ELSEVIER

Pharmacology, Biochemistry and Behavior 73 (2002) 327–332

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Group II mGlu receptor agonists inhibit behavioural and electrophysiological effects of DOI in mice

Aleksandra Kłodzinska[a], Maria Bijak[a], Krzysztof Tokarski[a], Andrzej Pilc[a,b,*]

[a]*Institute of Pharmacology, Polish Academy of Sciences, 31-343 Cracow, Smetna 12, Poland*
[b]*Institute of Public Health, Collegium Medicum, Jagiellonian University, Cracow, Poland*

Received 4 September 2001; received in revised form 5 February 2002; accepted 8 February 2002

Abstract

It has been suggested that metabotropic glutamate (mGlu) receptor agonists selective for Group II mGlu receptors may have antipsychotic action. Therefore, we studied whether the effects, which could be related to psychotomimetic action of hallucinogenic drugs, are inhibited by Group II mGlu receptor agonists. The selective mGlu2/3 agonists LY354740 and LY379268 inhibited (±)1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced head twitches in mice in a dose-dependent manner. Furthermore, LY379268 suppressed an increase in the frequency of spontaneous excitatory synaptic potentials induced by bath-applied DOI in layer V pyramidal cells recorded in the murine medial frontal cortex. The data indicate that Group II mGlu receptor agonists may counteract the effects of hallucinogenic drugs. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Cortical slices; DOI ((±)1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane); Head twitches; 5-HT_2 receptors; LY354740 ((+)-2-aminobicyclo [3,1,0] hexane-2,6-dicarboxylic acid); LY379268 ((−)2-oxa-4-aminobicyclo [3,1,0] hexane-2,6-dicarboxylic acid); Metabotropic glutamate receptors; Mice; Spontaneous EPSP

1. Introduction

It has been postulated that brain 5-HT_{2A} receptors may be involved in the pathogenesis and treatment of psychiatric disorders such as anxiety, depression and psychosis (Deakin, 1988; Schmidt et al., 1995). There is a good correlation between hallucinogenic potency of drugs and their affinity for 5-HT_{2A} receptors (Glennon et al., 1984; Titeler et al., 1988). Furthermore, 5-HT_{2A} antagonists block the psychotomimetic effects of hallucinogens in humans (Vollenweider et al., 1998). Therefore, it has been hypothesized that the 5-HT_{2A} receptor in the frontal cortex may be the primary site of action of hallucinogens and may by critically involved in the actions of many atypical antipsychotics (Aghajanian and Marek, 1999). Electrophysiological studies in rat cortical slices demonstrated that serotonin, as well as hallucinogens lysergic acid diethylamide (LSD) and (±)1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), induces a robust increase in spontaneous excitatory postsynaptic potentials (EPSPs) in layer V pyramidal neurons (Aghajanian and Marek, 1997). This effect is mediated via 5-HT_{2A} receptors and may underlie the hallucinogenic action of 5-HT_{2A} receptor agonists (Abi-Saab et al., 1999; Aghajanian and Marek, 1999). In behavioral studies in rodents, 5-HT_{2A} agonists induce head twitches, and this behaviour provides an experimental model to study 5-HT_2 receptor function in the brain (Green et al., 1983; Darmani et al., 1990).

There is growing evidence that interactions of excitatory amino acids (EAAs) and serotonin may be important for the control of many brain activities and play an important role in a wide range of behaviours (Arvanov et al., 1999; Martin et al., 1998; Kim et al., 1999; Loscher and Honack, 1993; Płaźnik et al., 1994, 1997). Electrophysiological studies have shown that serotonin exerts various modulatory effects on glutamatergic transmission, depending on the brain region studied and serotonin receptor subtype involved (Marek and Aghajanian, 1998; Schmitz et al., 1998). On the other hand, glutamate, via stimulation of metabotropic glutamate (mGlu) receptors, can also modulate some effects of 5-HT receptor activation. Aghajanian and Marek (1997) have demonstrated that a nonselective mGlu receptor agonist, 1-Aminocyclopentane-1,3-dicarboxylic acid (ACPD),

* Corresponding author. Institute of Pharmacology, Polish Academy of Sciences, 31-343 Cracow, Smetna 12, Poland. Tel.: +48-12-6623-284; fax: +48-12-637-4500.

