013–1033.
36. Bruno V, Battaglia G, Kingston A, et al. Neuroprotective activity of the potent and selective mGlu1a metabotropic glutamate receptor antagonist, (+)-2-methyl-4 carboxyphenylglycine (LY367385): Comparison with LY357366, a broader spectrum antagonist with equal affinity for mGlu1a and mGlu5 receptors. *Neuropharmacology* 1999;38:199–207.
37. Bruno V, Copani A, Knopfel T, et al. Activation of metabotropic glutamate receptors coupled to inositol phospholipid hydrolysis amplifies NMDA-induced neuronal degeneration in cultured cortical cells. *Neuropharmacology* 1995;34:1089–1098.
38. Bruno V, Ksiazek I, Battaglia G, et al. Selective blockade of metabotropic glutamate receptor subtype 5 is neuroprotective. *Neuropharmacology* 2000;39:2223–2230.
39. Busse CS, 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;29:1971–1979.
40. Carmody RJ, McGowan AJ, Cotter TG. Reactive oxygen species as mediators of photoreceptor apoptosis *in vitro*. *Exp Cell Res* 1999;248:520–530.
41. Catania MV, Landwehrmeyer GB, Testa CM, Standaert DG, Penney JB, Jr., Young AB. Metabotropic glutamate receptors are differentially regulated during development. *Neuroscience* 1994;61:481–495.
42. Cebers G, Zhivotovsky B, Ankarcrona M, Liljequist S. AMPA neurotoxicity in cultured cerebellar granule neurons: Mode of cell death. *Brain Res Bull* 1997;43:393–403.
43. Cha JH, Kosinski CM, Kerner JA, et al. Altered brain neurotransmitter receptors in transgenic mice expressing a portion of an abnormal human huntington disease gene. *Proc Natl Acad Sci USA* 1998;95: 6480–6485.
44. Chan SL, Griffin WS, Mattson MP. Evidence for caspase-mediated cleavage of AMPA receptor subunits in neuronal apoptosis and Alzheimer's disease. *J Neurosci Res* 1999;57:315–323.
45. Chang M, Zhang L, Tam JP, Sanders-Bush E. Dissecting G protein-coupled receptor signaling pathways with membrane- permeable blocking peptides. Endogenous 5-HT_{2C} receptors in choroid plexus epithelial cells. *J Biol Chem* 2000;275:7021–7029.
46. Chen N, Luo T, Raymond LA. Subtype-dependence of NMDA receptor channel open probability. *J Neurosci* 1999;19:6844–6854.
47. Chiamulera C, Epping-Jordan MP, Zocchi A, et al. Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice. *Nat Neurosci* 2001;4:873–874.
48. Choi DW, Yokoyama M, Koh J. Zinc neurotoxicity in cortical cell culture. *Neuroscience* 1988;24:67–79.
49. Chojnacka-Wojcik E, Klodzinska A, Pilc A. Glutamate receptor ligands as anxiolytics. *Curr Opin Invest Drugs* 2001;2:1112–1119.

50. Coccurello R, Breysse N, Amalric M. Simultaneous blockade of adenosine A2A and metabotropic glutamate mGlu5 receptors increase their efficacy in reversing Parkinsonian deficits in rats. *Neuropsychopharmacology* 2004;29:1451–1461.
51. Conn PJ, Pin JP. Pharmacology and functions of metabotropic glutamate receptors. *Annu Rev Pharmacol Toxicol* 1997;37:205–237.
52. Copani A, Bruno V, Battaglia G, et al. Activation of metabotropic glutamate receptors protects cultured neurons against apoptosis induced by beta-amyloid peptide. *Mol Pharmacol* 1995;47:890–897.
53. Cosford ND, Roppe J, Tehrani L, et al. [^{3}H]-methoxymethyl-MTEP and [^{3}H]-methoxy-PEPy: potent and selective radioligands for the metabotropic glutamate subtype 5 (mGlu5) receptor. *Bioorg Med Chem Lett* 2003;13:351–354.
54. Cosford ND, 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; 46:204–206.
55. Cowen MS, Djouma E, Lawrence AJ. The metabotropic glutamate 5 receptor antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine reduces ethanol self-administration in multiple strains of alcohol-preferring rats and regulates olfactory glutamatergic systems. *J Pharmacol Exp Ther* 2005;315:590–600.
56. Davis PK, Johnson GV. Energy metabolism and protein phosphorylation during apoptosis: A phosphorylation study of tau and high-molecular-weight tau in differentiated PC12 cells. *Biochem J* 1999;340:51–58.
57. de Labra C, Rivadulla C, Cudeiro J. Modulatory effects mediated by metabotropic glutamate receptor 5 on lateral geniculate nucleus relay cells. *Eur J Neurosci* 2005;21:403–410.
58. Dingledine R, Borges K, Bowie D, Traynelis SF. The glutamate receptor ion channels. *Pharmacol Rev* 1999; 51:7–61.
59. Dolan S, Kelly JG, Monteiro AM, Nolan AM. Up-regulation of metabotropic glutamate receptor subtypes 3 and 5 in spinal cord in a clinical model of persistent inflammation and hyperalgesia. *Pain* 2003;106: 501–512.
