

Effect of LSD on Prepulse Inhibition and Spontaneous Behavior in the Rat: A Pharmacological Analysis and Comparison between Two Rat Strains

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The goal of the present study was to better delineate the mechanisms of action of the prototypical hallucinogen LSD. LSD (0.03, 0.1 and 0.3 mg/kg, s.c.) produced locomotor hyperactivity, disruption of PPI and a number of behaviors indicative of 5-HT activation such as wet-dog shakes, back muscle contractions and forepaw treading. These various behavioral effects of LSD were studied in both Sprague-Dawley and Wistar rats, although with the exception of back muscle contractions which were more prominent in Sprague-Dawley rats, no major strain differences were detected. The PPI disruption induced by LSD (0.1 mg/kg) in Sprague-Dawley rats was completely reversed by pretreatment with the selective 5-HT_{2A} antagonist MDL 100907 (0.5 and 1 mg/kg, s.c.). In contrast, pretreatment with antagonists at 5-HT_{2C} (SB

242084 (0.5 mg/kg, i.p.)); 5-HT_{2B/2C} (SDZ SER 082 (1 mg/kg, s.c.)); 5-HT_{1A}, ((+)-WAY 100135 (1 and 20 mg/kg, s.c.)) and 5-HT₆ receptors, (RO 04-6790 (30 mg/kg, i.p.)), all failed to influence LSD-induced disruption of PPI. The dopamine DA_{2like} receptor antagonist, haloperidol (0.1 and 0.2 mg/kg, s.c.), was without effect against an LSD-induced disruption of PPI. Finally, selective blockade of 5-HT_{2A} but not 5-HT_{2C} receptors completely abolished the locomotor hyperactivity induced by LSD. These findings provide empirical evidence to support the view that the hallucinogenic effects of LSD are mediated by a direct agonist effect at 5-HT_{2A} receptors.

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Delineation of the neurobiological mechanisms underlying the profound effects of hallucinogens on perception, mood, and thought processes has been the subject of

great interest over the years. There is now increasing evidence that the two major classes of hallucinogens, the indolamines (e.g., LSD) and the phenethylamines (e.g., DOM and DOI) share a common site of action at 5-HT₂ receptor populations (Barnes and Sharp 1999; Aghajanian and Marek 2000). 5-HT₂ receptors consist of three distinct subtypes, namely 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} (for review see Barnes and Sharp 1999). They are G-protein-coupled receptors and share a high degree of homology in their amino acid sequences. Binding and cellular studies have shown that LSD, DOI, DOM and other related hallucinogens share a high affinity for the 5-HT_{2A/B/C} receptor subtypes (Egan et al. 1998; Nelson et al. 1999; Porter et al. 1999). Furthermore, a strong

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correlation exists between their binding affinity at the 5-HT_{2A/B/C} receptor subtypes and their hallucinogenic potencies in man (for review see Barnes and Sharp 1999; Roth et al. 1999; Aghajanian and Marek 1999).

Until recently, study of the exact contribution of individual 5-HT₂ receptor subtypes to the behavioral profile of hallucinogens has been hampered by the lack of selective ligands. The recent development of selective ligands for 5-HT_{2A} and 5-HT_{2C} receptor subtypes has provided the opportunity for a more precise investigation into their functional role. The 5-HT_{2A} receptor antagonist MDL 100907 has been reported to have at least 100-fold selectivity for 5-HT_{2A} over the 5-HT_{2C} receptor (Palfreyman et al. 1993; Kehne et al. 1996). The 5-HT_{2C} receptor antagonist SB 242084 has 100-fold selectivity for the 5-HT_{2C} over both 5-HT_{2A} and 5-HT_{2B} receptors (Bromidge et al. 1997; Kennett et al. 1997). On the other hand, the 5-HT_{2C/2B} receptor antagonist SDZ SER 082 displays 40-fold selectivity for the 5-HT_{2C} compared to the 5-HT_{2A} receptor, but similar affinity for the 5-HT_{2C} and 5-HT_{2B} receptor subtypes (Nozulak et al. 1995). Studies conducted with some of these 5-HT₂ subtype-selective antagonists have indicated that 5-HT_{2A} rather than 5-HT_{2C} receptor subtypes are crucial for the discriminative stimulus effects of DOI (Schreiber et al. 1994). 5-HT_{2A} receptor activation was also suggested to be the principal mechanism underlying the disruptive effects of DOI on prepulse inhibition and latent inhibition (Sipes and Geyer 1995; Padich et al. 1996; Hitchcock et al. 1997). Furthermore, it has been shown that a number of 5-HT behaviors evoked by DOI in rats, such as wet-dog shakes, forepaw treading and back muscle contractions are mediated by 5-HT_{2A} rather than 5-HT_{2C} receptors (Wettstein et al. 1999; Sánchez and Arnt 2000).

While there is compelling evidence that 5-HT_{2A} receptor subtypes are the principal sites of action for DOI, to the best of our knowledge little is known about the participation of 5-HT_{2A} or 5-HT_{2C} receptors in the mediation of the behavioral effects of LSD. This is partly due to the fact that most of the recent behavioral studies have typically focused on DOI, which shares many properties with LSD but has a less complicated pharmacology. Indeed, unlike DOI which displays a high selectivity for 5-HT₂ receptors, LSD interacts additionally with several 5-HT (e.g., 5-HT_{1A}, 5-HT₅, 5-HT₆ and 5-HT₇) and dopamine D_{2like} receptors (Creese et al. 1975; Plassat et al. 1992; Shen et al. 1993; Boess et al. 1997; Aghajanian and Marek 1999). Early studies using correlational analysis to drug discrimination assays has suggested both 5-HT_{2A} and 5-HT_{2C} receptors may be important for the stimulus effects of LSD (Titeler et al. 1988), although more recently the potency of a number of antagonists to reduce the discriminative stimulus effects of LSD was shown to be significantly correlated with 5-HT_{2A} rather than 5-HT_{2C} affinity (Fiorella et al. 1995). LSD was also reported to produce a biphasic

change in locomotion, which consisted of an initial decrease followed by an increase in locomotor and exploratory behavior (Adams and Geyer 1982). More importantly, although the initial suppression of investigatory behaviors produced by LSD and DOI in rat is similar, it is differentially influenced by 5-HT_{2A} and 5-HT_{2C} receptors (Krebs-Thomson et al. 1998). These findings suggest that at least in terms of locomotor activity, the mechanisms of action of DOI and LSD might not be identical (see also Mittman and Geyer 1991).

