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Behavioral Evidence for Interactions between a Hallucinogenic Drug and Group II Metabotropic Glutamate Receptors

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Recent electrophysiological studies in our laboratory have demonstrated a physiological interaction between 5-HT_{2A} and metabotropic glutamate2/3 (mGlu2/3) receptors in the medial prefrontal cortex. Several behavioral studies have found that phenethylamine hallucinogens with partial agonist activity at 5-HT_{2A} receptors induce head shakes when directly administered into the medial prefrontal cortex. The purpose of the present experiments was to examine whether an interaction occurs between mGlu2/3 and 5-HT_{2A} receptors on a behavioral level using head shakes induced by phenethylamine hallucinogens as a model of 5-HT_{2A} receptor activation. Administration of the mGlu2/3 agonist LY354740 (0.3–10 mg/kg, ip) suppressed head shakes induced by the phenethylamine hallucinogen 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI). Conversely, administration of the mGlu2/3 antagonist LY341495 (1 mg/kg, ip) enhanced the frequency of DOI-induced head shakes. Taken together, these results raise the possibility that the psychomimetic properties of hallucinogenic drugs may be mediated in part, via increased glutamate release following activation of 5-HT_{2A} receptors.

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KEY WORDS: *Phenethylamines; Hallucinogens; Serotonin; mGlu2/3 receptors; Head shakes; DOI; 5-HT_{2A} receptors; LY354740*

Activation of 5-hydroxytryptamine$_{2A}$ (5-HT_{2A}) receptors is thought to mediate many effects of ergoline (e.g., lysergic acid diethylamide; LSD), simple indoleamine (e.g., psilocybin), and phenethylamine (e.g., 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; DOI) hallucinogens in both rodents and humans (Glennon 1990; Marek and Aghajanian 1996; Titeler et al. 1988; Vollenweider et al. 1998). The administration of the 5-$HT_{2A/B/C}$ agonist DOI to rats elicits a constellation of behavioral and physiological effects including head shakes or head-twitches, skin jerks, forepaw treading, rearing, chewing, changes in locomotor activity, hyperthermia and neophobia (Gudelsky et al. 1986; Pranzatelli 1990; Wing et al. 1990). The head shakes induced by 5-HT agonists can be blocked by non-selective 5-HT_2 antagonists (Colpaert and Janssen 1983; Lucki et al. 1984; Peroutka et al. 1981; Yap and Taylor 1983). Moreover, studies employing antagonists selective for 5-HT_{2A} or 5-HT_{2C} receptors have shown that head shakes induced by DOI are mediated via activation of 5-HT_{2A} receptors (Schreiber et al. 1995; Willins and Meltzer 1997). Recent work similarly finds that DOI and other hallucinogenic drugs fail to induce head twitches when administered to 5-HT_{2A} receptor knockout mice, in contrast to wild-type mice (Gingrich et al. 1999). Thus, DOI-induced head shakes have become the most widely used behavioral model for the study of 5-HT_{2A} receptors in rodents.

It has been reported that local infusion of 1-(2,5-dimethoxyphenyl-4-bromo)-2-aminopropane (DOB) and

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DOI into the medial prefrontal cortex induces head shakes (Granhoff et al. 1992a; Willins and Meltzer 1997). 5-HT_{2A} receptors appear to be prominently expressed on the apical dendrites of pyramidal cells in the neocortex (Jakab and Goldman-Rakic 1998; Willins et al. 1997). In addition to activation of postsynaptic 5-HT_{2A} receptors on these pyramidal cells, 5-HT_{2A} agonists have a presynaptic action to release glutamate from afferents with a restricted laminar expression (Aghajanian and Marek 1997). The majority of these afferents appear to originate in the medial thalamus (Marek and Gewirtz 1999). Recently, we have found that activation of metabotropic glutamate2/3 (mGlu2/3) receptors suppresses the 5-HT_{2A} receptor-mediated increase in excitatory postsynaptic potentials/currents (EPSPs/EPSCs) in layer V medial prefrontal cortical pyramidal cells (Marek et al. 2000). Conversely, blockade of mGlu2/3 receptors by the mGlu2/3 antagonist LY341495 enhances the frequency and amplitude of 5-HT-induced EPSCs. This latter result suggests that endogenous glutamate, released by activation of 5-HT_{2A} receptors, tonically activates mGlu2/3 receptors that function to decrease the frequency of 5-HT-induced EPSCs. Taken together, these results imply that mGlu2/3 receptors (likely mGlu2, see Marek et al. (2000)) function as autoreceptors on thalamocortical terminals upon which 5-HT_{2A} receptor activation induces glutamate release.

