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ORIGINAL INVESTIGATION

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Agonist activity of LSD and lisuride at cloned $5HT_{2A}$ and $5HT_{2C}$ receptors

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Abstract Evidence from studies with phenylisopropylamine hallucinogens indicates that the $5HT_{2A}$ receptor is the likely target for the initiation of events leading to hallucinogenic activity associated with LSD and related drugs. Recently, lisuride (a purported non-hallucinogenic congener of LSD) was reported to be a potent antagonist at the $5HT_{2C}$ receptor and an agonist at the $5HT_{2A}$ receptor. LSD exhibited agonist activity at both receptors. These data were interpreted as indicating that the $5HT_{2C}$ receptor might be the initiating site of action for hallucinogens. To test this hypothesis, recombinant cells expressing $5HT_{2A}$ and $5HT_{2C}$ receptors were used to determine the actions of LSD and lisuride. LSD and lisuride were potent partial agonists at $5HT_{2A}$ receptors with EC_{50} values of 7.2 nM and 17 nM, respectively. Also, LSD and lisuride were partial agonists at $5HT_{2C}$ receptors with EC_{50} values of 27 nM and 94 nM, respectively. We conclude that lisuride and LSD have similar actions at $5HT_{2A}$ and $5HT_{2C}$ receptors in recombinant cells. As agonist activity at brain $5HT_{2A}$ receptors has been associated with hallucinogenic acitivity, these results indicate that lisuride may possess hallucinogenic activity, although the psychopharmacological effects of lisuride appear to be different from the hallucinogenic effects of LSD.

Key words Lisuride · Lysergic acid diethylamide (LSD) · 1-(2,5-Dimethoxy-4-methylphenyl)2-aminopropane (DOM) · *N*,*N*-Dimethyltryptamine (DMT) · 5-Hydroxytryptamine (5HT) · $5HT_{2A}$ receptor · $5HT_{2C}$ receptor · Inositol phosphate (IP) production · Hallucinogenic drug

Introduction

It is generally accepted that the $5HT_{2A}$ receptor is the site of action of the LSD-like hallucinogens, including phenylisopropylamines such as DOM 1-(2,5-dimethoxy-4-methylphenyl)2-aminopropane) and tryptamine hallucinogens such as DMT (*N,N*-dimethyltryptamine) (Glennon et al. 1984; Teitler et al. 1988; O'Brien 1996). The $5HT_{2A}$ receptor is a member of the $5HT_2$ receptor sub-family, comprising the $5HT_{2A}$, $5HT_{2B}$, and $5HT_{2C}$ receptors, which are G-protein coupled receptors linked to the inositol phosphate (IP) signal transduction system (Conn et al. 1985, 1986; Wainscott et al. 1993). The $5HT_{2A}$ receptor is found throughout the brain, with the highest density of sites in the cerebral cortex (Appel et al. 1990). The $5HT_{2A}$ receptor displays high affinity for several psychotropic drug classes including LSD-like hallucinogens and antipsychotics (Glennon et al. 1984; Teitler et al. 1988; Roth et al. 1994). There is a strong correlation between the binding affinities of "LSD-like" hallucinogenic drugs at the $5HT_{2A}$ receptor and their human hallucinogenic potencies. This pharmacological correlation as well as animal models of hallucinogenesis implicate the $5HT_{2A}$ receptor as the "LSD receptor" (Glennon et al. 1984; Teitler et al. 1988; Geyer and Krebs 1994). LSD-like hallucinogenic compounds act as agonists at the $5HT_{2A}$ receptor, as

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determined by signal transduction studies in which IP production was measured (Sanders-Bush et al. 1991). It has also been shown that selective $5HT_2$ antagonists can reverse the electrophysiological effects of hallucinogens on the locus coerulus, and the potencies of the hallucinogens in these electrophysiological studies correlated with their human hallucinogenic potencies (Rasmussen and Aghajanian 1986).