E-mail address: nfpilc@cyf-kr.edu.pl (A. Pilc).

PII: S0091-3057(02)00845-6

suppresses the increase in frequency of spontaneous EPSPs and excitatory postsynaptic currents (EPSCs) induced in rat cerebral cortex layer V pyramidal cells by 5-HT_{2A} receptor activation. Recently, Marek et al. (1999) and Aghajanian and Marek (1999), using intracellular recording from layer V pyramidal cells in the rat medial prefrontal cortex, provided evidence that two selective Group II mGlu agonists, (+)-2-aminobicyclo [3,1,0] hexane-2,6-dicarboxylic acid (LY354740) and (−)2-oxa-4-aminobicyclo [3,1,0] hexane-2,6-dicarboxylic acid (LY379268), also suppressed the increase in EPSCs induced by 5-HT. Furthermore, the mGlu 2/3 antagonist, (2*S*,1′*S*,2′*S*)-2-(9-xantyhylmethyl)-2-(2′-carboxycyclopropyl)glycine (LY341495), blocked the suppressant effect of LY354740 on the 5-HT-induced EPSCs. LY341495 (by blocking mGlu2/3 receptors) was also able to enhance the frequency and amplitude of spontaneous EPSCs induced by 5-HT (through activation of the 5-HT2A receptor) (Marek et al., 1999), suggesting that endogenous glutamate released by activation of 5-HT_{2A} receptors can activate presynaptic inhibitory Group II mGluR receptors. In parallel to these electrophysiological data, Gewirtz and Marek (2000) demonstrated that administration of LY354740 suppressed DOI-induced head twitches in rats.

In our experiments, we confirmed and extended those findings to mice. We investigated the action of potent and selective Group II mGlu receptor agonists LY354740 and LY379268 on DOI-induced head twitches in mice. Additionally, we studied the effect of LY379268 on DOI-induced spontaneous EPSPs using intracellular and patch-clamp recordings in layer V cortical cells in the mouse frontal cortex.

2. Materials and methods

2.1. Animals and housing

The Animal Care and Use Committee at the Institute of Pharmacology approved all experimental procedures. The experiments were carried out on mice (male Albino-Swiss, 24–26 or 20 g for electrophysiology). The animals were kept at an ambient temperature of 20 ± 1 °C and had free access to food (standard laboratory pellets) and tap water before the experiment.

2.2. Head twitch test

In order to habituate mice to the experimental environment, each animal was randomly transferred to a 12 cm (diameter) × 20 cm (height) glass cage, lined with sawdust 30 min before the treatment. Head twitches of mice were induced by DOI (2.5 mg/kg ip). Immediately after the treatment, the number of head twitches was counted during 20 min. LY354740, LY379268 and ketanserin were administered intraperitoneally 30 min before DOI. Each experimental group consisted of nine animals per dose, separate groups of animals were used for each dose of DOI and a total number of 145 mice were used thorough experiments. All injections were given to mice at a volume of 10 ml/kg.