In light of the above findings, the present study attempted to clarify further the pharmacological profile of LSD on PPI and locomotion. In the first series of experiments we characterized the behavioral profile of LSD in two commonly used rat strains, namely Sprague-Dawley and Wistar. Previous studies have shown that Sprague-Dawley and Wistar rats display different sensitivity to psychotomimetics (e.g., apomorphine, amphetamine and PCP) (Varty and Higgins 1994; Kinney et al. 1999) and antipsychotics (e.g., clozapine and risperidone) (Swerdlow et al. 1998; Varty et al. 1999), and thus it seemed worthwhile to examine whether they might show differential sensitivity to LSD. We first compared the effects of systemic administration of LSD on PPI and locomotor activity in both strains. In addition, we examined whether LSD could produce behavioral signs (wet-dog shakes, forepaw treading, back muscle contractions, penile erections/grooming) in Sprague-Dawley and Wistar rats, similar to that attributed to 5-HT_{2A} or 5-HT_{2C} receptor activation (Millan et al. 1997; Martin et al. 1998; Wettstein et al. 1999). Finally we studied the respective role of 5-HT_{2A} and 5-HT_{2C} receptors in the mediation of PPI deficits and locomotor hyperactivity produced by LSD in Sprague-Dawley rats using the most selective 5-HT_{2A} and 5-HT_{2C} receptor antagonists currently available. Given that LSD interacts with 5-HT_{1A}, 5-HT₆ and dopamine D_{2like} receptors, we also examined whether these receptors might contribute to the PPI deficits induced by LSD.

METHODS

Animals

Adult male (280–300g) Sprague-Dawley and Wistar rats (RCC Ltd., Fullinsdorf, Switzerland) were used. Following arrival at the holding facility, the animals were housed 4 per cage in a light and temperature controlled environment (lights on: 6 A.M.–6 P.M.) with food available *ad-libitum*. They were allowed one week of acclimation prior to testing. Experiments took place between 8 A.M. and 6 P.M..

Apparatus

Prepulse inhibition. Testing was conducted in eight startle devices (SRLAB, San Diego Instruments, San Di-

ego, California, USA) each consisting of a Plexiglas cylinder (8.8 cm diameter) mounted on a Plexiglas platform in a ventilated, sound-attenuated cubicle with a high frequency loudspeaker (28 cm above the cylinder) producing all acoustic stimuli. The background noise of each chamber was 68 dB. Movements within the cylinder were detected and transduced by a piezoelectric accelerometer attached to the Plexiglas base, digitized and stored by a computer. Beginning at the stimulus onset, 150 1-ms readings were recorded to obtain startle amplitude.

Locomotor activity and behavioral observations. Locomotor activity was measured using automated activity cages (36 × 24 × 19, L × W × H; Benwick Electronics, UK). Each cage was fitted with two sets of 19 infrared beams (12 front to back and 7 side to side with 2.5 cm space between two successive beams) located 5 and 15 cm off the cage floor. The activity detector operates by counting the number of times the beams changes from unbroken to broken (or *vice versa*) and incrementing the relevant counters. The interruption of the lower and upper sets of beams provided automated measures of horizontal and vertical activity, respectively. Non-cumulative records of photocell beam interruptions, for individual rats, were taken every five minutes in each experimental session. Mobile counts (interruption of three successive beams of the lower set of beams) were used to measure locomotor activity of the animals. For direct observations, the rats were placed individually in Macrolon cages (26 × 10 × 30 cm, L × W × H) with sawdust bedding. Mirrors placed behind the cages permitted an all-round view of the rats. Up to six rats were simultaneously scored by an observer blind to drug treatments.

Drugs

LSD, MDL 100907, SDZ SER 082, (+)-WAY 100135, RO 04-6790, and haloperidol (synthesized at Roche) were dissolved in NaCl 0.9% containing 0.3% Tween. SB 242084 was dissolved in 8% HP- β -cyclodextrin with 25 mM citric acid. MDL 100907, SDZ SER 082 and (+)-WAY 100135 were administered subcutaneously (s.c.) 30 minutes before the test. LSD and haloperidol were administered s.c. 5 and 10 minutes before the test, respectively. SB 242084 was given intraperitoneally (i.p.) 30 minutes before the test. All drugs were administered in a dose volume of 1 ml/kg.

General Procedure

The experimental procedures used in this study received approval from a local committee based on adherence to Swiss federal regulations and guidelines on animal experimentation.

Prepulse Inhibition. Prior to drug testing, the rats were each exposed to a single PPI session (identical to that used in experiment II) in order to ensure that the animals were assigned into balanced groups based on equivalent startle and PPI. For drug studies, the rats were used twice with a period of at least five days between two successive tests.

Experiment I. Naïve rats of each strain, Sprague-Dawley and Wistar, were tested in these series of experiments. Animals were given a subcutaneous injection of LSD (0.03, 0.1 and 0.3 mg/kg, $n = 8$ per dose) or vehicle (NaCl 0.9% containing 0.3% Tween), and 5 minutes later they were tested in a PPI paradigm. Each session was initiated with a 5-min acclimation period followed by 10 successive 120 dB trials. These trials were not included in the final data analysis. Eight different trial types were then presented: Startle pulse (ST120, 120 dB/40 msec duration), three prepulse stimulus given alone (70, 75 and 80 dB/20 msec duration: P70, P75 and P80 respectively), P70, P75 and P80 given 100 ms before the onset of the startle pulse (PP70, PP75 and PP80, respectively), and finally a trial where only the background noise (68 dB) was presented (NST) in order to measure the baseline movement in the cylinders. All trials were applied 8 times and presented in random order. The average inter-trial interval (ITI) was 15 sec (range 10–20 s).