These interactions between mGlu receptors and 5-HT_{2A} receptors are of interest from a clinical perspective. The therapeutic action of a number of "atypical" antidepressant drugs, which do not appreciably block monoamine uptake or monoamine oxidase, (e.g., mianserin, mirtazepine, nefazodone, trazodone) may be mediated, in part, via blockade of 5-HT_{2A} receptors (de Boer 1996; Eison et al. 1990; Marek et al. 1992; Wander et al. 1986). Similarly, blockade of 5-HT_{2A} receptors is thought to contribute to the therapeutic action of "atypical" antipsychotics such as clozapine, olanzepine, and risperidone (Altar et al. 1986; Ceulemans et al. 1985; Meltzer 1999; Meltzer et al. 1989; Rasmussen and Aghajanian 1988). Conversely, as discussed above, the psychotomimetic effects of hallucinogenic drugs is believed to involve activation of 5-HT_{2A} receptors. Thus, the aim of the present study was to evaluate whether mGlu2/3 agonists and antagonists modulate DOI-induced head shakes in a similar manner as previously observed to 5-HT-induced EPSCs from pyramidal cells of the medial prefrontal cortex slice *in vitro* preparation.

METHOD

Subjects

Fifty-nine male Sprague-Dawley rats (180–280 g, Harlan, Indianapolis, IN) were housed in suspended stainless steel wire cages (18 × 36 × 20 cm) with 2–4 rats occupying each cage. The colony room was maintained at ~20°C and relative humidity (60%). The room was illuminated 12 hours/day (7 A.M.–7 P.M.). All rats had free access to laboratory chow (Teklad 4% Rat Diet) and water except during experimental sessions. Most animals were injected with a moderate dose of DOI (1.25 mg/kg, ip) multiple times but with at least one week between injections to minimize homologous receptor down-regulation. The principles of laboratory animal care (NIH publication No. 85-23, revised 1985) were followed.

General Procedure

All experiments were performed between 10 A.M. and 4 P.M. The animals were transferred to an individual clear polycarbonate cage (43 × 21.5 × 20 cm) with a sawdust covered floor. All animals were habituated to this environment for 15 minutes before receiving a saline injection (1 ml/kg, ip). They were then videotaped and observed for a 30-min period. One or two days later, the rats were reintroduced into this same environment for a 15-min habituation period. The animals were then injected with either saline or 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI; IP, 5 mg/kg) 15 minutes following the initial injection of either vehicle or the mGlu agonist/antagonist.

Behavioral Observation

The animals were observed for 30 minutes following the DOI injection. The observation period began one minute following the DOI injection to allow for drug absorption. Head shake responses were counted in consecutive 5-min periods. Forward locomotion was also scored (movement from one end to the other end of the cage was scored as one cross). Backward locomotion, rearing, flat body posture, forepaw treading, skin jerks, chewing, and sniffing were observed but were not scored.

Statistical Analysis

All data are expressed as the mean ± SEM. The raw data were analyzed with a Wilcoxon matched pairs test (Statistica). Calculation of ID_{50} values were performed by non-linear curve fitting (Delta Graph) after expressing the data as percent suppression of the DOI-induced head shakes.

Drugs

(1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane HCl, (DOI) was purchased from RBI (Natick, MA). (1S,2S, 5R,6S)-2-aminobicyclo[3.1.0]hexane-2,6- dicarboxylate monohydrate (LY354740) and 2S-2-amino-2-(1S,2S-2-carboxycycloprop-1-yl) -2(xanthy-9-yl) propanoic acid (LY341495) were kindly provided by Drs. James A. Monn and Darryle D. Schoepp of the Lilly Research Lab-

oratories (Indianapolis, IN). Doses were calculated on the basis of the salt forms. The drugs were dissolved in saline, neutralized to a pH ~7.4, and injected IP in a volume of 1 ml/kg body weight.

RESULTS

Dose-dependent Induction of Head Shakes by DOI

Since a considerable variability exists in frequency of DOI-induced head shakes among individual rats, a within-subject analysis would provide a more sensitive measure of drug-induced changes. Therefore, we performed a preliminary dose-response curve and assessed the tolerance to repeated weekly injections of a near-maximal concentration of DOI. A low dose of DOI (0.32 mg/kg, n = 8; Figure 1) produced minimal head shakes while a 4-fold higher dose (1.25 mg/kg) produced a near-maximal frequency of head shakes compared to the 5 mg/kg dose. These results are similar to more extensive dose-response curves previously conducted (Pranzatelli 1990; Schreiber et al. 1995).