A recent study reported that the $5HT_{2C}$ receptor may be involved in the hallucinogenic process (Sanders-Bush and Breeding 1991). The $5HT_{2C}$ and the $5HT_{2A}$ receptors have similar molecular and pharmacological properties and have similar affinities for the phenylisopropylamine hallucinogens as well as for LSD (Teitler et al. 1987). Burris et al. (1991) compared the effects of LSD and a purported non-hallucinogenic congener of LSD, lisuride (a putative anti-parkinsonian agent), at rat $5HT_{2A}$ and $5HT_{2C}$ receptors. They reported that LSD and lisuride were agonists at the $5HT_{2A}$ receptor, whereas lisuride acted as an antagonist and LSD acted as an agonist at the $5HT_{2C}$ receptor (Burris et al. 1991). Assuming lisuride to be non-hallucinogenic, these authors concluded that the overall actions of lisuride and LSD at the $5HT_{2A}$ and $5HT_{2C}$ receptors implicated the $5HT_{2C}$ receptor as the site of action of LSD and LSD-like drugs.

In order to investigate further the roles of the $5HT_{2A}$ and $5HT_{2C}$ receptors in the hallucinogenic activity of LSD and related drugs, recombinant cells specifically expressing either the $5HT_{2A}$ or the $5HT_{2C}$ receptor (Teitler et al. 1990) were used to measure receptor-stimulated IP production by lisuride, LSD, DOM and 5HT. Our experimental results indicate that LSD and lisuride are agonists at both the $5HT_{2A}$ and $5HT_{2C}$ receptors, and imply that lisuride may possess hallucinogenic activity, although the overall clinical literature does not indicate such activity.

Materials and methods

Radioligand binding

Binding studies were performed as described previously (Teitler et al. 1990). Briefly, NIH-3T3 cells stably transfected with the rat $5HT_{2A}$ receptor (GF6 cells) were a generous gift from Dr. David Julius. A-9 cells stably transfected with the rat $5HT_{2C}$ receptor were a generous gift from Dr. Beth Hoffman (J1 cells). Cells were grown to confluence and suspended in 50 mM TRIS-HCl and centrifuged at 12 000 *g* for 30 min. The pellet was resuspended in buffer and centrifuged for 20 min. Assays were performed in 50 mM TRIS-HCl, 0.5 mM EDTA, 10 mM $MgCl_2$, 0.1% ascorbate (pH 7.4). ^{3}H-Ketanserin (0.5 nM) was used to label the $5HT_{2A}$ receptor. ^{3}H-Mesulergine (2.0 nM) was used to label the $5HT_{2C}$ receptor. Competition experiments were performed in triplicate in a 2.0 ml volume and 10 μM ketanserin ($5HT_{2A}$) and 1 μM mesulergine ($5HT_{2C}$) were used to determine non-specific binding. Membranes were incubated for 30 min at 37°C and then filtered on Schleicher and Schuell (Keene, N.H., USA) glass fiber filters (pre-soaked in 0.1% polyethyleneimine), and washed with 10 ml buffer. The filters were counted in a liquid scintillation counter at a 40% efficiency. Competition experiments were plotted and analyzed using Graphpad Prism.

Phosphatidylinositol metabolism assay

The PI metabolism assay used in the present studies was modified from methods of Berridge et al. (1982). Twenty four plates were seeded at a density of 2×10^5 cells/well with cells stably transfected with the $5HT_{2A}$ or $5HT_{2C}$ receptor. Twenty four hours after plating the cells, 0.25 μCi ^{3}H-myoinositol was added and the cells were incubated for 18 h in inositol-free, serum-free DMEM (GIBCO). Cells were rinsed with PBS and then incubated in serum-free media with 10 mM LiCl and 10 μM pargyline for 15 min. These procedures have been shown to essentially eliminate residual 5HT from the assay medium (Barker et al. 1994). Drugs were added to the recombinant cells and incubated in serum-free and inositol-free media for 30 min. The reactions were terminated by removing the media and adding 0.25 ml stop solution (1 M KOH, 7.6 mM NaOH, 18 mM Na Borate, and 3.8 mM EDTA) and 0.25 ml of a neutralization solution (7.5% HCl). Samples were extracted with methanol:chloroform (2:1) and loaded onto anion-exchange columns (AG-1X8 formate resin; Bio-Rad). Columns were washed with 10 ml 5 mM myoinositol and 10 ml 5 mM sodium borate/60 mM sodium formate. ^{3}H-inositol phosphates were eluted with 3 ml 1 M ammonium formate/100 mM formic acid. Ecoscint 17 ml was added to each tube and counted in a liquid scintillation counter at 40% efficiency.

