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The Stimulus Properties of LSD in C57BL/6 Mice¹

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Abstract

Rationale—Drug-induced stimulus control has proven to be a powerful tool for the assessment of a wide range of psychoactive drugs. Though a variety of species have been employed, the majority of studies have been in the rat. However, with the development of techniques which permit the genetic modification of mice, the latter species has taken on new importance. Lysergic acid diethylamide [LSD], the prototypic indoleamine hallucinogen, has not previously been trained as a discriminative stimulus in mice.

Objective—To demonstrate the feasibility of LSD-induced stimulus control in the mouse and to provide a preliminary characterization of the stimulus properties of LSD in that species.

Methods—Male C57BL/6 mice were trained using a left or right nose-poke operant on a fixed-ratio 10, water reinforced task following the injection of lysergic acid diethylamide [LSD, 0.17 or 0.30 mg/kg, SC; 15 min pretreatment] or vehicle.

Results—Stimulus control was established in 6 of 16 mice at a dose of LSD of 0.17 mg/kg after 39 sessions. An increase in dose to 0.30 mg/kg for the remaining mice resulted in stimulus control in an additional 5 subjects. In the low dose group, subsequent experiments demonstrated an orderly dose-effect relationship for LSD and a rapid offset of drug action with an absence of LSD effects 60 min after injection. When LSD [0.17 mg/kg] was administered in combination with the selective 5-HT_{2A} antagonist, M100907, LSD-appropriate responding was significantly but incompletely reduced to approximately 50%; concurrently, response rates declined significantly. In mice trained with a dose of LSD of 0.30 mg/kg, full generalization to the phenethylamine hallucinogen, [-]-2,5-dimethoxy-4-methylamphetamine [DOM] was observed.

Conclusions—The present data demonstrate the feasibility of LSD-induced stimulus control in the mouse. The general features of stimulus control by LSD in the mouse closely resemble those observed in the rat but the present data suggest that there may be significant differences as well.

Keywords

Drug discrimination; DOM; LSD; M100907; Mouse

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1. Introduction

The development of drug-induced stimulus control as a tool for the study of behaviorally active drugs [Overton, 1971; Harris and Balster, 1971; Winter, 1974, 1978a] has permitted pharmacological characterization in intact animals of a variety of psychoactive drugs including LSD [Hirschhorn and Winter, 1971; Glennon et al., 1982; Cunningham and Appel, 1987]. Although exceptions have been noted [Ator et al., 1993; Ator, 1994], there is a strong correlation between discriminative stimuli in non-verbal species and subjective effects reported by humans [Schuster and Johanson 1988; Balster 1990; Sanger et al. 1994; Brauer et al. 1997]. Although drug-induced stimulus control has been established in humans [for reviews see Kamien et al., 1993; Brauer et al., 1997; Dykstra et al., 1997] and in a number of animal species, the majority of studies have employed the rat [Stolerman and Kamien, 2004]. Nonetheless, the stimulus properties of a number of drugs have been examined in mice as well. These represent a range of pharmacological classes including stimulants such as cocaine [Middaugh et al., 1998] the amphetamines [Snoddy and Tessel; 1983], nicotine [Varvel et al., 1999; Stolerman et al. 1999], and pentylenetetrazole [Evans and Balster, 1992], the depressants morphine [Borlongan and Watanabe, 1997], pentobarbital [Balster and Moser, 1987; Rees and Balster, 1988], oxazepam [Rees and Balster, 1988], and ethanol [Rees and Balster, 1988; Grant et al., 1991; Middaugh et al., 1991], non-competitive NMDA antagonists including phencyclidine [Middaugh et al., 1988; English et al., 1999] and dizocilpine [Geter-Douglas and Witkin, 1999] as well as monoamine reuptake inhibitors [fluvoxamine, Gommans et al., 1998; nisoxetine, Snoddy and Tessel; 1983] and the atypical antipsychotic agent, clozapine [Philibin et al., 2005]. In the first, and at this time only, report of stimulus control by a hallucinogen in mice, Smith, Barrett, and Sanders-Bush [2003] employed the phenethylamine hallucinogen, 2,5-dimethoxy-4-iodo-amphetamine [DOI; Shulgin and Shulgin, 1991]. These authors emphasized the fact that the mouse, as presently compared with other species, provides the very great advantage that specific receptors may be deleted, so-called knockout mice [Gingrich and Hen, 2001; Bucan and Abel, 2002; Seong et al., 2002]. This advantage has already been exploited in investigations of stimulus control by nicotine in knockout mice lacking the *alpha7* subunit of the nicotinic receptor [Stolerman et al., 2004], by cocaine in mice absent the dopamine D₂ [Chausmer et al., 2002], D₄ [Katz et al., 2003], or D₅ [Elliot et al., 2003] receptors, and by ethanol in mice in which the *gamma*-aminobutyric acid type A receptor *delta* subunit is knocked out [Shannon et al., 2004]. In the present report, we describe the induction of stimulus control by LSD in C57BL/6 mice.