60. Domenici MR, Potenza RL, Martire A, et al. Chronic treatment with the mGlu5R antagonist MPEP reduces the functional effects of the mGlu5R agonist CHPG in the striatum of 6-hydroxydopamine-lesioned rats: Possible relevance to the effects of mGlu5R blockade in Parkinson's disease. *J Neurosci Res* 2005;80: 646–654.
61. Faden A, Allen J, Knoblach S. Exacerbation of neuronal death by activation of group I metabotropic glutamate receptors: Role of NMDA receptors and arachidonic acid release. *Abstracts of the 29th Annual Meeting of the Society for Neuroscience*. Miami Beach, FL, 1999; Abs 112.10.
62. Faden AI, Demediuk P, Panter SS, Vink R. The role of excitatory amino acids and NMDA receptors in traumatic brain injury. *Science* 1989;244:798–800.
63. Faden AI, O'Leary DM, Fan L, Bao W, Mullins PG, Movsesyan VA. Selective blockade of the mGluR1 receptor reduces traumatic neuronal injury *in vitro* and improves outcome after brain trauma. *Exp Neurol* 2001;167:435–444.
64. Ferraguti F, Corti C, Valerio E, Mion S, Xuereb J. Activated astrocytes in areas of kainate-induced neuronal injury upregulate the expression of the metabotropic glutamate receptors 2/3 and 5. *Exp Brain Res* 2001; 137:1–11.
65. Flor PJ, Battaglia G, Nicoletti F, Gasparini F, Bruno V. Neuroprotective activity of metabotropic glutamate receptor ligands. *Adv Exp Med Biol* 2002;513:197–223.
66. Francesconi A, Duvoisin RM. Opposing effects of protein kinase C and protein kinase A on metabotropic glutamate receptor signaling: Selective desensitization of the inositol trisphosphate/Ca^{2+} pathway by phosphorylation of the receptor-G protein-coupling domain. *Proc Natl Acad Sci USA* 2000;97:6185–6190.
67. Friberg IK, Young AB, Standaert DG. Differential localization of the mRNAs for the pertussis toxin insensitive G-protein alpha sub-units Gq, G11, and Gz in the rat brain, and regulation of their expression after striatal deafferentation. *Brain Res Mol Brain Res* 1998;54:298–310.
68. Gasparini F, Floersheim P, Flor PJ, et al. Discovery and characterization of non-competitive antagonists of group I metabotropic glutamate receptors. *Farmaco* 2001;56:95–99.
69. Gasparini F, Lingenhohl K, Stoehr N, et al. 2-Methyl-6-(phenylethynyl)-pyridine (MPEP), a potent, selective and systemically active mGlu5 receptor antagonist. *Neuropharmacology* 1999;38:1493–1503.
70. Ghasemzadeh MB, Nelson LC, Lu XY, Kalivas PW. Neuroadaptations in ionotropic and metabotropic glutamate receptor mRNA produced by cocaine treatment. *J Neurochem* 1999;72:157–165.
71. Ghosh PK, Baskaran N, van den Pol AN. Developmentally regulated gene expression of all eight metabotropic glutamate receptors in hypothalamic suprachiasmatic and arcuate nuclei — a PCR analysis. *Brain Res Dev Brain Res* 1997;102:1–12.

72. Goforth P, Ellis E, Satin L. Enhancement of AMPA-mediated current after traumatic injury in cortical neurons. *J Neurosci* 1999;19:P7367–7374.
73. Goforth PB, Ellis EF, Satin LS. Loss of AMPA receptor desensitization after mechanical injury of cortical neurons is dependent upon NMDA receptors and CAMKII. *Abstracts of the 30th Annual Meeting of the Society for Neuroscience*. New Orleans, 2000; Abs 186.13.
74. Golembiowska K, Konieczny J, Ossowska K, Wolfarth S. The role of striatal metabotropic glutamate receptors in degeneration of dopamine neurons: Review article. *Amino Acids* 2002;23:199–205.
75. 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;45:484–492.
76. Gong QZ, Phillips LL, Lyeth BG. Metabotropic glutamate receptor protein alterations after traumatic brain injury in rats. *J Neurotrauma* 1999;16:893–902.
77. Green MD, Yang X, Cramer M, King CD. *In vitro* metabolic studies on the selective metabotropic glutamate receptor sub-type 5 (mGluR5) antagonist 3-[(2-methyl-1,3-thiazol-4-yl) ethynyl]-pyridine (MTEP). *Neurosci Lett* 2006;391:91–95.
78. Hama AT. Acute activation of the spinal cord metabotropic glutamate subtype-5 receptor leads to cold hypersensitivity in the rat. *Neuropharmacology* 2003;44:423–430.
79. Hama AT, Urban MO. Antihyperalgesic effect of the cannabinoid agonist WIN 55,212-2 is mediated through an interaction with spinal metabotropic glutamate-5 receptors in rats. *Neurosci Lett* 2004;358: 21–24.
80. Harrison AA, Gasparini F, Markou A. Nicotine potentiation of brain stimulation reward reversed by DH beta E and SCH 23390, but not by eticlopride, LY 314582 or MPEP in rats. *Psychopharmacology (Berl)* 2002; 160:56–66.