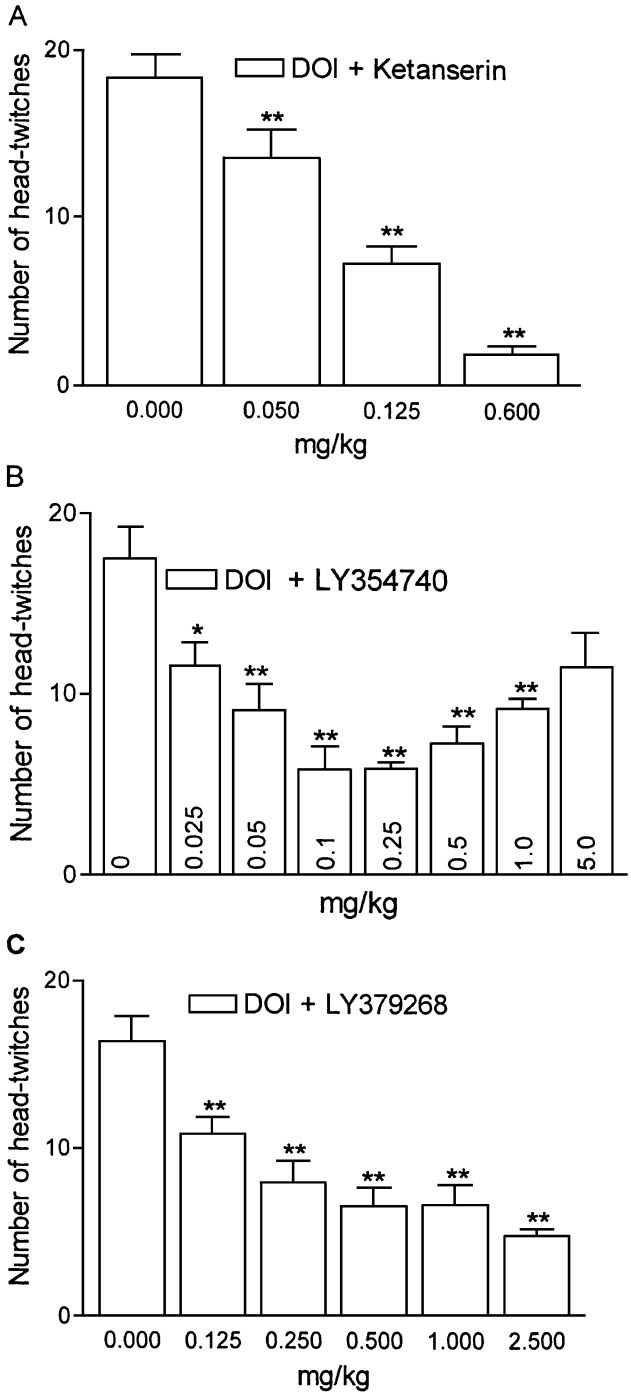

Fig. 1. (A) Dose-dependent suppression of the frequency of DOI-induced head twitches by the 5-HT_2 receptor antagonist ketanserin. Ketanserin was used as a positive control in our study. (B) Dose-dependent suppression of the frequency of DOI-induced head twitches by the Group II mGlu receptor agonist LY354740. (C) Dose-dependent suppression of the frequency of DOI-induced head twitches by the group II mGlu receptor agonist LY379268. Nine mice were used to test each dose of drugs.

The data obtained were presented as means ± S.E.M. and evaluated using a one-way ANOVA, followed by Dunnett's post hoc determination using, GraphPad Prism version 3.00 for Windows (GraphPad Software, San Diego CA, USA).

2.3. Electrophysiological studies

Male mice (20 g) were decapitated, their frontal cortices were dissected and cut into 400-μm-thick slices. The slices were kept in a gassed (95% O_2/5% CO_2) artificial cerebrospinal fluid (ACSF) consisting of (in mM): 126 NaCl, 4 KCl, 2.5 $CaCl_2$, 1.3 $MgSO_4$, 1.25 KH_2PO_4, 26 $NaHCO_3$ and 10 glucose, pH 7.4. A single slice was transferred to the recording chamber (volume 1 ml) and superfused with ACSF at a rate of 1.5 ml/min. Recordings were made from layer V neurons of the frontal cortex. Microelectrodes were pulled on a Flaming–Brown horizontal puller model P-87 (Sutter Instruments, Novato, CA, USA). For intracellular recordings, electrodes were filled with 2 M KCl (resistance 30–50 MΩ). Signals were recorded and amplified using an Axoprobe-1A amplifier (Axon Instruments, Foster City, CA, USA). A CED 1401 interface (CED, Cambridge, UK) connected to a personal computer was used for data acquisition (SIGVAG software, Cambridge Electronics, UK). Intracellular recordings were made at 32 °C.