2. Materials and Methods

2.1. Subjects

Male C57BL/6 mice were obtained from Harlan Sprague Dawley, Inc. at an age of 8 weeks. They were housed in a temperature-controlled room under a constant 12:12 h light-dark cycle. All experiments were conducted during the light phase. Access to water was restricted to 20 min per day immediately after training and test sessions. Animals used in these studies were maintained in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals as amended August 2002. All experimental protocols were approved by the Institutional Animal Care and Use Committee of the University at Buffalo.

2.2. Discrimination training

Four small animal test chambers [MED Associates ENV-307W-CT] were used for all experiments. These were housed in larger light-proof, sound-insulated boxes which contained a house light and an exhaust fan. Chambers contained two snout-poke modules [MED Associates ENV-3BM] mounted at opposite ends of one wall. Centered between the operanda was a dipper which delivered 0.1 ml of water. Sessions were managed by a micro-computer

using operant control software [MED-PC State Notation, Version IV]. Subjects were trained to discriminate LSD from saline using a pretreatment time of 15 min and an initial dose of 0.17 mg/kg [subcutaneous injection] extrapolated from previous work in our laboratory in the rat [Hirschhorn and Winter, 1971]. A fixed ratio 10 [FR10] schedule of reinforcement was employed. Drug-induced stimulus control was assumed to be present when, in five consecutive sessions, 83% or more of all responses prior to the delivery of the first reinforcer were on the appropriate side.

2.3. Test procedures

After stimulus control was established with the training agents, tests were conducted once per week in each animal so long as performance did not fall below the criterion level of 83% correct responding in any one of the previous three training sessions, i.e., no more than two incorrect responses prior to completion of the FR10 on the correct side. Half of the test sessions were conducted the day after saline training sessions with the remainder following LSD training sessions. During test sessions, no responses were reinforced and the session was terminated after the emission of ten responses on either manipulandum. The distribution of responses between the two manipulanda was expressed as a percentage of total responses emitted on the drug-appropriate manipulandum. Response rate was calculated for each session by dividing the total number of responses emitted on both manipulanda by the elapsed time prior to 10 responses on either manipulandum. Throughout the text, pretreatment times refer to the elapsed time between drug administration and testing, e.g., a 60 min pretreatment time for M100907 means that it was given 45 min before LSD when the latter was given using its usual 15 min pretreatment time.

2.4. Drugs

All drugs used in behavioral experiments were dissolved in 0.9% saline solution and injected in a volume of 3.0 ml/kg bodyweight. The subcutaneous route was employed for all drugs. LSD and [-]-2,5-dimethoxy-4-methyl-amphetamine [DOM] were supplied by the National Institute on Drug Abuse [Rockville, MD, USA]. M100907 was synthesized in our laboratories [Ullrich and Rice, 2000].

2.6. Statistical analysis

Behavioral data were assessed for statistical significance using individual applications of paired Student's *t*-test and 1-way repeated measures analysis of variance [ANOVA] followed by pairwise comparisons using the Holm-Sidak method. Differences were considered statistically significant if the probability of their having arisen by chance was < 0.05 . All analyses were conducted using SPSS for Windows [SPSS Inc.].

3. Results

3.1 Stimulus control by LSD

Preliminary experiments in 16 mice established that a dose of LSD of 0.17 mg/kg was not rate suppressant. All mice then began training at that dose. Six of the animals reached criterion performance in a mean of 39 sessions [range = 22–74, figure 1, upper panel]. Response rates in those mice were consistently higher following treatment with LSD as compared with vehicle administration [control: 25 responses per minute [rpm]; LSD: 44 rpm; $P = 0.004$; figure 1, lower panel]. For the remaining mice, the dose was then increased to 0.3 mg/kg and, following 11 days of training, stimulus control was present in an additional 5 animals [figure 2, upper panel]. Though less pronounced than that seen in figure 1, the rate differential between LSD and vehicle treatments remained [control: 20 rpm; LSD: 30 rpm; $P = 0.038$; figure 2, lower

panel]. Stimulus control was not established in the remaining 5 mice and they were removed from the study.