Experiment II. Only Sprague-Dawley rats were used in these series of experiments. Animals were pretreated with MDL 100907 (1 and 0.5 mg/kg, $n = 7$ per dose), SB 242084 (0.5 mg/kg, $n = 8$), SDZ SER 082 (1 mg/kg, $n = 8$), (+)-WAY 100135 (1 and 20 mg/kg, $n = 8$ per dose), RO 04-6790 (30 mg/kg, $n = 8$) or haloperidol (0.1 and 0.2 mg/kg, $n = 8$ per dose) alone or in combination with LSD (0.1 mg/kg $n = 6$ –8 per group) according to a 2 × 2 factorial design. Control groups received injections of the corresponding vehicles for each treatment ($n = 6$ –8 per group). Each PPI session was initiated with a 5-min acclimation period followed by 10 successive 120 dB trials. These trials were not included in the analysis. Four different trial types were then presented: Startle pulse (ST120, 120 dB/40 msec), prepulse stimulus given alone (P75, 75 dB/20 ms), P75 given 100 ms before the onset of the startle pulse (PP75), and finally a trial where only the background noise (68 dB) was presented (NST) in order to measure the baseline movement in the cylinders. All trials were applied 10 times and presented in random order. The average inter-trial interval (ITI) was 15 sec (range 10–20 s).

Locomotor Activity and Behavioral Observations

Experiment I. Thirty-six naïve rats of each strain, Sprague-Dawley and Wistar, were used. Animals were first familiarized with the experimental cages for 60 minutes prior to any drug treatment. After habituation,

they received a subcutaneous injection of LSD (0.03, 0.1 and 0.3 mg/kg, $n = 8$ per dose) and their locomotor activity was measured 5 minutes later for 60 minutes.

Experiment II. A further group of experimentally naïve Sprague-Dawley rats were pretreated with an injection of MDL 100907 (0.5 mg/kg, s.c., $n = 8$) or SB 242084 (0.5 mg/kg, i.p., $n = 8$) alone or in combination with LSD (0.1 mg/kg, $n = 8$ per group). Control groups received injections of the corresponding vehicles for each treatment ($n = 8$ per group). The locomotor activity test started 5 minutes after LSD administration and lasted for 60 minutes.

Experiment III. One week after the locomotor activity study (Experiment I), animals were randomly allocated to vehicle and LSD (0.03, 0.1 and 0.3 mg/kg, $n = 8$ per dose) groups. The incidence of penile erection, penile grooming, wet-dog shakes and back muscle contractions was scored continuously during the 60-min session. The presence or absence of forepaw treading and chewing was also scored for 60 minutes in blocks of 5-min intervals. All scores were cumulated for the whole session, i.e. a maximal score per animal is 12.

Statistical Analysis

Effects of LSD on PPI were analyzed using a 3-way ANOVA with strain and LSD treatment as a between-subjects factor and trials (PP70, PP75 and PP80) as the repeated measure. Mean startle magnitude from the 120 dB trial, locomotor activity (mobile counts) and the 5-HT behaviors, wet-dog shakes, penile grooming and back muscle contractions, were analyzed using 2-way ANOVA with strain and LSD dose as between-subject factor. Forepaw treading and chewing were analyzed as medians and interquartile range with group comparisons made by Mann-Whitney U-test following a significant main effect according to the Kruskal-Wallis test. Drug interaction data were analyzed using a 2-way ANOVA with LSD and challenge drug as between-subject factors. Individual comparisons were carried out using Newman-Keuls *post-hoc* test whenever the ANOVA indicated statistically significant main effect or interaction. The % PPI was determined according to the formula $(100 \times (\text{ST120} - \text{PP70, PP75 or PP80}) / \text{ST120})$.

RESULTS

Behavioral Profile of LSD in Sprague-Dawley and Wistar rats

Prepulse Inhibition. LSD (0.03, 0.1 and 0.3 mg/kg) dose-dependently disrupted PPI in Sprague-Dawley and Wistar rats (main effect of treatment: $F_{3,55} = 15.5$, $p < .001$; treatment X trials interaction $F_{6,110} = 5.2$, $p < .001$; Figure 1, Panel A). The 3-way ANOVA failed however to reveal a significant main effect of strain ($F_{1,55} = 2.1$,

NS), strain X treatment interaction ($F_{3,55} = 0.9$, NS) or strain X treatment X trial interaction ($F_{6,110} = 0.7$, NS), thus indicating that LSD had comparable effects on PPI in both strains. *Post hoc* tests at each trial type indicated that the two highest doses of LSD (0.1 and 0.3 mg) significantly disrupted PPI at both 75 and 80 dB prepulse intensities in Sprague-Dawley rats. In Wistar rats, all doses of LSD (0.03, 0.1 and 0.3 mg) significantly reduced PPI at the 75 dB prepulse intensity, in contrast, only the two highest doses had a significant effect on PPI at the 80 dB prepulse intensity ($p < .05$, Student Newman Keuls).

Wistar rats displayed a significantly higher startle response to the 120 dB pulse than Sprague-Dawley rats ($F_{1,55} = 64.4$, $p < .001$, Figure 1, Panel B). Administration of LSD reduced startle reactivity in Sprague-Dawley rats ($F_{3,55} = 4.2$, $p < .05$), and *post hoc* tests indicated that only the highest dose (0.3 mg/kg) had a significant effect (Figure 1, Panel B). In contrast, none of the doses of LSD significantly reduced the baseline startle magnitude in Wistar rats, although there was a clear trend at the 0.3 mg/kg dose. Consequently, no strain differences in the ability of LSD to reduce the baseline startle magnitude were detected (strain X treatment interaction: ($F_{3,55} = 2.6$, NS),

Locomotor Activity. LSD (0.03, 0.1 and 0.3 mg/kg) markedly increased locomotor activity in Sprague-Dawley and Wistar rats (Figure 1, Panel C). The increase in locomotion was evident immediately during the first 5-min interval, and reached a maximum during the first 15–20 minutes of the test session. A gradual return to the control values was then noted during the second half of the test session depending on the dose. The 2-way ANOVA revealed a significant main effect of LSD ($F_{3,56} = 15.8$, $p < .001$), and *post hoc* tests indicated that all doses of LSD (0.03, 0.1 and 0.3 mg/kg) significantly increased locomotor activity in both strains. The 2-way ANOVA failed however to reveal a strain difference in response to the locomotor stimulant effects of LSD (main strain effects: $F_{1,56} = 1.3$, NS; and strain X LSD interaction: $F_{3,42} = 0.6$, NS).