K_i, EC_{50}, IC_{50} values and concentration-response curves were generated using GraphPad Prism. Statistical analyses were done using a Student's *t*-test.

Results

Radioligand binding studies show that LSD and lisuride have high affinity for $5HT_{2A}$ and $5HT_{2C}$ receptors (Table 1). Preliminary experiments using 1 μM concentrations of drugs indicated that LSD, lisuride and DOM, a well-characterized phenylisopropylamine hallucinogen, possess agonist activity at the $5HT_{2A}$ and $5HT_{2C}$ receptors. At 1 μM LSD, lisuride, and DOM produced 5-fold, 4-fold and 14-fold increases, respectively, over basal IP levels at $5HT_{2A}$ receptors (data not shown). At $5HT_{2C}$ receptors, LSD, lisuride and DOM produced 3.6-fold, 2.3-fold and 10-fold increases, respectively, in IP levels (data not shown). 5HT produced a 15-fold stimulation over basal levels at both receptors. To characterize further the agonist activity of LSD, lisuride, and DOM, dose-response curves were generated (Fig. 1). LSD and lisuride potently stimulated the $5HT_{2A}$ receptor with EC_{50} values of 7 nM and 17 nM, respectively and the $5HT_{2C}$ receptor with EC_{50} values of 27 nM and 94 nM, respectively (Table 1). 5HT stimulated $5HT_{2A}$ and $5HT_{2C}$ receptors with EC_{50} values of 61 nM and 77 nM, respectively. Figure 1 indicates that LSD and lisuride are partial agonists at $5HT_{2A}$ and $5HT_{2C}$ receptors. LSD had an efficacy of 32% and 26% at $5HT_{2A}$ and $5HT_{2C}$ receptors, respectively (*t*-value, *df* 9.2,4; 12,4) (Table 1). Similarly, lisuride had an efficacy of 26% and 17% at

Table 1 Affinities and efficacies of hallucinogens at recombinant $5HT_{2A}$ and $5HT_{2C}$ receptors. ^{3}H-Ketanserin was used to label $5HT_{2A}$ receptors in stably transfected NIH-3T3 cells. ^{3}H-Mesulergine was used to label $5HT_{2C}$ receptors in stably transfected in A-9 cells. $5HT_{2A}$ and $5HT_{2C}$ receptor stimulation of IP production was measured following anion exchange chromatography. Percentage of 5HT stimulation was determined using 10 μm drug and expressed as a percentage of maximal IP stimulation produced by 10 μm 5HT. The data are expressed as the mean ± SEM of three independent experiments performed in triplicate. *$P < 0.05$ versus 5HT. *t*-Value, *df* for LSD and lisuride at the $5HT_{2A}$ receptor (9.2,4; 12,4), *t*-value, *df* for LSD, lisuride, and DOM at the $5HT_{2C}$ receptor (12,4; 14,4; 4,4)

Drug	K_i(nM)		EC_{50} (nM)		% 5HT stimulation	
	$5HT_{2A}$	$5HT_{2C}$	$5HT_{2A}$	$5HT_{2C}$	$5HT_{2A}$	$5HT_{2C}$
LSD	1.3 ± 0.6	10 ± 4.4	7.2 ± 1.0	27 ± 9.2	32 ± 5.1*	26 ± 1.2*
Lisuride	12 ± 4.6	20 ± 1.1	17 ± 2.0	94 ± 24	26 ± 3.0*	17 ± 0.2*
DOM	225 ± 115	370 ± 24	77 ± 20	166 ± 7.8	88 ± 6.3	70 ± 0.8*
5HT	262 ± 57	349 ± 29	61 ± 16	77 ± 9.5	100 ± 5.3	100 ± 6.1