81. Heidbreder CA, Bianchi M, Lacroix LP, et al. Evidence that the metabotropic glutamate receptor 5 antagonist MPEP may act as an inhibitor of the norepinephrine transporter *in vitro* and *in vivo*. *Synapse* 2003;50:269–276.
82. Hendricson AW, Guth PS. Signal discrimination in the semicircular canals: A role for group I metabotropic glutamate receptors. *Neuroreport* 2002;13:1765–1768.
83. Herzig V, Capuani EM, Kovar KA, Schmidt WJ. Effects of MPEP on expression of food-, MDMA- or amphetamine-conditioned place preference in rats. *Addict Biol* 2005;10:243–249.
84. Herzig V, Schmidt WJ. Effects of MPEP on locomotion, sensitization and conditioned reward induced by cocaine or morphine. *Neuropharmacology* 2004;47:973–984.
85. Hodge CW, Miles MF, Sharko AC, et al. The mGluR5 antagonist MPEP selectively inhibits the onset and maintenance of ethanol self-administration in C57BL/6J mice. *Psychopharmacology (Berl)* 2006;183: 429–438.
86. Holohean AM, Hackman JC, Davidoff RA. Mechanisms involved in the metabotropic glutamate receptor-enhancement of NMDA-mediated motoneurone responses in frog spinal cord. *Br J Pharmacol* 1999;126: 333–341.
87. Homayoun H, Stefani MR, Adams BW, Tamagan GD, Moghaddam B. Functional interaction between NMDA and mGlu5 Receptors: Effects on working memory, instrumental learning, motor behaviors, and dopamine release. *Neuropsychopharmacology* 2004;29:1259–1269.
88. Hudson LJ, Bevan S, McNair K, et al. Metabotropic glutamate receptor 5 upregulation in A-fibers after spinal nerve injury: 2-Methyl-6-(phenylethynyl)-pyridine (MPEP) reverses the induced thermal hyperalgesia. *J Neurosci* 2002;22:2660–2668.
89. Hyman SE. Addiction: A disease of learning and memory. *Am J Psychiatry* 2005;162:1414–1422.
90. Iijima M, Chaki S. Separation-induced ultrasonic vocalization in rat pups: Further pharmacological characterization. *Pharmacol Biochem Behav* 2005;82:652–657.
91. Kachroo A, Orlando LR, Grandy DK, Chen JF, Young AB, Schwarzschild MA. Interactions between metabotropic glutamate 5 and adenosine A2A receptors in normal and parkinsonian mice. *J Neurosci* 2005;25: 10414–10419.
92. Kammermeier PJ, Xiao B, Tu JC, Worley PF, Ikeda SR. Homer proteins regulate coupling of group I metabotropic glutamate receptors to N-type calcium and M-type potassium channels. *J Neurosci* 2000;20: 7238–7245.
93. Kawabata S, Kohara A, Tsutsumi R, et al. Diversity of calcium signaling by metabotropic glutamate receptors. *J Biol Chem* 1998;273:17381–17385.

94. Kenny PJ, Paterson NE, Boutrel B, et al. Metabotropic glutamate 5 receptor antagonist MPEP decreased nicotine and cocaine self-administration but not nicotine and cocaine-induced facilitation of brain reward function in rats. *Ann NY Acad Sci* 2003;1003:415–418.
95. Kew JN. Positive and negative allosteric modulation of metabotropic glutamate receptors: Emerging therapeutic potential. *Pharmacol Ther* 2004;104:233–244.
96. Kim JH, Vezina P. Metabotropic glutamate receptors in the rat nucleus accumbens contribute to amphetamine-induced locomotion. *J Pharmacol Exp Ther* 1998;284:317–322.
97. Klodzinska A, Tatarczynska E, Chojnacka-Wojcik E, Nowak G, Cosford ND, Pilc A. Anxiolytic-like effects of MTEP, a potent and selective mGlu5 receptor agonist does not involve GABA(A) signaling. *Neuropharmacology* 2004;47:342–350.
98. Klodzinska A, Tatarczynska E, Chojnacka-Wojcik E, Pilc A. Anxiolytic-like effects of group I metabotropic glutamate antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) in rats. *Pol J Pharmacol* 2000;52: 463–466.
99. Kozela E, Pilc A, Popik P. Inhibitory effects of MPEP, an mGluR5 antagonist, and memantine, an *N*-methyl-D-aspartate receptor antagonist, on morphine antinociceptive tolerance in mice. *Psychopharmacology (Berl)* 2003;165:245–251.
100. Krupp JJ, Vissel B, Thomas CG, Heinemann SF, Westbrook GL. Interactions of calmodulin and alpha-actinin with the NR1 subunit modulate Ca^{2+}-dependent inactivation of NMDA receptors. *J Neurosci* 1999;19: 1165–1178.
101. Lan JY, Skeberdis VA, Jover T, Zheng X, Bennett MV, Zukin RS. Activation of metabotropic glutamate receptor 1 accelerates NMDA receptor trafficking. *J Neurosci* 2001;21:6058–6068.