Previous work has shown that a single acute moderate dose of DOI (1 mg/kg), unlike a large dose (7 mg/kg), does not result in down-regulation of 5-HT$_{2A}$ binding sites (Buckholtz et al. 1988). In contrast, repeated daily treatment with a moderate dose of DOI (1 mg/kg) does down-regulate 5-HT$_{2A}$ binding sites (Buckholtz et al. 1988; McKenna et al. 1989). Therefore, we tested the frequency of head shakes in a group of rats administered DOI (1.25 mg/kg, ip) over four consecutive weeks with drug injections seven days apart. The DOI-induced head shakes were non-significantly decreased during the fourth week to 86% of the frequency from the first week (Figure 2). DOI also induced a 4–5-fold increase in forward locomotion as assessed by longitudinal cage crosses. There was no change in forward locomotion as assessed by longitudinal cage crosses from week 1 to week 4 (not shown).

The mGlu2/3 Agonist LY354740 Suppressed DOI-induced Head Shakes

The selective mGlu2/3 agonist LY354740 (0.3–10 mg/kg, ip; Figure 3) suppressed the frequency of DOI-induced head shakes with an apparent ED$_{50}$ ~1.1 mg/kg and a maximal suppression of ~60% at the 3 mg/kg dose. LY354740 did not significantly suppress the DOI-induced increase in forward locomotion, although a non-significant trend in this direction was present at the 3 mg/kg dose (not shown, $p = .13$). Similar to a previous report (Cartmell et al. 1999), we did not observe any behavioral effects of LY354740 (10 mg/kg, ip).

The mGlu2/3 Antagonist LY341495 Enhances DOI-induced Head Shakes

The efficacy of the selective mGlu2/3 antagonist LY341495 to enhance DOI-induced head shakes was tested using a dose of the drug (1 mg/kg) which has been found to effectively block the suppressant action of the mGlu2/3 agonists LY354740 and LY379268 on the motoric disruption induced by phencycline (Cart-

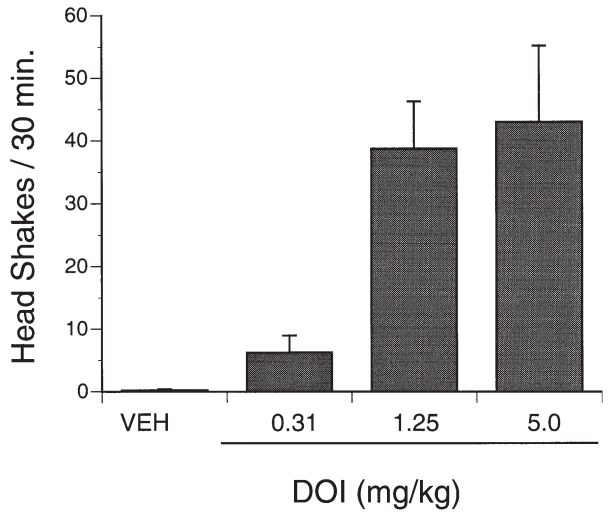

Figure 1. Dose-dependent increase in the frequency of DOI-induced head shakes. Rats were injected (ip; 1 ml/kg) immediately prior to a 30 min observation period. Four rats received all three DOI doses at intervals of at least one week. An additional four rats were tested a single time with a single DOI dose.

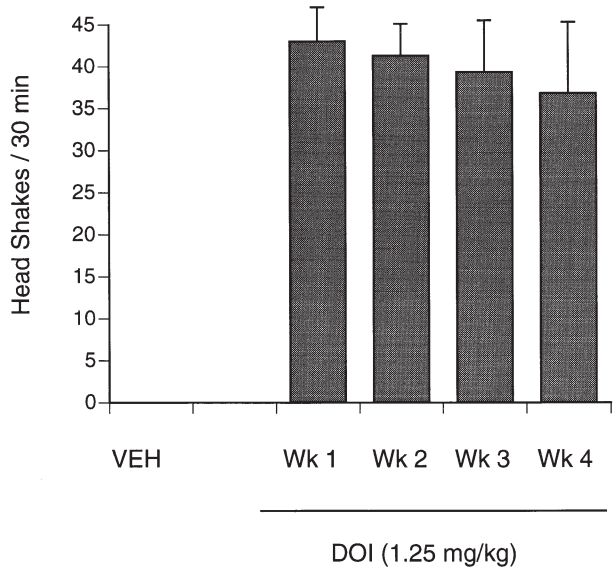

Figure 2. Effects of repeated weekly DOI-injections on the frequency of head shakes. The rats were injected with DOI (1.25 mg/kg; ip; $n = 6$) at weekly intervals. Note that there were no spontaneous head shakes when these rats were administered the vehicle injection.