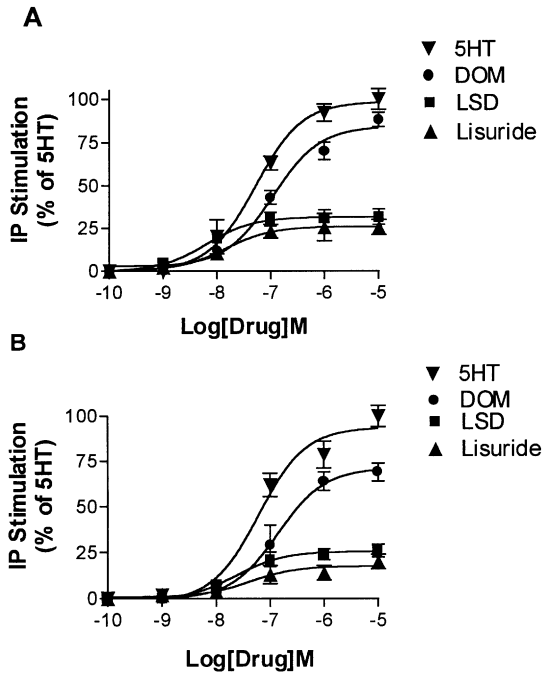

Fig. 1 **A** $5HT_{2A}$ receptor-mediated IP stimulation by LSD, lisuride, DOM, and 5HT. The data are the mean ± SEM of three independent experiments and are expressed as a percentage of maximal stimulation by 10 μM 5HT. **B** $5HT_{2C}$ receptor-mediated IP stimulation by LSD, lisuride, DOM, and 5HT. The data are the mean ± SEM of three separate experiments performed in triplicate and are expressed as a percentage of maximal stimulation produced by 10 μM5HT

$5HT_{2A}$ and $5HT_{2C}$ receptors, respectively (*t*-value, *df* 12,4; 14,4).

In a cell line selectively expressing $5HT_{2A}$ receptors, $5HT_{2A}$ receptor antagonists inhibited IP production by a 50 nM concentration of LSD or lisuride (Fig. 2). Ketanserin, methysergide, mianserin, and spiperone blocked IP production stimulated by LSD or lisuride, the highest degree of blockade occurring with the most potent $5HT_{2A}$ antagonists spiperone and ketanserin. Inositol phosphate production stimulated by 1 μM LSD or lisuride was potently antagonized by ketanserin, with IC_{50} values of 58 nM and 34 nM, respectively (data not shown).

In cells selectively expressing $5HT_{2C}$ receptors, the $5HT_{2C}$ receptor antagonists mesulergine, methysergide and mianserin inhibited IP production by 50 nM LSD or lisuride (Fig. 2). Stimulation of the $5HT_{2C}$ receptor by 1 μM LSD or lisuride was potently antagonized by mesulergine, with IC_{50} values of 12 nM and 63 nM (data not shown).

Discussion

These studies were performed to determine the actions of LSD, lisuride (a purported non-hallucinogenic congener of LSD), and DOM (an "LSD-like") hallucinogenic phenylisopropylamine) at $5HT_{2A}$ and $5HT_{2C}$ receptors heterologously expressed in recombinant mammalian cell lines. We took advantage of a recombinant cell line to obtain a system in which receptors are expressed at a high density: thus the efficacy of weak partial agonists that may be undetectable in other systems is easily measurable in recombinant cells. LSD and lisuride were found to act similarly at $5HT_{2A}$ and $5HT_{2C}$ receptors, displaying partial agonist activity at both receptors. DOM displayed full agonist activity at $5HT_{2A}$ receptors and close to full activity at $5HT_{2C}$ receptors, relative to the endogenous neurotransmitter 5HT. The key observation in this study was the agonist activity of lisuride at the $5HT_{2C}$ receptor, as a previous report had indicated that lisuride was an antagonist at the $5HT_{2C}$ receptor (Burris et al. 1991). The effects of LSD and lisuride we observed are consistent with the reports of partial agonist activity of LSD and lisuride at $5HT_{2A}$ receptors in signal transduction measurements in primary cell cultures (Burris et al. 1991) and the partial agonist activity of LSD at $5HT_{2A}$ receptors using electrophysiological techniques (Marek and Aghajanian 1996).