102. Lea PM, Custer SJ, Stoica BA, Faden AI. Modulation of stretch-induced enhancement of neuronal NMDA receptor current by mGluR1 depends upon presence of glia. *J Neurotrauma* 2003;20:1233–1249.
103. Lea PM, Custer SJ, Vicini S, Faden AI. Neuronal and glial mGluR5 modulation prevents stretch-induced enhancement of NMDA receptor current. *Pharmacol Biochem Behav* 2002;73:287–298.
104. Lea PM, Faden AI. Modulation of metabotropic glutamate receptors as potential treatment for acute and chronic neurodegenerative disorders. *Drug News Persp* 2003;16:513–522.
105. Lea PM, Movsesyan VA, Faden AI. Neuroprotective activity of the mGluR5 antagonists MPEP and MTEP against acute excitotoxicity differs and does not reflect actions at mGluR5 receptors. *Br J Pharmacol* 2005;145:527–534.
106. Lee AC, Wong RK, Chuang SC, Shin HS, Bianchi R. Role of synaptic metabotropic glutamate receptors in epileptiform discharges in hippocampal slices. *J Neurophysiol* 2002;88:1625–1633.
107. Lee B, Platt DM, Rowlett JK, Adewale AS, Spealman RD. Attenuation of behavioral effects of cocaine by the metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)-pyridine in squirrel monkeys: Comparison with dizocilpine. *J Pharmacol Exp Ther* 2005;312:1232–1240.
108. Li W, Neugebauer V. Differential roles of mGluR1 and mGluR5 in brief and prolonged nociceptive processing in central amygdala neurons. *J Neurophysiol* 2004;91:13–24.
109. Lojkova D, Mares P. Anticonvulsant action of an antagonist of metabotropic glutamate receptors mGluR5 MPEP in immature rats. *Neuropharmacology* 2005;49(Suppl 1):219–229.
110. Lyeth BG, Gong QZ, Shields S, Muizelaar JP, Berman RF. Group I metabotropic glutamate antagonist reduces acute neuronal degeneration and behavioral deficits after traumatic brain injury in rats. *Exp Neurol* 2001;169:191–199.
111. Malherbe P, Kratochwil N, Zenner MT, et al. Mutational analysis and molecular modeling of the binding pocket of the metabotropic glutamate 5 receptor negative modulator 2-methyl-6-(phenylethynyl)-pyridine. *Mol Pharmacol* 2003;64:823–832.
112. Mares P, Folbergrova J, Kubova H. Excitatory aminoacids and epileptic seizures in immature brain. *Physiol Res* 2004;53(Suppl 1):S115–124.
113. Mares P, Mikulecka A. MPEP, an antagonist of metabotropic glutamate receptors, exhibits anticonvulsant action in immature rats without a serious impairment of motor performance. *Epilepsy Res* 2004;60:17–26.
114. Meli E, Picca R, Attucci S, et al. Activation of mGlu1 but not mGlu5 metabotropic glutamate receptors contributes to postischemic neuronal injury *in vitro* and *in vivo*. *Pharmacol Biochem Behav* 2002;73: 439–446.
115. Merlin LR. Differential roles for mGluR1 and mGluR5 in the persistent prolongation of epileptiform bursts. *J Neurophysiol* 2002;87:621–625.
116. Micheli F. Methylphenylethynylpyridine (MPEP) Novartis. *Curr Opin Invest Drugs* 2000;1:355–359.

117. Miller S, Romano C, Cotman CW. Growth factor upregulation of a phosphoinositide-coupled metabotropic glutamate receptor in cortical astrocytes. *J Neurosci* 1995;15:6103–6109.
118. Mills CD, Fullwood SD, Hulsebosch CE. Changes in metabotropic glutamate receptor expression following spinal cord injury. *Exp Neurol* 2001;170:244–257.
119. Mills CD, Johnson KM, Hulsebosch CE. Group I metabotropic glutamate receptors in spinal cord injury: Roles in neuroprotection and the development of chronic central pain. *J Neurotrauma* 2002;19:23–42.
120. Moldrich RX, Chapman AG, De Sarro G, Meldrum BS. Glutamate metabotropic receptors as targets for drug therapy in epilepsy. *Eur J Pharmacol* 2003;476:3–16.
121. Montoliu C, Llansola M, Cucarella C, Grisolia S, Felipo V. Activation of the metabotropic glutamate receptor mGluR5 prevents glutamate toxicity in primary cultures of cerebellar neurons. *J Pharmacol Exp Ther* 1997;281:643–647.
122. Movsesyan VA, O'Leary DM, Fan L, et al. mGluR5 antagonists 2-methyl-6-(phenylethynyl)-pyridine and (E)-2-methyl-6-(2-phenylethenyl)-pyridine reduce traumatic neuronal injury *in vitro* and *in vivo* by antagonizing *N*-methyl-D-aspartate receptors. *J Pharmacol Exp Ther* 2001;296:41–47.
123. Mukhin A, Fan L, Faden AI. Activation of metabotropic glutamate receptor subtype mGluR1 contributes to post-traumatic neuronal injury. *J Neurosci* 1996;16:6012–6020.
124. Nagaraja RY, Becker A, Reymann KG, Balschun D. Repeated administration of group I mGluR antagonists prevents seizure-induced long-term aberrations in hippocampal synaptic plasticity. *Neuropharmacology* 2005;49(Suppl 1):179–187.