Behavioral Observations. Administration of LSD-induced various behavioral effects in Sprague-Dawley and Wistar rats that essentially consisted of wet-dog shakes and back muscle contractions, with occasional forepaw treading and chewing (Table 1). The 2-way ANOVA revealed a significant increase in the incidence of wet-dog shakes in both strains (main treatment effect: $F_{3,56} = 10.0$, $p < .001$), and *post hoc* tests indicated that only the two lower doses of LSD (0.03 and 0.1 mg) had a significant effect in Sprague-Dawley rats. In contrast, all doses of LSD significantly increased the incidence of wet-dog shakes in Wistar rats. However, no significant differences in the effects of LSD on wet-dog shakes were detected between the two strains (strain X

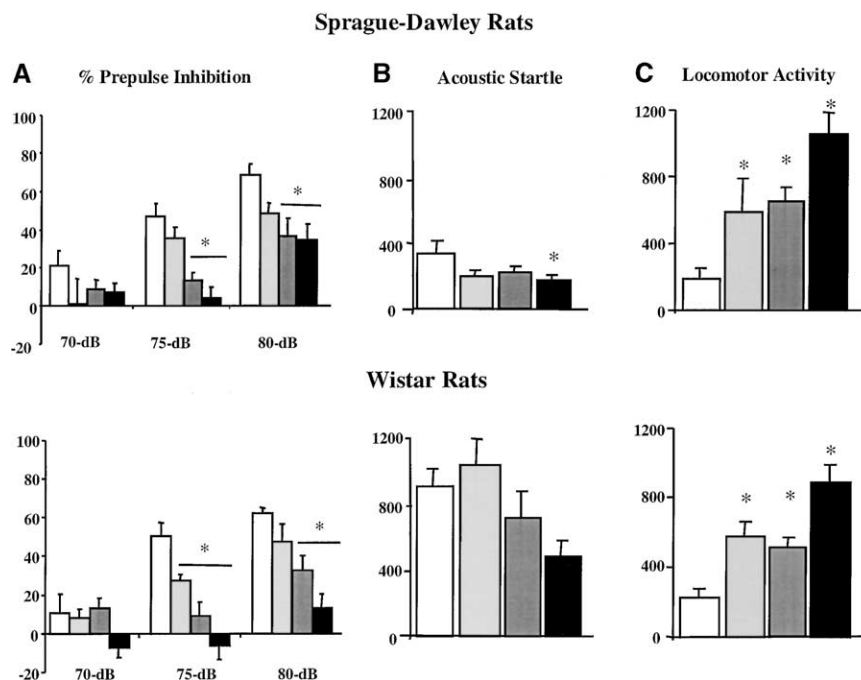


Figure 1. Effects of LSD (0.03, 0.1 and 0.3 mg/kg, s.c.) on (A) prepulse inhibition, (B) acoustic startle, and (C) locomotor activity in Sprague-Dawley and Wistar rats. Values represent mean \pm S.E.M. for each group. $n = 7-8$ per group. * $p < .05$, significantly different from vehicle-treated animals. Open bars: vehicle treatments; gray bars: LSD 0.03 mg/kg; crossed bars: LSD 0.1 mg/kg; black bars: LSD 0.3 mg/kg.

LSD interaction: $F_{3,56} = 2.5$, NS). LSD also induced back muscle contractions, and significant effects were detected at the highest dose (0.3 mg/kg) in both strains. However, there was a clear strain difference in the incidence of back muscle contractions produced by LSD as indicated by a significant main effect of strain ($F_{3,56} = 17.5$, $p < .001$) and strain \times LSD interaction ($F_{3,56} = 10.2$, $p < .001$). Significant increases in forepaw treading and chewing behaviors were also observed in both strains following administration of LSD ($p < .05$, Kruskal-Wallis test). In Sprague-Dawley rats, LSD had significant effects at the two highest doses (0.1 and 0.3 mg/kg) on forepaw treading and significant effects at all doses on chewing ($p < .05$, Mann-Whitney U-test). In Wistar rats, only 0.3 mg/kg LSD significantly increased forepaw treading, but the two highest doses (0.1 and 0.3 mg/kg) had significant effects on chewing ($p < .05$, Mann-Whitney U-test). In neither Wistar nor Sprague-Dawley rats was any notable change in penile erection/grooming identified following LSD pretreatment (Table 1).

Drug Interaction Studies

Effect of 5-HT₂ Receptor Antagonists against an LSD (0.1 Mg/Kg)-Induced PPI Disruption in Sprague-Dawley Rats. In all experiments, LSD (0.1 mg/kg) significantly disrupted PPI in Sprague-Dawley rats. Pretreatment with MDL 100907 (1 mg/kg) alone induced a facilitation of PPI ($F_{1,27} = 24.2$, $p < .001$, Figure 2, Panel A) MDL 100907 also reversed the disruption of PPI pro-

duced by LSD but the 2-way ANOVA just failed to reveal a significant interaction between MDL 100907 and LSD ($F_{1,27} = 4.0$, $p = .06$). Neither drug treatment altered the baseline startle amplitude (Table 2). Because pretreatment with MDL 100907 (1 mg/kg) alone affected PPI, a lower dose (0.5 mg/kg) was tested. MDL 100907 (0.5 mg/kg) administered alone had no effects on basal PPI but prevented the PPI deficit induced by LSD (MDL 100907 \times LSD interaction, $F_{1,23} = 11.0$, $p < .05$; Figure 2, Panel B). In this experiment, LSD significantly reduced the baseline startle amplitude ($F_{1,23} = 7.4$, $p < .05$) and the pretreatment with MDL 100907 failed to influence this effect (MDL 100907 \times LSD interaction, $F_{1,23} = 0.1$, $p > .05$; Table 2).

Pretreatment with the selective 5-HT_{2C} receptor antagonist SB 242084 (0.5 mg/kg) was without any effect on basal PPI ($F_{1,27} = 1.6$, NS, Figure 2, Panel C). SB 242084 also failed to reverse LSD-induced disruption of PPI as indicated by the lack of a significant SB 242084 \times LSD interaction ($F_{1,27} = 3.6$, NS). Administration of LSD alone significantly decreased the baseline startle amplitude, ($F_{1,27} = 26.7$, $p < .001$; Table 2). Even though SB 242084 significantly enhanced the startle reactivity ($F_{1,27} = 7.8$, $p < .01$), it failed to reverse the effect of LSD on this measure.