For whole-cell patch-clamp recordings electrodes were filled with (in mM): 130 K-gluconate, 5 KCl, 0.3 $CaCl_2$, 2 $MgCl_2$, 1 EGTA, 10 HEPES, 5 Na_2-ATP, 0.4 Na-GTP, osmomolarity 290 mosM, pH 7.2, resistance 4–8 MΩ. Individual neurons were visualized using an upright microscope (Zeiss Axioskop) equipped with a long-range water immersion objective (× 40) and an infrared camera. Signals were recorded using a SEC 05L amplifier (NPI, Germany), digitized and analyzed with a PC equipped with a data acquisition system (pClamp, Axon Instruments). All patch-clamp recordings were made at room temperature. Cells of RMP more negative than − 55 mV and overshooting action potentials were accepted for further studies.

Drugs kept as concentrated stocks were diluted in ACSF just before the experiment and applied in the superfusate. After stable baseline recording, we applied DOI (for 6–10 min) and subsequently DOI and LY379268 (for 6–10 min). Our preliminary experiments demonstrated that the effect of DOI on spontaneous EPSPs does not desensitize over a 20-min application. The frequency of spontaneous synaptic potentials was measured at 20-s intervals.

All the values are given as means ± S.E.M. (mean % of the control). Statistical comparisons of the mean values were carried out by Student's *t* test.

2.4. Drugs

DOI was dissolved in saline. Ketanserin (Janssen), LY379268 and LY354740 were suspended in a 1% aqueous solution of Tween-80. All the compounds were administered intraperitoneally, picrotoxin was from Sigma; 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and DOI were obtained from Research Biochemicals (Natick, MA).

3. Results

3.1. DOI-induced head twitches

Ketanserin used as a positive control in our study, produced a dose-dependent decrease (by 90% after the highest dose) in the number of head twitches [$F(3,32) = 33,389$, $P < .01$] (Fig. 1A). The Group II mGlu receptor agonists LY354740 (0.025–1 mg/kg) significantly [$F(7,59) = 10.152$, $P < .001$] decreased DOI-induced head twitches (Fig. 1B). The maximal inhibition (by 64%) occurred after a dose of 0.1 mg/kg. The dose–response curve to LY354740 was bell-shaped so that the compound at a dose of 5 mg/kg was inactive in this test. Another Group II mGlu receptor agonist LY379268 (0.125–2.5 mg/kg) significantly (by 70%) in a monophasic manner inhibited (even at the lowest

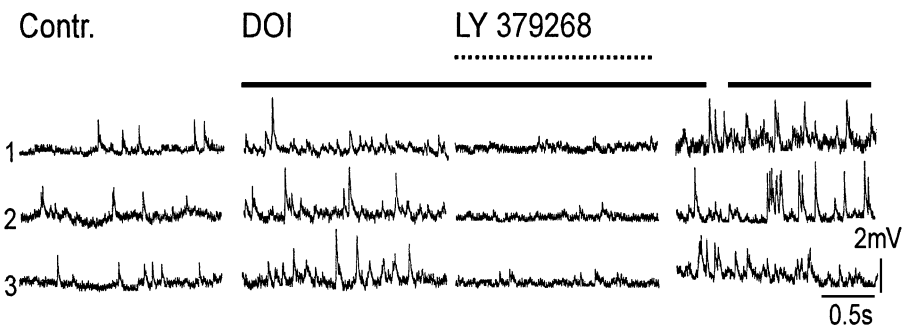

Fig. 2. Reversible suppression by LY379268 of the enhancement of spontaneous EPSPs induced by DOI. (1, 2, 3) Consecutive traces under basal conditions (Contr.; frequency of spontaneous EPSPs 2–0.18 Hz), 10 min during application of DOI (10 μM; frequency of EPSPs 7.8–0.35 Hz), 1 min after application of LY379268 (1 μM) in the continued presence of DOI (frequency of EPSPs 1.7–0.14 Hz) and 5 min after application of LY379268 (frequency of EPSPs 7.3–0.5 Hz). The halluconogen DOI is a selective, partial 5-$HT_{2A/2c/}$ receptor antagonist.

dose) the DOI-induced head twitches [$F(5,48) = 13.5$, $P < .0001$] (Fig. 1C).