125. Narita M, Suzuki M, Niikura K, et al. Involvement of spinal metabotropic glutamate receptor 5 in the development of tolerance to morphine-induced antinociception. *J Neurochem* 2005;94:1297–1305.
126. Nestler EJ. Historical review: Molecular and cellular mechanisms of opiate and cocaine addiction. *Trends Pharmacol Sci* 2004;25:210–218.
127. Neugebauer V, Chen PS, Willis WD. Role of metabotropic glutamate receptor subtype mGluR1 in brief nociception and central sensitization of primate STT cells. *J Neurophysiol* 1999;82:272–282.
128. Neugebauer V, Li W, Bird GC, Bhave G, Gereau RWt. Synaptic plasticity in the amygdala in a model of arthritic pain: Differential roles of metabotropic glutamate receptors 1 and 5. *J Neurosci* 2003;23:52–63.
129. Neugebauer V, Lucke T, Schaible HG. Requirement of metabotropic glutamate receptors for the generation of inflammation-evoked hyperexcitability in rat spinal cord neurons. *Eur J Neurosci* 1994;6:1179–1186.
130. Nicotera P, Lipton SA. Excitotoxins in neuronal apoptosis and necrosis. *J Cereb Blood Flow Metab* 1999;19:583–591.
131. 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;53:1009–1018.
132. 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;335:252–266.
133. Oka A, Takashima S. The up-regulation of metabotropic glutamate receptor 5 (mGluR5) in Down's syndrome brains. *Acta Neuropathol (Berl)* 1999;97:275–278.
134. O'Leary DM, Movsesyan V, Vicini S, Faden AI. Selective mGluR5 antagonists MPEP and SIB-1893 decrease NMDA or glutamate-mediated neuronal toxicity through actions that reflect NMDA receptor antagonism. *Br J Pharmacol* 2000;131:1429–1437.
135. Olive MF, McGeehan AJ, Kinder JR, et al. The mGluR5 antagonist 6-methyl-2-(phenylethynyl)pyridine decreases ethanol consumption via a protein kinase C epsilon-dependent mechanism. *Mol Pharmacol* 2005;67:349–355.
136. Orlando LR, Dunah AW, Standaert DG, Young AB. Tyrosine phosphorylation of the metabotropic glutamate receptor mGluR5 in striatal neurons. *Neuropharmacology* 2002;43:161–173.
137. Ossowska K, Konieczny J, Wardas J, Golembiowska K, Wolfarth S, Pilc A. The role of striatal metabotropic glutamate receptors in Parkinson's disease. *Amino Acids* 2002;23:193–198.
138. 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;49:447–455.
139. 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: 413–420.
140. Oueslati A, Breysse N, Amalric M, Kerkerian-Le Goff L, Salin P. Dysfunction of the cortico-basal ganglia-cortical loop in a rat model of early parkinsonism is reversed by metabotropic glutamate receptor 5 antagonism. *Eur J Neurosci* 2005;22:2765–2774.

141. Pagano A, Ruegg D, Litschig S, et al. The non-competitive antagonists 2-methyl-6-(phenylethynyl)pyridine and 7-hydroxyiminocyclopropan[*b*]chromen-1*a*-carboxylic acid ethyl ester interact with overlapping binding pockets in the transmembrane region of group I metabotropic glutamate receptors. *J Biol Chem* 2000;275:33750–33758.
142. Page ME, Szeliga P, Gasparini F, Cryan JF. Blockade of the mGlu5 receptor decreases basal and stress-induced cortical norepinephrine in rodents. *Psychopharmacology (Berl)* 2005;179:240–246.
143. Palazzo E, de Novellis V, Marabese I, et al. Interaction between vanilloid and glutamate receptors in the central modulation of nociception. *Eur J Pharmacol* 2002;439:69–75.
144. Palazzo E, Marabese I, de Novellis V, et al. Metabotropic and NMDA glutamate receptors participate in the cannabinoid-induced antinociception. *Neuropharmacology* 2001;40:319–326.
145. Palucha A, Branski P, Pilc A. Selective mGlu5 receptor antagonist MTEP attenuates naloxone-induced morphine withdrawal symptoms. *Pol J Pharmacol* 2004;56:863–866.
146. Paterson NE, Markou A. The metabotropic glutamate receptor 5 antagonist MPEP decreased break points for nicotine, cocaine and food in rats. *Psychopharmacology (Berl)* 2005;179:255–261.
147. Paterson NE, Semenova S, Gasparini F, Markou A. The mGluR5 antagonist MPEP decreased nicotine self-administration in rats and mice. *Psychopharmacology (Berl)* 2003;167:257–264.
148. Pietraszek M, Rogoz Z, Wolfarth S, Ossowska K. Opposite influence of MPEP, an mGluR5 antagonist, on the locomotor hyperactivity induced by PCP and amphetamine. *J Physiol Pharmacol* 2004;55:587–593.
149. Pietraszek M, Sukhanov I, Maciejak P, et al. Anxiolytic-like effects of mGlu1 and mGlu5 receptor antagonists in rats. *Eur J Pharmacol* 2005;514:25–34.