Pretreatment with the 5-HT_{2B/C} antagonist SDZ SER 082 (1 mg/kg) alone had no effect on basal PPI ($F_{1,27} = 0.2$, NS, Figure 3, Panel D), and also failed to reverse LSD-induced disruption of PPI (SDZ SER 082 \times LSD interaction, $F_{1,27} = 0.4$, NS). As shown in Table 2, adminis-

Table 1. Behavioral syndromes (Mean \pm SEM or Median and Interquartile range) induced by LSD (mg/kg) in Sprague-Dawley and Wistar Rats

		Wet dog shakes	Back muscle contractions	Forepaw Treading	Chewing	Penile grooming
Sprague-Dawley	Vehicle	1 \pm 0	0 \pm 0	0 (0–0)	1 (0–3)	1.4 \pm 0.3
	0.03 mg/kg	12 \pm 3*	4 \pm 4	0 (0–2)	5 (4–7)*	0.5 \pm 0.3
	0.1 mg/kg	11 \pm 4*	3 \pm 2	1 (1–2)*	7 (7–8)*	0.3 \pm 0.2
	0.3 mg/kg	8 \pm 2	28 \pm 7**	2 (1–4)*	5 (4–5)*	0 \pm 0
Wistar	Vehicle	1 \pm 1	0 \pm 0	0 (0–0)	3 (1–3)	0.3 \pm 0.2
	0.03 mg/kg	7 \pm 1	0 \pm 0	0 (0–0)	4 (3–5)	1.5 \pm 0.4
	0.1 mg/kg	13 \pm 1*	1 \pm 0	1 (0–1)	6 (5–6)*	1.5 \pm 0.5
	0.3 mg/kg	15 \pm 3*	2 \pm 1*	3 (3–5)*	7 (6–9)*	1.3 \pm 0.5

* $p < .05$, significantly different from vehicle-treated animals, Student Newman Keuls or Mann-Whitney U tests. ** $p < .05$, significantly different from Wistar rats. $n = 8$ rats per treatment group.

tration of LSD significantly reduced the baseline startle amplitude ($F_{1,27} = 7.0$, $p < .05$), and pretreatment with SDZ SER 082 failed to reverse this effect ($F_{1,27} = 0.02$, NS).

Effect of 5-HT_{1A}, 5-HT₆ and DA_{2like} Receptor Antagonists against an LSD-Induced PPI Disruption in Sprague-Dawley Rats. Pretreatment with the selective 5-HT_{1A} receptor antagonist (+)-WAY 100135 (1 and 20 mg/kg) had no effects on basal PPI, and also failed to antagonize an LSD-induced disruption of PPI (Figure 3, Panels A and B). The 2-way ANOVA failed to indicate a significant main effect of (+)-WAY 100135 (1 mg/kg: $F_{1,28} = 0.2$, NS; 20 mg/kg: $F_{1,28} = 0.1$, NS) or significant (+)-WAY 100135 \times LSD interaction (1 mg/kg: $F_{1,28} = 0.8$, NS; 20mg/kg: $F_{1,28} = 0.5$, NS). None of the drug treatments affected startle reactivity (Table 2).

Pretreatment with the selective 5-HT₆ antagonist RO 04-6790 (30 mg/kg) had no effect on basal PPI ($F_{1,28} = 0.03$, NS), and also failed to influence LSD-induced disruption of PPI ($F_{1,28} = 0.03$, NS, Figure 3, Panel C). None of the drug treatments affected basal startle (Table 2).

The dopamine D_{2-like} receptor antagonist, haloperidol (0.1 and 0.2 mg/kg), also failed to affect basal PPI or reverse the effect of LSD (Figure 3, Panels E and F). The

2-way ANOVA failed to show a significant main effect of haloperidol (0.1 mg/kg: $F_{1,27} = 0.9$, NS; 0.2 mg/kg: $F_{1,25} = 0.1$, NS) or significant haloperidol \times LSD interaction (0.1 mg/kg: $F_{1,27} = 0.0$, NS; 0.2 mg/kg: $F_{1,25} = 1.0$, NS). Haloperidol (0.1 mg/kg) significantly reduced the baseline startle response ($F_{1,27} = 4.8$, $p < .05$). In this experiment, LSD had no effects on baseline startle ($F_{1,27} = 0.2$, NS), and also failed to influence the startle reduction induced by haloperidol (haloperidol \times LSD interaction: $F_{1,27} = 0.8$, NS, Table 2). Again, haloperidol (0.2 mg/kg) significantly reduced baseline startle ($F_{1,25} = 4.7$, $p < .05$). In this experiment, the startle response was also reduced by LSD ($F_{1,25} = 9.3$, $p < .05$). The 2-way ANOVA failed to reveal any significant haloperidol \times LSD interaction ($F_{1,25} = 2.3$, NS).

Effect of 5-HT₂ receptor antagonists against LSD-induced locomotor hyperactivity in Sprague-Dawley rats. Figure 4 illustrates the effects of the selective 5-HT_{2A} and 5-HT_{2C} receptor antagonists MDL 100907 (0.5 mg/kg) and SB 242084 (0.5 mg/kg), respectively, on the locomotor hyperactivity induced by LSD. Administration of LSD (0.1 mg/kg) alone increased locomotor hyperactivity while pretreatment with MDL 100907 or SB

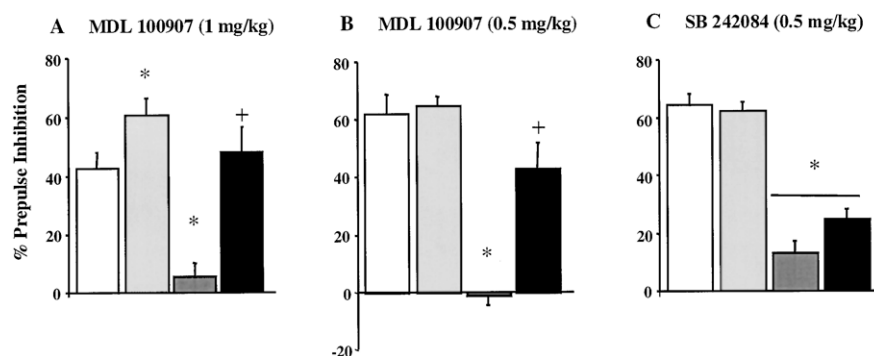


Figure 2. Effects of MDL 100907 (0.5 and 1 mg/kg, s.c.) and SB 242084 (0.5 mg/kg, i.p.) on the disruption of PPI induced by LSD (0.1 mg/kg, s.c.) in Sprague-Dawley rats. Values represent mean \pm S.E.M. for each group. $n = 6$ –8 per group. * $p < .05$, significantly different from vehicle-treated animals, and + $p < .05$, significantly different from LSD-treated animals. Open bars: vehicle/vehicle treatments; gray bars: drug/vehicle treatments; crossed bars: vehicle/LSD treatments; black bars: drug/LSD treatments.