3.2. DOI-induced EPSPs

To investigate DOI-induced EPSPs intracellular and patch-clamp current-clamp recordings were made from layer V cortical cells (two thirds the distance between the pial surface and the subcortical white matter) in the presence of picrotoxin (50 μM). The cells recorded in the present study had electrophysiological characteristics of regularly spiking pyramidal neurons (McCormick et al., 1985). While recorded intracellularly, their resting membrane potential (RMP) was 72 ± 5 mV and input resistance (R_{in}) was 30 ± 5 MΩ ($n = 4$; 0.2 nA, 500-ms test pulse). In patch-clamp recordings, RMP was -67 ± 2 mV and R_{in} was 272 ± 26 MΩ ($n = 8$). The basal spontaneous synaptic activity in cortical cells was from 0.5 to 2.0 Hz (mean 1.5 ± 0.1 Hz, $n = 11$). Synaptic potentials were blocked by the non-NMDA glutamatergic receptor antagonist CNQX (5 μM; $n = 5$), indicating that they represent excitatory postsynaptic potentials (EPSPs). DOI (10 μM) enhanced the frequency of spontaneous EPSPs two- to tenfold (mean $350 \pm 60\%$ $n = 11$; Fig. 2). LY379268 (1 μM), when applied with DOI, reversibly suppressed EPSPs to the control or below control level (Fig. 2; mean $53 \pm 10\%$ of the control, $n = 11$).

4. Discussion

Recently discovered, selective, potent and systemically active agonists of Group II mGlu receptors show a wide variety of effects of possible clinical importance. It has been shown in animal studies that agonists of Group II mGlu receptors exhibit anxiolytic-like effects (Helton et al., 1998; Kłodzińska et al., 1999), exhibit antiaddictive effects (Helton et al., 1997; Kłodzińska et al., 1999), inhibit tolerance to analgesic effects of morphine (Popik et al., 2000), and possess antiseizure activity (Kłodzińska et al., 1999, 2000), as well as antiparkinsonian actions (Konieczny et al., 1998). Possible antipsychotic action of these substances has also been demonstrated. Moghaddam and Adams (1998) have shown that Group II mGlu receptor agonists may ameliorate symptoms of acute phencyclidine psychosis as LY354740 inhibited the behavioural effects of phencyclidine, including the phencyclidine-induced motor behaviours (Cartmell et al., 1999, 2000). However, the findings that LY354740 inhibits effects phencyclidine was not confirmed by some other authors (Ossowska et al., 2000; Schreiber et al., 2000). The recently described interactions between glutamate and serotonin (see Section 1), which were proposed as a new target for antipsychotic drugs (Aghajanian and Marek, 1999), were described for experiments conducted on rats. Therefore, we decided to investigate some of those findings could be replicated on mice.

Our study shows that the 5-HT_{2A} receptor ligand DOI induces a barrage of spontaneous EPSPs in layer V pyramidal neurons in the mice cortical slice, which is in line with the data obtained for rat cortical pyramidal neurons (Marek et al., 1999). Furthermore, like in the rat (Marek et al., 1999), the selective agonist of presynaptic Group II mGlu receptors LY379268 potently blocked the effect of DOI. Therefore, the data obtained on mice extend and replicate the experimental results from rats, indicating that mice can be another species to test for possible antipsychotic effects of Group II mGlu receptor agonists.

DOI-induced head twitches in mice, which are due to stimulation of 5-HT_{2A} receptors (Darmani et al., 1990), were suppressed by Group II mGlu receptor agonists, confirming and extending the findings of Gewirtz and Marek (2000), providing data that, in mice, the in vitro electrophysiological results can be extended to the in vivo effects of DOI.