150. Pike B, Zhao X, Newcomb J, Glenn C, Anderson D, Hayes R. Stretch injury causes calpain and caspase-3 activation and necrotic and apoptotic cell death in septo-hippocampal cell cultures. *J Neurotrauma* 2000; 17:P283–298.
151. Pilc A, Klodzinska A, Branski P, et al. Multiple MPEP administrations evoke anxiolytic- and antidepressant-like effects in rats. *Neuropharmacology* 2002;43:181–187.
152. Pisani A, Gubellini P, Bonsi P, et al. Metabotropic glutamate receptor 5 mediates the potentiation of *N*-methyl-D-aspartate responses in medium spiny striatal neurons. *Neuroscience* 2001;106:579–587.
153. Porter RH, 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;315:711–721.
154. Rao AM, Hatcher JF, Dempsey RJ. Neuroprotection by group I metabotropic glutamate receptor antagonists in forebrain ischemia of gerbil. *Neurosci Lett* 2000;293:1–4.
155. Reid SN, Romano C, Hughes T, Daw NW. Developmental and sensory-dependent changes of phosphoinositide-linked metabotropic glutamate receptors. *J Comp Neurol* 1997;389:577–583.
156. Richardson-Burns SM, Haroutunian V, Davis KL, Watson SJ, Meador-Woodruff JH. Metabotropic glutamate receptor mRNA expression in the schizophrenic thalamus. *Biol Psychiatry* 2000;47:22–28.
157. Ritzen A, Mathiesen JM, Thomsen C. Molecular pharmacology and therapeutic prospects of metabotropic glutamate receptor allosteric modulators. *Basic Clin Pharmacol Toxicol* 2005;97:202–213.
158. Rodrigues RJ, Alfaro TM, Rebola N, Oliveira CR, Cunha RA. Co-localization and functional interaction between adenosine A(2A) and metabotropic group 5 receptors in glutamatergic nerve terminals of the rat striatum. *J Neurochem* 2005;92:433–441.
159. Rorick-Kehn LM, Hart JC, McKinzie DL. Pharmacological characterization of stress-induced hyperthermia in DBA/2 mice using metabotropic and ionotropic glutamate receptor ligands. *Psychopharmacology (Berl)* 2005;183:226–240.
160. Salt TE, Binns KE, Turner JP, Gasparini F, Kuhn R. Antagonism of the mGlu5 agonist 2-chloro-5-hydroxyphenylglycine by the novel selective mGlu5 antagonist 6-methyl-2-(phenylethynyl)-pyridine (MPEP) in the thalamus. *Br J Pharmacol* 1999;127:1057–1059.
161. Saugstad JA, Marino MJ, Folk JA, Hepler JR, Conn PJ. RGS4 inhibits signaling by group I metabotropic glutamate receptors. *J Neurosci* 1998;18:905–913.
162. Schiefer J, Sprunken A, Puls C, et al. The metabotropic glutamate receptor 5 antagonist MPEP and the mGluR2 agonist LY379268 modify disease progression in a transgenic mouse model of Huntington's disease. *Brain Res* 2004;1019:246–254.
163. Schoepp DD, Jane DE, Monn JA. Pharmacological agents acting at subtypes of metabotropic glutamate receptors. *Neuropharmacology* 1999;38:1431–1476.
164. Schroeder JP, Overstreet DH, Hodge CW. The mGluR5 antagonist MPEP decreases operant ethanol self-administration during maintenance and after repeated alcohol deprivations in alcohol-preferring (P) rats. *Psychopharmacology (Berl)* 2005;179:262–270.

165. Schulz B, Fendt M, Gasparini F, Lingenhohl K, Kuhn R, Koch M. The metabotropic glutamate receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) blocks fear conditioning in rats. *Neuropharmacology* 2001;41:1–7.
166. Sensi SL, Yin HZ, Carriedo SG, Rao SS, Weiss JH. Preferential Zn^{2+} influx through Ca^{2+}-permeable AMPA/kainate channels triggers prolonged mitochondrial superoxide production. *Proc Natl Acad Sci USA* 1999;96:2414–2419.
167. Sensi SL, Yin HZ, Weiss JH. Glutamate triggers preferential Zn^{2+} flux through Ca^{2+} permeable AMPA channels and consequent ROS production. *Neuroreport* 1999;10:1723–1727.
168. Sheng M, Kim E. The Shank family of scaffold proteins. *J Cell Sci* 2000;113(Pt 11):1851–1856.
169. Shigemoto R, Nakanishi S, Mizuno N. Distribution of the mRNA for a metabotropic glutamate receptor (mGluR1) in the central nervous system: An *in situ* hybridization study in adult and developing rat. *J Comp Neurol* 1992; 322:121–135.
170. Simonian NA, Getz RL, Leveque JC, Konradi C, Coyle JT. Kainate induces apoptosis in neurons. *Neuroscience* 1996;74:675–683.
171. Simonian NA, Getz RL, Leveque JC, Konradi C, Coyle JT. Kainic acid induces apoptosis in neurons. *Neuroscience* 1996;75:1047–1055.