Table 2. Effect of Various 5-HT Receptor Antagonists and the D_{2like} Receptor Antagonist Haloperidol Alone or in Combination with LSD (0.1 mg/kg) on Mean Baseline Startle Amplitudes in Sprague-Dawley Rats. **p* < .05 vs. Veh/Veh Group

Study	Treatment	Startle	Study	Treatment	Startle
MDL 100,907 (0.5 mg/kg)	Veh/Veh	315 ± 62	(+) -WAY 100,135 (1 mg/kg)	Veh/Veh	247 ± 43
	MDL/Veh	324 ± 36		WAY/Veh	272 ± 42
	Veh/LSD	204 ± 25*		Veh/LSD	170 ± 12
	MDL/LSD	201 ± 35*		WAY/LSD	236 ± 54
MDL 100,907 (1 mg/kg)	Veh/Veh	219 ± 31	(+) -WAY 100,135 (20 mg/kg)	Veh/Veh	459 ± 78
	MDL/Veh	308 ± 50		WAY/Veh	544 ± 95
	Veh/LSD	225 ± 36		Veh/LSD	350 ± 53
	MDL/LSD	288 ± 42		WAY/LSD	431 ± 62
SB 242,084 (0.5 mg/kg)	Veh/Veh	346 ± 38	Haloperidol (0.1 mg/kg)	Veh/Veh	395 ± 91
	SB/Veh	628 ± 114*		Hal/Veh	187 ± 41*
	Veh/LSD	172 ± 29		Veh/LSD	305 ± 83
	SB/LSD	210 ± 18		Hal/LSD	220 ± 41*
SDZ SER 082 (1 mg/kg)	Veh/Veh	523 ± 106	Haloperidol (0.2 mg/kg)	Veh/Veh	434 ± 94
	SDZ/Veh	369 ± 74		Hal/Veh	245 ± 51*
	Veh/LSD	322 ± 65*		Veh/LSD	199 ± 26*
	SDZ/LSD	191 ± 28*		Hal/LSD	166 ± 24*
Ro 04-6790 (30 mg/kg)	Veh/Veh	188 ± 29			
	Ro/Veh	190 ± 32			
	Veh/LSD	233 ± 42			
	Ro/LSD	161 ± 30			

242084 was without any effect on this measure. Pretreatment with MDL 100907 completely blocked the locomotor hyperactivity induced by LSD ($F_{1,28} = 7.1$, $p < .05$). In contrast, pretreatment with SB 242084 was without effect ($F_{1,28} = 1.6$, NS).

DISCUSSION

With the exception of locomotor hyperactivity, the various behaviors produced by LSD were comparable to those reported with other related hallucinogens such as DOI. Thus, like DOI, LSD produced a robust disruption of PPI in both Wistar and Sprague-Dawley rats (Sipes and Geyer 1994 1995; Varty and Higgins 1995; Padich et al. 1996) and induced a range of behaviors including wet-dog shakes, back muscle contractions and forepaw treading (Pranzatelli 1990; Fone et al. 1991; Wettstein et al. 1999). However, unlike DOI which has a high selectivity for 5-HT₂ receptor populations, LSD interacts with other 5-HT (e.g., 5-HT_{1A}, 5-HT_{2A/B/C}, 5-HT₆) and dopamine D_{2like} receptors (Creese et al. 1975; Plasat et al. 1992; Shen et al. 1993; Boess et al. 1997; Aghajanian and Marek 1999). One aim of this study was therefore to clarify the possible contribution of these various receptors in the mediation of the behavioral effects of LSD, particularly the disruptive effects of this hallucinogen on PPI, which to the best of our knowledge has yet to be characterized.

In line with previous findings (Geyer 1998), administration of LSD to rats induced a dose-dependent disruption of PPI. Interestingly, pretreatment with the selective 5-HT_{2A} receptor antagonist MDL 100907 was

able to prevent these effects. Selective blockade of 5-HT_{2A} receptors also completely blocked the locomotor stimulant effects of LSD. It is unlikely that the blockade of LSD-induced locomotor hyperactivity by MDL 100907 is related to non-specific effects. Firstly, animals pretreated with MDL 100907 alone were relatively more active than controls during the peak hyperactivity induced by LSD (10–25-min intervals, Figure 4). Secondly, we have previously found that MDL 100907 at the same dose (0.5 mg/kg) has no effect on the spontaneous activity of rats in a novel environment (Higgins et al. 2001; see also Moser et al. 1996). Collectively these findings strongly suggest that activation of 5-HT_{2A} receptors is the principal mechanism underlying the PPI deficits and locomotor hyperactivity observed with LSD. Blockade of 5-HT_{2A} receptors also enhanced basal PPI, suggesting some degree of endogenous 5-HT tone at the 5-HT_{2A} receptor that reduces sensorimotor gating. However, this facilitation could only be seen under a condition in which the basal level of PPI was low (Figure 2, Panel A), and therefore would suggest that variations in basal PPI levels observed across experiments may be in part related to changes in endogenous 5-HT tonicity. Local infusion of MDL 100907 into the ventral pallidum was reported to increase basal PPI (Sipes and Geyer 1997); it is therefore possible that this site may be one of the brain areas mediating the PPI facilitation observed following systemic administration of MDL 100907.