The effect of LY354740 on DOI-induced head twitches differs between rats and mice in two aspects. In mice, LY354740 inhibited the DOI-induced head twitches at much lower doses comparing to rats; furthermore, in our experiments, LY354740 inhibited the effect of DOI in a bell-shaped manner. The bioavailability of drug may account for the differences; in our experiments, LY354740 was suspended in Tween without pH adjustments, while in Gewirtz and Marek (2000) experiments, the substance was dissolved in saline and was neutralised to pH 7.4. Furthermore, in our experiments for each mice, a single injection of DOI was applied, while in Gewirtz and Marek (2000) experiments, multiple injections of DOI were applied. The possibility of homologous receptor down-regulation resulting in the down-regulation of DOI-induced head shakes, could account for the differences observed. The pharmacokinetic interactions could also occur in experiments with multiple drug administration.

LY379268 reduced DOI-induced head twitches in a monophasic manner. The differences between LY354740 and LY379268 may be accounted for by the finding that LY379268 in a low micromolar range of concentrations is able to stimulate Group III mGlu receptors (Schoepp et al., 1999) (mainly of mGlu6/8 subtype), but whether this contributes towards its efficacy remains to be investigated. Both substances have opposing effects in general on cortical glucose utilisation (Lam et al., 1999), which can also contribute to behavioural effects induced by both drugs.

Group II mGlu receptors have both post- and presynaptic localisation and may serve as autoreceptors at glutamatergic synapses (Ugolini and Bordi, 1995). It has been proposed that activation of presynaptic mGlu receptors located on glutamatergic nerve terminals causes a decrease in glutamate release, therefore inhibiting glutamatergic excitatory transmission (for a review, see Glaum and Miller, 1994). Hence, agents stimulating presynaptic autoreceptors (including Group II mGluR receptors) can act as functional antagonists of the glutamatergic system (Lovinger and

Mccool, 1995; Manzoni and Bockaert, 1995; Manzoni et al., 1995). In cortical glutamate nerve terminals, Group II mGlu receptors function as inhibitory autoreceptors (Conn and Pin, 1997), and it has been postulated that in those terminals, glutamate release is enhanced by $5HT_{2A}$ receptor activation (see Aghajanian and Marek, 2000). Therefore, an increase in glutamate release induced by $5\text{-}HT_{2A}$ receptor agonists such as DOI can be counteracted by activation of Group II glutamate receptors. Whether effects of hallucinogenic drugs can be inhibited by Group II mGlu receptor agonists remains to be investigated.

There are suggestions that stimulation of $5HT_{2A}$ receptors is involved in psychotomimetic action of hallucinogenic drugs (Glennon et al., 1984). It has been postulated that an increase of glutamate release is responsible for psychotomimetic effects of NMDA receptor antagonists (Moghaddam and Adams, 1998; Moghaddam et al., 1997). If an increase in glutamate release is involved in the psychotomimetic effects of DOI, and NMDA receptor antagonists, the suppression of glutamate release represents a novel strategy for the treatment of schizophrenia (Moghaddam and Adams, 1998) and Group II mGlu receptor antagonists may be substances with possible antipsychotic properties.

Acknowledgments

The study was supported by the Institute of Pharmacology, Polish Academy of Sciences. The authors are grateful to Dr. D.D. Schoepp from Eli Lilly, Indianapolis, IN, for the generous gift of LY354740 and LY379268.

References

Abi-Saab WM, Bubser M, Roth RH, Deutch AY. 5-HT2 receptor regulation of extracellular GABA levels in the prefrontal cortex. Neuropsychopharmacology 1999;20:92–6.

Aghajanian GK, Marek GJ. Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. Neuropharmacology 1997;36:589–99.

Aghajanian GK, Marek GJ. Serotonin–glutamate interactions: a new target for antipsychotic drugs. Neuropsychopharmacology 1999;21:122–33.