172. Simonyi A, Miller LA, Sun GY. Region-specific decline in the expression of metabotropic glutamate receptor 7 mRNA in rat brain during aging. *Brain Res Mol Brain Res* 2000;82:101–106.
173. Simonyi A, Schachtman TR, Christoffersen GR. The role of metabotropic glutamate receptor 5 in learning and memory processes. *Drug News Persp* 2005;18:353–361.
174. Simonyi A, Xia J, Igbavboa U, Wood WG, Sun GY. Age differences in the expression of metabotropic glutamate receptor 1 and inositol 1,4,5-trisphosphate receptor in mouse cerebellum. *Neurosci Lett* 1998;244: 29–32.
175. Simonyi A, Zhang JP, Sun GY. Changes in mRNA levels for group I metabotropic glutamate receptors following in utero hypoxia-ischemia. *Brain Res Dev Brain Res* 1999;112:31–37.
176. Skeberdis VA, Lan J, Opitz T, Zheng X, Bennett MV, Zukin RS. mGluR1-mediated potentiation of NMDA receptors involves a rise in intracellular calcium and activation of protein kinase C. *Neuropharmacology* 2001;40:856–865.
177. Slassi A, Isaac M, Edwards L, et al. Recent advances in non-competitive mGlu5 receptor antagonists and their potential therapeutic applications. *Curr Top Med Chem* 2005;5:897–911.
178. Smolders I, Lindekens H, Clinckers R, et al. *In vivo* modulation of extracellular hippocampal glutamate and GABA levels and limbic seizures by group I and II metabotropic glutamate receptor ligands. *J Neurochem* 2004;88:1068–1077.
179. Snyder EM, Philpot BD, Huber KM, Dong X, Fallon JR, Bear MF. Internalization of ionotropic glutamate receptors in response to mGluR activation. *Nat Neurosci* 2001;4:1079–1085.
180. Spooren W, Gasparini F. mGlu5 receptor antagonists: A novel class of anxiolytics? *Drug News Persp* 2004; 17:251–257.
181. Spooren WP, 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;406:403–410.
182. Spooren WP, Schoeffter P, Gasparini F, Kuhn R, Gentsch C. Pharmacological and endocrinological characterisation of stress-induced hyperthermia in singly housed mice using classical and candidate anxiolytics (LY314582, MPEP and NKP608). *Eur J Pharmacol* 2002;435:161–170.
183. Spooren WP, Vassout A, Neijt HC, 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: 1267–1275.
184. Steckler T, Lavreysen H, Oliveira AM, et al. Effects of mGlu1 receptor blockade on anxiety-related behaviour in the rat lick suppression test. *Psychopharmacology (Berl)* 2005;179:198–206.
185. Steckler T, Oliveira AF, Van Dyck C, et al. Metabotropic glutamate receptor 1 blockade impairs acquisition and retention in a spatial Water maze task. *Behav Brain Res* 2005;164:52–60.
186. Stefani A, Pisani A, Mercuri NB, Calabresi P. The modulation of calcium currents by the activation of mGluRs. Functional implications. *Mol Neurobiol* 1996;13:81–95.
187. Stoop R, Conquet F, Pralong E. Determination of group I metabotropic glutamate receptor subtypes involved in the frequency of epileptiform activity *in vitro* using mGluR1 and mGluR5 mutant mice. *Neuropharmacology* 2003;44:157–162.
188. Strasser U, Lobner D, Behrens MM, Canzoniero LM, Choi DW. Antagonists for group I mGluRs attenuate excitotoxic neuronal death in cortical cultures. *Eur J Neurosci* 1998;10:2848–2855.

189. Swanson CJ, Baker DA, Carson D, Worley PF, Kalivas PW. Repeated cocaine administration attenuates group I metabotropic glutamate receptor-mediated glutamate release and behavioral activation: A potential role for Homer. *J Neurosci* 2001;21:9043–9052.
190. Tambeli CH, Young A, Levine JD, Gear RW. Contribution of spinal glutamatergic mechanisms in heterosegmental antinociception induced by noxious stimulation. *Pain* 2003;106:173–179.
191. Tan S, Sagara Y, Liu Y, Maher P, Schubert D. The regulation of reactive oxygen species production during programmed cell death. *J Cell Biol* 1998;141:1423–1432.
192. Tatarczynska E, Klodzinska A, Chojnacka-Wojcik E, et al. Potential anxiolytic- and antidepressant-like effects of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist. *Br J Pharmacol* 2001;132:1423–1430.
193. Tavalin SJ, Ellis EF, Satin LS. Inhibition of the electrogenic Na pump underlies delayed depolarization of cortical neurons after mechanical injury or glutamate. *J Neurophysiol* 1997;77:632–638.
194. Temple MD, OLeary DM, Faden AI. The role of glutamate receptors in the pathophysiology of traumatic central nervous system injury. In: Miller LA, Hayes RL, Newcomb JK, Eds. Head trauma: basic, preclinical, and clinical directions. New York: John Wiley & Sons, Inc., 2001;87–113.
195. Tessari M, Pilla M, Andreoli M, Hutcheson DM, Heidbreder CA. Antagonism at metabotropic glutamate 5 receptors inhibits nicotine- and cocaine-taking behaviours and prevents nicotine-triggered relapse to nicotine-seeking. *Eur J Pharmacol* 2004;499:121–133.