Despite a high affinity of LSD for 5-HT_{2C} receptors, which is of a similar order to that at the 5-HT_{2A} receptor (Egan et al. 1998; Porter et al. 1999), they do not appear to contribute to the observed behavioral effects of this

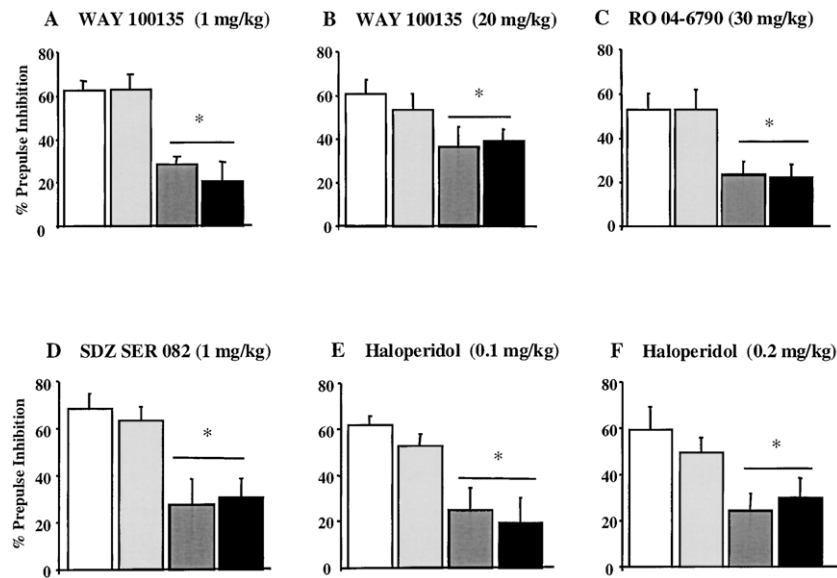


Figure 3. Effects of (+)-WAY 100135 (1 and 20 mg/kg, s.c.), Ro 04-6790 (30 mg/kg, i.p.), SDZ SER 082 (1 mg/kg, s.c.) and haloperidol (0.1 and 0.2 mg/kg, s.c.) on the disruption of PPI induced by LSD (0.1 mg/kg, s.c.) in Sprague-Dawley rats. Open bars: vehicle/vehicle treatments; gray bars: drug/vehicle treatments; crossed bars: vehicle/LSD treatments; black bars: drug/LSD treatments. Values represent mean \pm S.E.M. for each group. $n = 6-8$ per group. * $p < .05$, significantly different from vehicle-treated animals.

drug. For instance, at none of the doses of LSD tested were any behavioral signs ascribed to 5-HT_{2C} receptor activation such as penile grooming/erections and hypoactivity observed (Kennett et al. 1997; Millan et al. 1997; Martin et al. 1998). Rather, LSD evoked a range of behavioral changes (wet-dog shakes, back muscle contractions, forepaw treading) that are attributed to 5-HT_{2A} receptor activation (Wettstein et al. 1999; Sánchez and Arnt 2000). Furthermore, the 5-HT_{2C} antagonist SB 242084 at a dose of 0.5 mg/kg failed to antagonize the locomotor stimulant effect of LSD. This antagonist blocks the locomotor hypoactivity induced by the preferential 5-HT_{2C} agonist mCPP, with an approximate ED₅₀ of 0.1 mg/kg (unpublished findings; see also Kennett et al. 1997). Furthermore, we have recently shown that SB 242084 at the dose of 0.5 mg/kg completely reverses several of the behavioral effects of the 5-HT_{2C} agonist Ro 60-0175 (Grottick et al. 2000; Higgins et al. 2001). Hence, the failure of this antagonist to prevent the locomotor stimulant effects of LSD strongly argues against an involvement of 5-HT_{2C} receptors in mediating the behavioral effects of LSD. As with the locomotor stimulant effects of LSD, the disruption of PPI was not affected by blockade of 5-HT_{2C} receptors. The 5-HT_{2C} antagonists, SDZ SER 082 or SB 242084, each administered at behaviorally active doses (Nozulak et al. 1995; Kennett et al. 1997; Mora et al. 1997; Grottick et al. 2000) failed to attenuate the PPI deficits induced by LSD. These findings are consistent with those reported by Sipes and Geyer (1995) showing that SDZ SER 082 was ineffective in normalizing the PPI deficits induced by DOI. Furthermore,

mCPP was found to reduce startle reactivity without affecting basal PPI (Sipes and Geyer 1994). Taken together, these findings strongly suggest that the 5-HT_{2C} receptor may not be involved in the modulation of sensorimotor inhibitory processes. It is worth noting that SB 242,084 significantly increased basal startle response, which together with the inhibitory effects of mCPP on this measure suggests that 5-HT_{2C} receptor modulation may influence startle reactivity. In the current study LSD significantly decreased basal startle, although pretreatment with SB 242,084 failed to prevent this effect, again suggesting that LSD acted via 5-HT_{2C} independent receptor mechanisms to influence this measure. Finally, the negative data obtained with SDZ SER 082, which is also a high affinity 5-HT_{2B} receptor antagonist (Nozulak et al. 1995), makes it unlikely that this receptor subtype is involved in the effects of LSD on startle reactivity and sensorimotor gating.

We also failed to find any evidence for 5-HT_{1A} or 5-HT₆ receptors in the disruptive effects of LSD on PPI. Pretreatment with behaviorally active doses (1 mg/kg: Forster et al. 1995; 20 mg/kg: Sipes and Geyer 1995) of the selective 5-HT_{1A} receptor antagonist, (+)WAY 100135, were without effect on the PPI deficits induced by LSD. This is an important observation as direct 5-HT_{1A} receptor agonists (e.g., 8-OH-DPAT) have been reported to disrupt PPI (Rigdon and Weatherspoon 1992; Sipes and Geyer 1995). LSD also has a high affinity for 5-HT₆ receptors (Boess et al. 1997); however, pretreatment with a behaviorally active dose of the selective 5-HT₆ receptor antagonist, RO 04-6790 (Sleight et