Burris et al. (1991) reported that lisuride is an antagonist at $5HT_{2C}$ receptors in rat choroid plexus epithelial cells. Citing the accepted observation that lisuride does not produce the obvious hallucinogenic activity associated with LSD and related hallucinogenic drugs of abuse, they proposed that the pharmacological

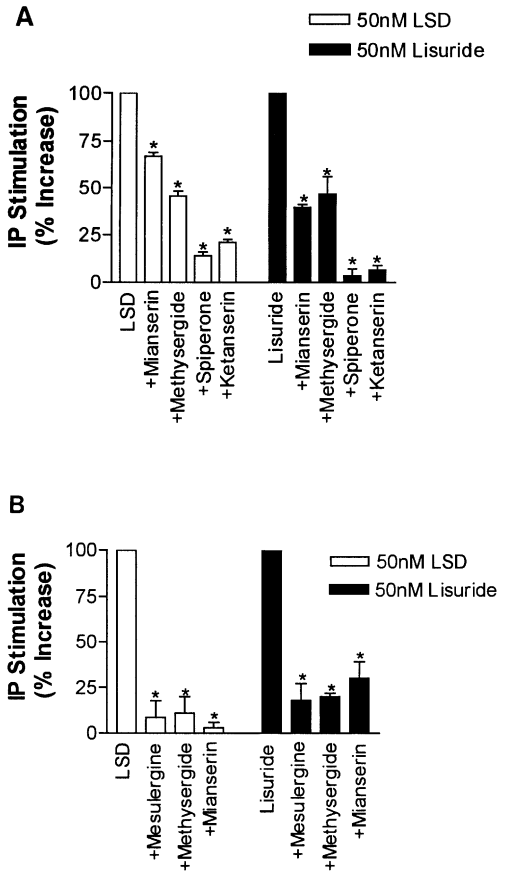

Fig. 2 **A** Antagonist inhibition of LSD and lisuride-stimulated IP production at the $5HT_{2A}$ receptor. NIH-3T3 cells stably transfected with the $5HT_{2A}$ receptor were challenged with 50 nM LSD or lisuride in the presence of 1 μM antagonist. The results are expressed as the percentage increase in IP production and are the mean ± SEM of four independent experiments performed in duplicate. IP levels for 50 nM LSD and lisuride were 6120 ± 291 dpms and 3912 ± 277 dpms, respectively. $^*P < 0.05$ versus LSD or lisuride in the absence of antagonist. (*t*-value, *df*) LSD + mianserin, + methysergide, + spiperone, + ketanserin (17,4; 22,4; 43,4; 52,4). Lisuride + mianserin, + methysergide, + spiperone, + ketanserin (40,4; 3.5,4; 27,4; 57,4). **B** Inhibition of LSD and lisuride stimulation of the $5HT_{2C}$ receptor by $5HT_{2C}$ antagonists. A9 cells stably transfected with $5HT_{2C}$ receptors were challenged with 50 nM LSD or lisuride in the presence of 1 μM mianserin, methysergide, or mesulergine. The data are representative of four independent experiments performed in duplicate and are expressed as the mean ± SEM. IP levels for 50 nM LSD and 50 nM lisuride were 14 446 ± 1862 dpms and 4685 ± 162 dpms, respectively. $^*P < 0.05$ versus LSD or lisuride in the absence of antagonist. (*t*-value, *df*) LSD + mesulergine, + methysergide, + mianserin (10,4; 10,4; 32,4). Lisuride + mesulergine, + methysergide, + mianserin (9,4; 39, 4; 8,4)

profile of LSD and lisuride at the $5HT_{2A}$ and $5HT_{2C}$ receptors indicated that the $5HT_{2C}$ may be a more likely candidate for the key receptor mediating the effects of LSD and LSD-like hallucinogens. Our results indicate that lisuride has partial agonist activity at the $5HT_{2C}$ receptor, similar to that of LSD. The observation that lisuride could antagonize 5HT stimulation of $5HT_{2C}$ receptors is expected due to the partial agonist activity of lisuride. It is well established that partial agonists, especially those with low efficacy such as lisuride, will antagonize the activity of full agonists. The important point is that our studies indicate that lisuride and LSD can display partial agonist activity at both the $5HT_{2A}$ and $5HT_{2C}$ receptors.