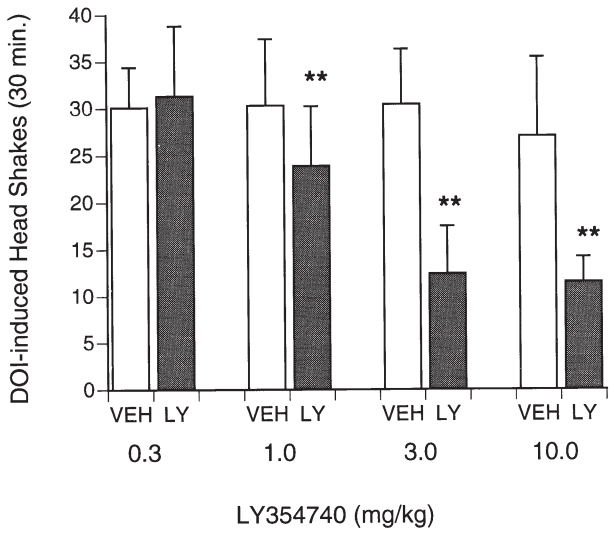

Figure 3. Dose-dependent suppression of the frequency of DOI-induced head shakes by the mGlu2/3 agonist LY354740 (0.3–10 mg/kg, ip). The open bars indicate the frequency of DOI-induced head shakes when separate groups (n = 7 for 0.3–3 mg/kg; n = 4 for 10 mg/kg) of rats were pretreated with the LY354740 vehicle. The closed bars indicate the frequency of DOI-induced head shakes during the 30 min observation period following pretreatment with varying doses of LY354740. ** $p < .01$, significantly different from respective control, Wilcoxon matched pairs test.

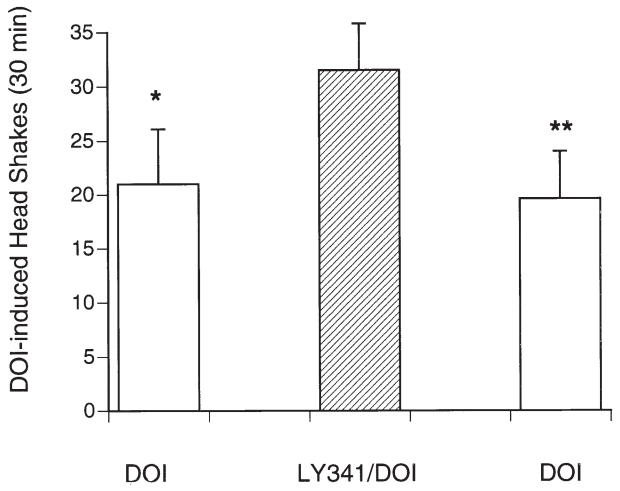

Figure 4. The mGlu2/3 antagonist LY341495 (1 mg/kg, ip; n = 12) increases the frequency of DOI-induced head shakes. The open bars show the frequency of DOI-induced head shakes one week prior to and one week following pretreatment with LY341495. The hatched bar indicates the frequency of DOI-induced head shakes following pretreatment with LY341495. * $p < .05$, significantly different from the combination of DOI/LY341945. ** $p < .01$, significantly different from the combination of DOI/LY341495 using the Wilcoxon matched pairs test.

mell et al. 1999). We also found that LY341495 (1 mg/kg, ip), as reported previously (Cartmell et al. 1999), did not have any behavioral effects by itself. The present experiment involved an A-B-A design where DOI (1.25 mg/kg) was administered three times with at least one week between injections and the mGlu2/3 antagonist was administered before DOI the second week. The head shake frequency with the combination of LY341945 and DOI was significantly increased to 150% of the value for the first week of DOI ($p < .05$; Figure 4) and was significantly increased to 161% of the value for the third week of DOI ($p < .01$). While a trend was present for an increase in forward locomotion for the combination of LY341495 and DOI to 143% compared to the value for the first week of DOI ($p = .14$), the combination did significantly increase forward locomotion to 188% ($p < .05$; not shown) compared to the third week of DOI.