3.2. Dose-effect relationship for LSD and antagonism by M100907

In mice trained with a dose of LSD of 0.17 mg/kg, both higher and lower doses were tested [figure 3]. As expected, LSD-appropriate responding following 0.08 mg/kg was intermediate in nature, i.e., significantly different from both training conditions [$F(5,2) = 23.987$; $P < 0.004$; pairwise comparisons: vehicle versus 0.08: $P < 0.05$; 0.08 versus 0.17: $P < 0.02$]. Also as expected, a dose of LSD higher than the training dose, 0.3 mg/kg, did not result in a significantly greater degree of stimulus control but the response rate was significantly reduced [$P < 0.02$; figure 3, lower panel]. When mice were pretreated with the selective 5-HT_{2A} antagonist, M100907, stimulus control by the training dose of LSD was significantly reduced. However, simultaneous comparison of vehicle, the training dose of LSD, and the combination of LSD and M100907 by one-way repeated measures ANOVA revealed the antagonism to be intermediate in nature, i.e., the combination was significantly different from both training conditions [$F(4,2) = 53.248$; $P < 0.02$; pairwise comparisons: vehicle versus combination, $P < 0.05$; combination versus LSD, $P < 0.03$]. Interestingly, when given alone, M100907 had a significant rate-suppressant effect when compared with vehicle [$P < 0.03$]. Subsequently, the dose-effect relationship for M100907 alone and in combination with the training dose of LSD was established [figure 4]. It is seen that no dose of M100907 completely antagonized LSD, all doses of M100907 were rate suppressant, and that, at the higher doses of M100907, rate was still further suppressed when given in combination with LSD.

3.3. Time course for LSD-induced stimulus control

The data of figure 5 indicate that in mice trained with LSD using a pretreatment time of 15 min, stimulus control is still present after 30 min but that the effect is lost after 60 min. Similarly, rate enhancement following LSD is present at 15 and 30 min relative to vehicle control but is absent at 60 min.

3.4. Generalization to DOM

The results of tests of generalization of stimulus control by LSD to [-]-DOM are shown in figure 6. In contrast with the data shown in figures 3–5, in which tests were conducted in mice trained with a dose of LSD of 0.17 mg/kg, the tests represented in figure 6 are from mice trained using LSD at a dose of 0.3 mg/kg. For the phenethylamine hallucinogen, [-]-DOM, an intermediate degree of LSD-appropriate responding was seen at a dose of 0.6 mg/kg and complete substitution was observed following a dose of 1.2 mg/kg. The higher dose significantly suppressed the rate of responding relative to vehicle treatment.

4. Discussion

The data of figures 1 and 2 indicate that a dose of LSD of 0.17–0.30 mg/kg administered subcutaneously 15 min before training will establish stimulus control in a majority of C57BL/6 mice. For the group of six mice trained at a dose of 0.17 mg/kg [figure 1], the number of sessions required to reach criterion performance [39] and the rate of emission of the nose-poke operant [44 rpm] may be compared with that observed in the rat. In a group of six F-344 rats recently trained in our laboratory using a dose of 0.10 mg/kg [i.p.] and a 15-min pretreatment time, a mean of 22 [SEM = 1] sessions was required to reach criterion performance with a rate of lever-press responding of 27 [SEM = 6] per minute [unpublished observations] which was not significantly different from the rate following vehicle [20 $\pm$ 3]. The fact that when the dose was increased to 0.30 mg/kg, an additional 5 mice quickly reached criterion performance [figure 2] suggests that our original training dose of 0.17 mg/kg may not have been optimal. Also suggestive that optimal training conditions were not employed is the fact that stimulus

control was not achieved in 5 of the original 16 mice trained. However, in the mice in which stimulus control was achieved, our rat/mouse potency ratio for LSD of 1.7–3.0 is in reasonable agreement with the ratio for DOI of 3.3 reported by Smith et al. [2003]. In that study, DOI produced modest decreases in response rate as compared with the present observation of significant increases in rate of responding at the LSD dose of 0.17 mg/kg. It must be noted however that direct comparisons, particularly with respect to response rates, are made difficult by experimental differences between our studies including the schedule of reinforcement [VI 30 sec vs FR 10], the operant utilized [lever press versus nose-poke], and the basis for determining response rates.