Aghajanian GK, Marek GJ. Serotonin model of schizophrenia: emerging role of glutamate mechanisms. Brain Res Brain Res Rev 2000;31:302–12.

Arvanov VL, Liang X, Magro P, Roberts R, Wang RY. A pre- and postsynaptic modulatory action of 5-HT and the 5-HT2A, 2C receptor agonist DOB on NMDA-evoked responses in the rat medial prefrontal cortex. Eur J Neurosci 1999;11:2917–34.

Cartmell J, Monn JA, Schoepp DD. The metabotropic glutamate 2/3 receptor agonists drugs. LY354740 and LY379268 selectively attenuate phencyclidine versus d-amphetamine motor behaviors in rats. J Pharmacol Exp Ther 1999;291:161–70.

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

Conn PJ, Pin JP. Pharmacology and functions of metabotropic glutamate receptors. Annu Rev Pharmacol Toxicol 1997;37:205–37.

Darmani NA, Martin BR, Pandey U, Glennon RA. Pharmacological characterization of ear-scratch response in mice as a behavioral model for selective 5-HT2-receptor agonists and evidence for 5-HT1B– and 5-HT2–receptor interactions. Pharmacol, Biochem Behav 1990;37:95–9.

Deakin JF. 5HT2 receptors, depression and anxiety. Pharmacol, Biochem Behav 1988;29:819–20.

Gewirtz JC, Marek GJ. Behavioral evidence for interactions between a hallucinogenic drug and group II metabotropic glutamate receptors. Neuropsychopharmacology 2000;23:569–76.

Glaum SR, Miller RJ. Acute regulation of synaptic transmission by metabotropic glutamate receptors. In: Conn PJ, Patel J, editors. The metabotropic glutamate receptors. Totowa (NJ): Humana; 1994. p. 147–72.

Glennon RA, Titeler M, McKenney JD. Evidence for 5-HT2 involvement in the mechanism of action of hallucinogenic agents. Life Sci 1984;35:2505–11.

Green AR, O'Shaughnessy K, Hammond M, Schachter M, Grahame-Smith DG. Inhibition of 5-hydroxytryptamine-mediated behaviour by the putative 5-HT2 antagonist pirenperone. Neuropharmacology 1983;22:573–8.

Helton DR, Tizzano JP, Monn JA, Schoepp DD, Kallman MJ. LY354740: a metabotropic glutamate receptor agonist which ameliorates symptoms of nicotine withdrawal in rats. Neuropharmacology 1997;36:1511–6.

Helton DR, Tizzano JP, Monn JA, Schoepp DD, Kallman MJ. Anxiolytic and side-effect profile of LY354740: a potent, highly selective, orally active agonist for group II metabotropic glutamate receptors. J Pharmacol Exp Ther 1998;284:651–60.

Kim HS, Park IS, Lim HK, Choi HS. NMDA receptor antagonists enhance 5-HT2 receptor-mediated behavior, head-twitch response, in PCPA-treated mice. Arch Pharm Res 1999;22:113–8.

Kłodzińska A, Chojnacka-Wójcik E, Pałucha A, Brański P, Popik P, Pilc A. Potential anti-anxiety, anti-addictive effects of LY354740, a selective group II glutamate metabotropic receptors agonist in animal models. Neuropharmacology 1999;38:1831–9.

Kłodzińska A, Bijak M, Chojnacka-Wójcik E, Kroczka B, Świader M, Czuczwar SJ, Pilc A. Roles of group II metabotropic glutamate receptors in modulation of seizure activity. Naunyn-Schmiedeberg's Arch Pharmacol 2000;361:283–8.

Konieczny J, Ossowska K, Wolfarth S, Pilc A. LY354740, a group II metabotropic glutamate receptor agonist with potential antiparkinsonian properties in rats. Naunyn-Schmiedeberg's Arch Pharmacol 1998;358:500–2.