DISCUSSION

The first main finding from the present study is that activation of mGlu2/3 receptors by the highly selective mGlu2/3 agonist LY354740 (Monn et al. 1997; Schoepp et al. 1997) suppressed the frequency of DOI induced head shakes. The second main finding from the present study is that blockade of mGlu2/3 receptors by the selective mGlu2/3 antagonist LY341495 (Kingston et al. 1998) enhanced the frequency of DOI-induced head shakes. These results are in complete accord with our recent report that selective mGlu2/3 agonists suppress, while the selective mGlu2/3 antagonist LY341495 enhances, the frequency and amplitude of synaptic currents/potentials induced by 5-HT_{2A} receptor activation from recordings of layer V pyramidal cells using an *in vitro* slice preparation of the medial prefrontal cortex. Taken together, these results suggest that a physiological interaction between 5-HT_{2A} and mGlu2/3 receptors exists with respect to DOI-induced head shakes.

While many of the rigid glutamate analogs such as the Lilly drugs used int he present work are highly selective for mGlu receptors compared to other metabotropic or glutamate ionotropic receptors owing to the relatively unique structure of mGlu receptors (Conn and Pin 1997), additional pharmacological interpretations of the present data are possible. First, the mGlu ligands used could be acting on novel mGlu receptors which have not been cloned or pharmacologically identified. Second, LY341945 appears to be only ~3–7-fold selective at the mGlu2 vs. the mGlu8 receptor (Kingston et al. 1998). Thus, the enhancement of DOI-induced head shakes by this compound could be due to an interaction with mGlu8 receptors. However, in contrast to this slight selectivity of LY341495 for mGlu2 vs. mGlu8 receptors, the mGlu2/3 agonist LY354740 appears to be ~120–1200-fold selective for mGlu2/3 than for mGlu8

receptors (Monn et al. 1999). Thus, the most parsimonious explanation for the opposing effects of the mGlu2/3 agonist LY354740 and the mGlu2/3 antagonist LY341495 with respect to DOI-induced head shakes would be that either mGlu2 and/or mGlu3 modulates the effects of 5-HT_{2A} receptor activation by hallucinogenic phenethylamines.

The suppression and enhancement of DOI-induced head shakes by a mGlu2/3 agonist and a mGlu2/3 antagonist implicitly argues for a physiological interaction between 5-HT_{2A} receptors and glutamatergic neurotransmission. These results are in agreement with a recent report that both competitive and non-competitive NMDA *antagonists* enhance, while NMDA suppresses, the head-twitch response in mice induced by 5-HT_{2A} receptor activation (Kim et al. 1998). While the exact pathways by which this interaction occur have not been demonstrated, it is known that blockade of NMDA receptors increases glutamate release in the medial prefrontal cortex with a resulting increase in AMPA receptor activation (Moghaddam et al. 1997; Moghaddam and Adams 1998). This increased AMPA receptor activation in the medial prefrontal cortex is thought to mediate, in part, the psychotomimetic effects of NMDA antagonists. We have recently reviewed evidence suggesting that the psychotomimetic effects of both hallucinogens and non-competitive NMDA antagonists may result from a hyperglutamatergic state in the prefrontal cortex in both rodents and humans (Aghajanian and Marek 1999).

The present findings are consistent with the hypothesis that the primary action of the mGlu2/3 agonist LY354740, as an autoreceptor agonist, is to suppress pathologically enhanced glutamate release (Schoepp et al. 1999). Previous studies have found that LY354740 (10 mg/kg, ip) does not alter basal efflux of glutamate in the striatum or medial prefrontal cortex, but does block the increased glutamate release induced by veratridine or phencyclidine (Battaglia et al. 1997; Moghaddam and Adams 1998). In our electrophysiological studies of prefrontal pyramidal cells, LY354740 appeared to preferentially suppress the *frequency* of 5-HT-induced EPSCs while having no action on basal EPSC amplitude or frequency (Marek et al. 2000).