Lisuride is classified primarily as a dopamine receptor agonist, although it possesses agonist activity at $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$, and adrenergic receptors. Lisuride is occasionally used as an anti-parkinsonian agent, due to its D_2 dopamine receptor agonist actions (Gershanik et al. 1988). Several studies have compared the activity of lisuride and LSD in whole animal models. Lisuride has been generally regarded as non-hallucinogenic and has been reported to differ in its actions in comparison to its hallucinogenic congener, LSD. In drug discrimination studies, rats have been reported to discriminate LSD from lisuride in a two-lever paradigm (White and Appel 1982; Winter 1994). In studies in which lisuride mimicked LSD in rats and monkeys, it was proposed that dopamine receptors play a predominant role in the drug stimulus effects of lisuride, and only a secondary role in the LSD cue (Holohean et al. 1982; Nielsen 1985). In electrophysiological studies, LSD has been found to potentiate the excitomodulatory effect of 5HT on glutamic acid-induced excitations in the rat facial motor nucleus, while lisuride exhibited no potentiation of 5HT (McCall and Aghajanian 1980). Differences in the pharmacological properties of LSD and lisuride were also apparent in locomotor activity studies where lisuride failed to mimic the effects of LSD and resembled the activity produced by apomorphine (Adams and Geyer 1985).

Several drug discrimination studies have demonstrated that rats respond similarly upon the administration of LSD and lisuride, and in LSD-trained monkeys, lisuride can substitute for LSD (Nielsen 1985; White 1986). Lisuride, at low doses, has been found partially to generalize to a DOM stimulus, which has been well characterized as a $5HT_{2A}$ receptor response (Glennon and Hauck 1985). In whole animal studies, lisuride demonstrated $5HT_{2A}$ agonist activity (Marini et al. 1981). Also, lisuride induces a head-twitch response in rats and shrews (Granoff et al. 1992; Darmani et al. 1994), a well characterized $5HT_{2A}$ receptor agonist-induced response. Taken together, these data suggest that lisuride can mimic LSD in some animal models. However, the psychopharmacological information on lisuride do not support classifying lisuride as a hallucinogen, as there is no substantial literature reporting acute "LSD-like" effects of this drug. There are a few reports that are suggestive of some psychotomimetic activity of lisuride, including visual hallucinations; dreamlike feelings; and increased perception of external stimuli (LeWitt et al. 1982; Nutt et al. 1985; Todes 1986; Critchley et al. 1988; Fernandez Pardal et al. 1988; Gershanik et al. 1988; Obeso et al. 1988; Vaamende

et al. 1991). The prevailing sense is that these effects are associated with chronic dopamine receptor agonist treatment, and are observed with other anti-parkinsonian regimens.

In summary, our data using recombinant cells expressing $5HT_{2A}$ or $5HT_{2C}$ receptors indicate that LSD and lisuride are partial agonists at both receptors. The reasons for a previous report indicating that lisuride was an antagonist at the $5HT_{2C}$ receptor may have to do with the system in which the studies were performed, a primary culture derived from rat choroid plexus (Burris et al. 1991). Due to a different stoichiometry of receptors and G-proteins that generally exists in recombinant cells allowing for more efficient coupling of the receptor and G-protein, weak partial agonist effects are readily observed. With the exception of a few compounds, experimental data from recombinant cells have been consistent with studies from choroid plexus. However, the effects produced by LSD and LSD-related hallucinogens in choroid plexus epithelial cells and recombinant cells may differ from the effects of hallucinogens at neuronal $5HT_{2C}$ receptors, due to the difference in the cell biology of the two systems. In more recent work, Sanders–Bush and coworkers have observed $5HT_{2C}$ agonist activity of lisuride in recombinant cells expressing $5HT_{2C}$ receptors (personal communication). As the agonist activity of lisuride at the $5HT_{2A}$ receptor and antagonist activity at the $5HT_{2C}$ receptor were interpreted as indicating that the $5HT_{2C}$ receptor displayed a pharmacological profile more consistent with the site-of-action of LSD-like hallucinogens (Burris et al. 1991), the agonist activity of lisuride reported herein indicates that the $5HT_{2A}$ receptor remains a more likely candidate as the key receptor triggering the hallucinogenic effects of LSD and related drugs. However, a contribution from $5HT_{2C}$ receptors cannot be eliminated, based on the information available at this time.

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