Lam AGM, Monn JA, Schoepp DD, Lodge D, Mcculloch J. Group II selective metabotropic glutamate receptor agonists and local cerebral glucose use in the rat. J Cereb Blood Flow Metab 1999;19:1083–91.

Loscher W, Honack D. Effects of the novel 5-HT1A receptor antagonist, (+)-WAY 100135, on stereotyped behaviour induced by the NMDA receptor antagonist dizocilpine in rats. Eur J Pharmacol 1993;242:99–104.

Lovinger DM, Mccool BA. Metabotropic glutamate receptor-mediated presynaptic depression at corticostriatal synapses involves mGLuR2 or 3. J Neurophysiol 1995;73:1076–83.

Manzoni O, Bockaert J. Metabotropic glutamate receptors inhibiting excitatory synapses in the CA1 area of rat hippocampus. Eur J Neurosci 1995;7:2518–23.

Manzoni OJ, Castillo PE, Nicoll RA. Pharmacology of metabotropic glutamate receptors at the mossy fiber synapses of the guinea pig hippocampus. Neuropharmacology 1995;34:965–71.

Marek GJ, Aghajanian GK. The electrophysiology of prefrontal serotonin systems: therapeutic implications for mood and psychosis. Biol Psychiatry 1998;44:1118–27.

Marek GJ, Wright RA, Schoepp DD, Monn JA, Aghajanian GK. Physiological antagonism between 5-hydroxytryptamine(2A) and group II metabotropic glutamate receptors in prefrontal cortex. J Pharmacol Exp Ther 1999;292:76–87.

Martin P, Carlsson ML, Hjorth S. Systemic PCP treatment elevates brain extracellular 5-HT: a microdialysis study in awake rats. NeuroReport 1998;9:2985–8.

McCormick DA, Connors BW, Lighthall JW, Prince DA. Comparative electrophysiology of pyramidal and sparsely spiny stellate neurons of the neocortex. J Neurophysiol 1985;54:782–806.

Moghaddam B, Adams BW. Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. Science 1998;281: 1349–52.

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;17:2921–7.

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;19:87–94.

Płaźnik A, Kostowski W, Stefański R. Limbic mechanisms of anxiolytics acting on 5-HT receptors. Pol J Pharmacol 1994;46:473–7.

Płaźnik A, Jessa M, Nazar M. The behavioral effects of NMDA antagonists in serotonin depleted rats. Pharmacol, Biochem Behav 1997;58: 159–66.

Popik P, Kozela E, Pilc A. Selective agonist of group II glutamate metabotropic receptors, LY354740, inhibits tolerance to analgesic effects of morphine in mice. Br J Pharmacol 2000;130:1425–31.

Schmidt CJ, Sorensen SM, Kehne JH, Carr AA, Palfreyman MG. The role of 5-HT2A receptors in antipsychotic activity. Life Sci 1995;56: 2209–22.

Schmitz D, Gloveli T, Empson RM, Draguhn A, Heinemann U. Serotonin reduces synaptic excitation in the superficial medial entorhinal cortex of the rat via a presynaptic mechanism. J Physiol 1998;508:119–29.

Schoepp DD, Jane DE, Monn JA. Pharmacological agents acting at subtypes of metabotropic glutamate receptors. Neuropharmacology 1999; 38:1431–76.

Schreiber R, Lowe D, Voerste A, Devry J. LY354740 affects startle responding but not sensorimotor gating or discriminative effects of phencyclidine. Eur J Pharmacol 2000;388:R3–4.

Titeler M, Lyon RA, Glennon RA. Radioligand binding evidence implicates the brain 5-HT2 receptor as a site of action for LSD and phenylisopropylamine hallucinogens. Psychopharmacology (Berl) 1988;94:213–6.

Ugolini A, Bordi F. Metabotropic glutamate group II receptors are responsible for the depression of synaptic transmission induced by ACPD in the dentate gyrus. Eur J Pharmacol 1995;294:403–10.

Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, Vogel H, Hell D. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. NeuroReport 1998;9:3897–902.