The locus of the 5-HT_{2A} and mGlu2/3 receptor physiological interaction with respect to DOI-induced head shakes is not known given the systemic route of administration for all drugs in the present study. However, 5-HT_2 agonists appear to induce head shakes both subcortically (Bedard and Pycock 1977; Lucki and Minugh-Purvis 1987) and in the medial prefrontal cortex (Granhoff et al. 1992b; Willins and Meltzer 1997). The localization of 5-HT_{2A} receptors in the brain is consistent with both subcortical and cortical sites for the induction of head shake responses by hallucinogenic drugs. The 5-HT_{2A} receptor generally has a restricted expression at subcortical sites, but is strongly expressed in cranial and spinal motoneurons (Pompeiano et al. 1994; Wright et al. 1995). Certainly, one of the highest densities of 5-HT_{2A} receptors found in the brain is in layer V of the neocortex and medial prefrontal cortex (Blue et al. 1988; Lopez-Gimenez et al. 1997). With respect to the present behavioral results, the striking laminar correlation between the peak density of [^{125}I]DOI and [^{3}H]LY354740 binding sites in the midlayer of the rat medial prefrontal cortex (Marek et al. 2000) is of great interest. The peak densities of 5-HT_{2A} and mGlu2/3 binding appear to coincide with the terminal arborizations of the midline and intralaminar thalamic nuclei (Berendse and Groenewegen 1991; Blue et al. 1988). We also have recently reported that with recordings from layer V pyramidal cells of the medial prefrontal cortex that medial thalamic lesions decrease the frequency of 5-HT-induced EPSCs by ~60% (Marek and Gewirtz 1999). Both the 5-HT_{2A} and the mGlu2, but not the mGlu3, receptors appear to be expressed within the midline and thalamic intralaminar thalamic nuclei (Ohishi et al. 1993a; Ohishi et al. 1993b; Raghupathi et al. 1996). Thus, it is tempting to speculate that the behavioral interaction between 5-HT_{2A} and mGlu2/3 receptors demonstrated here may reflect modulation of thalamocortical terminals. However, local administration, rather than systemic administration of DOI and the mGlu agonists/antagonists will be required to demonstrate that the critical site of interaction between 5-HT_{2A} and mGlu2/3 receptors with respect to DOI-induced head shakes is in the medial prefrontal cortex.

Interestingly, LY354740 did not appear to completely suppress DOI-induced head shakes. MGlu2 receptors have a prominent expression in forebrain areas but have a relative weak expression in the cerebellum, lower brainstem and spinal cord (Ohishi et al. 1997; Ohishi et al. 1993a). Thus, mGlu agonists might not be able to suppress DOI-induced head shakes that are mediated through circuits independent of the prefrontal cortex involving subcortical pathways.

Clinical interest in these findings stems from the suggestion that the psychotomimetic effects of hallucinogenic drugs are mediated via activation of 5-HT_{2A} receptors (Glennon 1990), whereas the thymoleptic action of atypical antidepressant drugs (Marek et al. 1992) and atypical antipsychotic drugs (Meltzer 1999) may, in part, involve blockade of 5-HT_{2A} receptors. In fact, the potency and efficacy of the D_2/5-HT_{2A} antagonist pirenpirone in blocking the behavioral effects of LSD in rodents led to the clinical development of the atypical antipsychotic drug risperidone (Colpaert and Janssen 1983; Colpaert et al. 1982; Janssen et al. 1988). One strategy for novel drug design in the treatment of mood and psychotic disorders might be to investigate other transmitter systems which modulate the behavioral effects of hallucinogens in rodents. In this context it is interesting to note that previous studies have found that 5-HT_{1A}

agonists (Arnt and Hyttel 1989; Darmani et al. 1990; Schreiber et al. 1995; Willins and Meltzer 1997), nicotine (Tizabi et al. 1999), and μ-opioid agonists (Alvaro et al. 1998; Corne et al. 1963; Vetulani et al. 1980) suppress head shakes in rodents induced by 5-HT_{2A} agonists. Agonists for 5-HT_{1A} (Amsterdam 1992; Haddjeri et al. 1998; Meltzer 1999; Newman-Tancredi et al. 1998; Wilcox et al. 1996), nicotine (Adler et al. 1998; Covey et al. 1997), and μ-opioid (Bodkin et al. 1995; Carlson and Simpson 1963; Comfort 1977; Gold et al. 1977; O'Brien et al. 1984) receptors are suspected to play a role in the treatment and/or pathophysiology of both depression and schizophrenia. The present findings are consistent with previous reports that group II mGlu agonists may have therapeutic effects in the treatment of schizophrenia (Cartmell et al. 1999; Moghaddam and Adams 1998). In addition, the suppression by group II mGlu agonists of responses mediated by 5-HT_{2A} receptor activation also suggests these mGlu agonists may have antidepressant properties. Thus, understanding the locus and mechanism of physiological and behavioral interactions between 5-HT_{2A} and mGlu receptors may be of considerable heuristic value.

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