196. Testa CM, Standaert DG, Young AB, Penney JB, Jr. Metabotropic glutamate receptor mRNA expression in the basal ganglia of the rat. *J Neurosci* 1994;14:3005–3018.
197. Thomas LS, Jane DE, Gasparini F, Croucher MJ. Glutamate release inhibiting properties of the novel mGlu(5) receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP): Complementary *in vitro* and *in vivo* evidence. *Neuropharmacology* 2001;41:523–527.
198. Thuault SJ, Davies CH, Randall AD, Collingridge GL. Group I mGluRs modulate the pattern of non-synaptic epileptiform activity in the hippocampus. *Neuropharmacology* 2002;43:141–146.
199. Tu JC, Xiao B, Naisbitt S, et al. Coupling of mGluR/Homer and PSD-95 complexes by the Shank family of postsynaptic density proteins. *Neuron* 1999;23:583–592.
200. Tu JC, Xiao B, Yuan JP, et al. Homer binds a novel proline-rich motif and links group 1 metabotropic glutamate receptors with IP3 receptors. *Neuron* 1998;21:717–726.
201. Turle-Lorenzo N, Breysse N, Baunez C, Amalric M. Functional interaction between mGlu 5 and NMDA receptors in a rat model of Parkinson's disease. *Psychopharmacology (Berl)* 2005;179:117–127.
202. Varney MA, Gereau RWt. Metabotropic glutamate receptor involvement in models of acute and persistent pain: Prospects for the development of novel analgesics. *Curr Drug Targets CNS Neurol Disord* 2002;1:283–296.
203. Varty GB, 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;179:207–217.
204. Vernon AC, Palmer S, Datla KP, Zbarsky V, Croucher MJ, Dexter DT. Neuroprotective effects of metabotropic glutamate receptor ligands in a 6-hydroxydopamine rodent model of Parkinson's disease. *Eur J Neurosci* 2005;22:1799–1806.
205. Vezina P, Kim JH. Metabotropic glutamate receptors and the generation of locomotor activity: Interactions with midbrain dopamine. *Neurosci Biobehav Rev* 1999;23:577–589.
206. Walker K, Reeve A, Bowes M, et al. mGlu5 receptors and nociceptive function II. mGlu5 receptors functionally expressed on peripheral sensory neurones mediate inflammatory hyperalgesia. *Neuropharmacology* 2001;40:10–19.
207. Wardas J, Pietraszek M, Wolfarth S, Ossowska K. The role of metabotropic glutamate receptors in regulation of striatal proenkephalin expression: Implications for the therapy of Parkinson's disease. *Neuroscience* 2003;122:747–756.
208. Weber JT, Rzigalinski BA, Willoughby KA, Moore SF, Ellis EF. Alterations in calcium-mediated signal transduction after traumatic injury of cortical neurons. *Cell Calcium* 1999;26:289–299.
209. Wieronska JM, Smialowska M, Branski P, et al. In the amygdala anxiolytic action of mGlu5 receptors antagonist MPEP involves neuropeptide Y but not $GABA_A$ signaling. *Neuropsychopharmacology* 2004;29:514–521.
210. Wilson CL, Puntis M, Lacey MG. Overwhelmingly asynchronous firing of rat subthalamic nucleus neurones in brain slices provides little evidence for intrinsic interconnectivity. *Neuroscience* 2004;123:187–200.

211. Yan QJ, Rammal M, Tranfaglia M, Bauchwitz RP. Suppression of two major Fragile X Syndrome mouse model phenotypes by the mGluR5 antagonist MPEP. *Neuropharmacology* 2005;49:1053–1066.
212. Yang X, Chen W. *In vitro* microsomal metabolic studies on a selective mGluR5 antagonist MTEP: Characterization of *in vitro* metabolites and identification of a novel thiazole ring opening aldehyde metabolite. *Xenobiotica* 2005;35:797–809.
213. Yu SP, Yeh CH, Sensi SL, et al. Mediation of neuronal apoptosis by enhancement of outward potassium current. *Science* 1997;278:114–117.
214. Zakharova ES, Danysz W, Bespalov AY. Drug discrimination analysis of NMDA receptor channel blockers as nicotinic receptor antagonists in rats. *Psychopharmacology (Berl)* 2005;179:128–135.
215. Zhang L, Rzigalinski BA, Ellis EF, Satin LS. Reduction of voltage-dependent Mg^{2+} blockade of NMDA current in mechanically injured neurons. *Science* 1996;274:1921–1923.
216. Zhong J, Gerber G, Kojic L, Randic M. Dual modulation of excitatory synaptic transmission by agonists at group I metabotropic glutamate receptors in the rat spinal dorsal horn. *Brain Res* 2000;887:359–377.
217. Zhu CZ, Hsieh G, Ei-Kouhen O, et al. Role of central and peripheral mGluR5 receptors in post-operative pain in rats. *Pain* 2005;114:195–202.
218. Zhu CZ, Wilson SG, Mikusa JP, et al. Assessing the role of metabotropic glutamate receptor 5 in multiple nociceptive modalities. *Eur J Pharmacol* 2004;506:107–118.