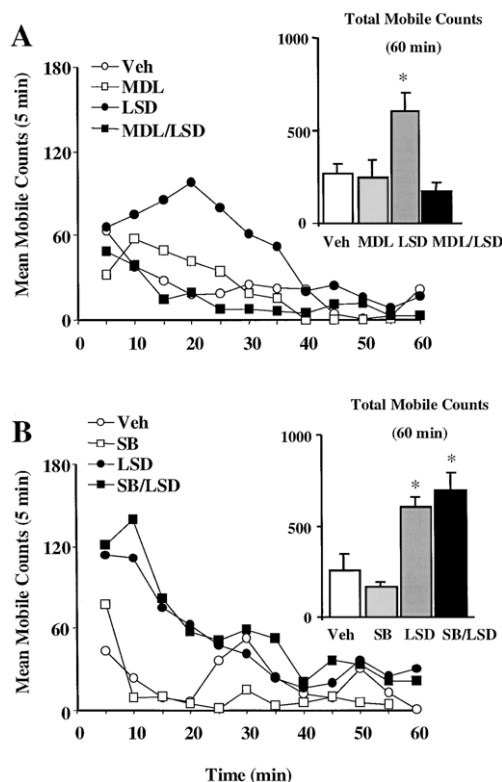


Figure 4. Effects of MDL 100907 (0.5 mg/kg, s.c.) and SB 242084 (0.5 mg/kg, i.p.) on the locomotor activity induced by LSD (0.1 mg/kg, s.c.) in Sprague-Dawley rats. Open bars: vehicle/vehicle treatments; gray bars: drug/vehicle treatments; crossed bars: vehicle/LSD treatments; black bars: drug/LSD treatments. Values represent mean \pm S.E.M. for each group. $n = 6-8$ per group. * $p < .05$, significantly different from vehicle-treated animals.

al. 1998; Bentley et al. 1999), failed to antagonize the disruption of PPI induced by LSD. It is therefore unlikely that 5-HT₆ receptors are involved in the disruptive effects of LSD on PPI.

The blockade of DA_{2like} receptors was also without any effect on the PPI deficit induced by LSD. The lowest dose of haloperidol (0.1 mg/kg) we used was previously shown to block the disruption of PPI induced by apomorphine (Mansbach et al. 1988; Rigdon and Viik 1991; Swerdlow and Geyer 1993; Varty and Higgins 1995). Furthermore, no attenuation of an LSD-induced PPI deficit was observed following pretreatment with a higher dose (0.2 mg/kg) of haloperidol. These data are consistent with the observations of Varty and Higgins (1995) that a DOI-induced PPI disruption was insensitive to the DA_{2like} receptor antagonists haloperidol and raclopride. Similarly, Padich et al. (1996) failed to reverse a DOI-induced auditory- and visual-PPI deficit with haloperidol (0.25 mg/kg). Taken together with the present findings with LSD, it would seem that 5-HT_{2A} receptor activation disrupts PPI through a DAergic-independent mechanism (possibly glutamatergic; see

Aghajanian and Marek 1999 2000). Notably, these three studies utilized both Wistar and Sprague-Dawley rat strains. However, research by Sipes and Geyer (1994) suggest that a DOI-induced disruption is blocked by haloperidol, although a direct effect of haloperidol at 5-HT_{2A} receptors could not be excluded (see discussion, Sipes and Geyer 1994). Clearly, a more thorough evaluation involving multiple rat strains and highly subtype selective DA antagonists against DOI and LSD-induced PPI disruptions are necessary to ultimately clarify any role of DA systems in 5-HT_{2A} agonist-induced PPI disruptions. An alternative approach might be to evaluate the potency of DOI and/or LSD PPI disruptions in the various lines of DA receptor knockout mice presently available, which seem to show normal baseline PPI (Ralph et al. 1999).

Finally, it should be stressed that LSD interacts with other 5-HT receptors including 5-HT₅ and 5-HT₇, and it is thus possible that they too may contribute to its behavioral effects. For instance, it was recently found that the stimulatory effect of LSD on exploratory activity was attenuated in mice lacking 5-HT_{5A} receptors, thus indicating that the former receptors may be involved in the psychostimulant effects of LSD (Grailhe et al. 1999). However, it must be noted that LSD-induced PPI disruption was completely blocked by MDL 100907, which has a relatively low affinity for 5-HT₇ receptors (1nM 5-HT_{2A} vs. 226nM 5-HT₇) and particularly for the 5-HT_{5A} subtype (>10,000nM) (Kehne et al. 1996). Nonetheless, the respective contribution of 5-HT₅ and 5-HT₇ receptor subtypes in mediating the effects of LSD on PPI would need to be formally studied, once selective antagonists of these receptors become generally available.

Finally, the present study addressed strain differences in the behavioral effects of LSD. It has previously been reported that Sprague-Dawley and Wistar rats display differential sensitivities to PPI disruption induced by psychotomimetics such as apomorphine, amphetamine and PCP (Rigdon 1990; Varty and Higgins 1994; Kinney et al. 1999). The ability of antipsychotics (clozapine and risperidone) to reverse apomorphine- or dizocilpine-induced deficits also appears to differ between these two strains (Swerdlow et al. 1998; Varty et al. 1999). In the present study we found that LSD was equally disruptive in both rat strains. Interestingly, it was recently shown that reversal of dizocilpine-induced deficits in PPI with the 5-HT_{2A} antagonist MDL 100907 did not differ between Sprague-Dawley and Wistar rats (Varty et al. 1999). It may be that although inter-strain differences exist with respect to drugs acting through DA receptors, Sprague-Dawley and Wistar rats do not differ significantly in their response to agents acting primarily via 5-HT_{2A} receptors. Consistent with this suggestion, we found that LSD had similar effects on locomotor activity in Sprague-Dawley and Wistar rats, and that the incidence of the number of

5-HT_{2A} receptor-mediated behaviors (wet-dog shakes, forepaw treading and chewing) evoked by LSD was comparable in both strains. The only obvious difference was a marked increase in the number of back muscle contractions elicited by a dose of 0.3mg/kg LSD in Sprague-Dawley rats.

In conclusion, the present study suggests that LSD-induced PPI disruption and locomotor changes are mediated via 5-HT_{2A} receptor activation. LSD also produces a number of other behaviors characteristic of 5-HT_{2A} receptor agonism such as wet-dog shakes, forepaw treading and back muscle contractions. These behavioral effects of LSD, with the exception of locomotor hyperactivity, are similar to those previously reported with other related hallucinogens such as DOI, most likely because both hallucinogens share a common mechanism of action at 5-HT_{2A} receptors.

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