The dose effect relationship for LSD shown in figure 3 for animals trained at 0.17 mg/kg is as expected in that a higher dose [0.3 mg/kg] was comparable to the training dose in terms of LSD-appropriate responding but produced a significant reduction in response rate while a lower dose [0.08 mg/kg] yielded an intermediate level of drug-appropriate responding. An unexpected finding seen in figure 3 is the absence of complete blockade of LSD by the selective 5-HT_{2A} selective antagonist, M100907, and a suppression of response rates by M100907 alone and by the combination of LSD and M100907. These observations stand in contrast with our earlier findings in the rat in which LSD-induced stimulus control was completely antagonized by M100907 without a change in response rate [Winter et al., 2004] as well as with the results reported by Smith et al. [2003] for DOI in the mouse. In the latter study, increasing doses of M100907 produced a dose-related and eventually complete antagonism of DOI without significant effects on rate of responding. We have previously observed in rats trained with LSD that 5-methoxy-*N,N*-dimethyltryptamine [MDMT], an indoleamine hallucinogen which includes a prominent 5-HT_{1A} receptor-mediated component in its actions [Spencer et al., 1987], produces significant suppression of responding when combined with the non-selective serotonergic antagonists, pizotyline and pirenperone [Winter and Rabin, 1988]. Furthermore, MDMT-induced stimulus control is partially antagonized both by pindolol, a non-selective 5-HT_{1A} receptor antagonist, and by the selective 5-HT_{1A} receptor antagonist, WAY-100635 [Winter et al., 2000]. In light of these previous observations, one may account for the discrepancy between the present results with M100907 in combination with LSD and those of Smith et al. [2003] for DOI plus M100907 by invoking agonist activity by LSD at 5-HT_{1A} receptors, an effect not produced by DOI. Though plausible, this suggestion cannot explain the absence of a rate-suppressant effect of the combination of LSD and M100907 in the rat [Winter et al. 2004] or the decreases in rate produced by M100907 when given alone to mice [present figures 3 and 4].

In an attempt to explore further the interactions of M100907 with the stimulus effects of LSD, we examined a range of doses of M100907 both alone and in combination with the training dose of LSD [figure 4]. The hypothesis to be tested was that antagonism of LSD by M100907, whether partial or complete, is independent of rate suppression by M100907. Unfortunately, the data of figure 4 are relatively uninformative in that even at the lowest dose tested [0.01 mg/kg], antagonism appears to be intermediate in nature and the rate of responding is still suppressed.

The data presented in figure 5 indicate that following the administration of LSD at a dose of 0.17 mg/kg, stimulus control is present in the mouse for at least 30 min but then rapidly declines over the subsequent 30 minutes. We are unaware of directly comparable studies in rats trained with LSD but previous studies in our laboratory which examined the time course of the stimulus effects of LSD in rats trained with the phenethylamine hallucinogen, [-]-DOM, are informative [Fiorella et al., 1995]. In that investigation, we observed full substitution of LSD for [-]-DOM over a range of 15 to 90 minutes followed by a rapid decline to control levels. This finding in conjunction with the data of figure 5 suggest that the stimulus effects of LSD decline more rapidly in the mouse than in the rat. With respect to the pharmacokinetics of LSD, there appear

to have been no directly comparable studies in mice and rats of the rate of metabolism of LSD [for review see Sankar, 1975] but it is reasonable to assume that the half life for LSD is related to body size. Thus, for example, estimates of the half life of LSD in the mouse range from 7 to 37 minutes [Lanz et al., 1955; Stoll et al., 1955; Haley and Rutschmann, 1957] as compared with 100 minutes in monkeys [Axelrod et al., 1957], and 175 minutes in humans [Aghajanian and Bing, 1964]. It must be noted however that these estimates were based on different routes of administration and doses in the respective species.

A conclusion of the initial report of stimulus control by hallucinogens was that LSD, an indoleamine hallucinogen, and mescaline, a phenethylamine hallucinogen, “produce qualitatively similar interoceptive cues in the rat” [Hirschhorn and Winter, 1971]. Subsequent evidence that stimulus control by both types of hallucinogens is mediated by serotonergic mechanisms was provided by the observation that the stimulus effects of both LSD and mescaline in the rat are blocked by serotonergic antagonists [Browne and Ho, 1975; Winter, 1975; 1978b]. Many subsequent investigations have found symmetrical generalization between indoleamine and phenethylamine hallucinogens. Thus, the data of figure 6 showing full generalization of LSD to DOM in mice trained with LSD at a dose of 0.3 mg/kg are not surprising. However, DOM was seen to have significant rate-suppressing effects at all doses tested and only 3 of 5 subjects completed testing at a dose of 1.0 mg/kg. Rate suppression by both racemic and [-]-DOM has previously been noted in rats trained with LSD [Winter and Rabin, 1988; Fiorella et al., 1995]. It should be noted that the data for antagonism of LSD by M100907 and for the time course of stimulus control by LSD were obtained in mice trained with a dose of LSD of 0.17 mg/kg whereas the generalization of LSD to DOM was demonstrated in mice trained with a dose of 0.3 mg/kg. Because of the influence which the training dose may have on subsequent tests of generalization and antagonism [Shannon and Holtzman, 1979; Mumford and Holtzman, 1991; Comer et al., 1991], the present data should be interpreted with caution.

In summary, the present data indicate that mice are amenable to training with LSD as a discriminative stimulus although requiring somewhat higher doses than those previously employed in the rat. A notable difference between mice and rats in which stimulus control has been established with LSD are their respective interactions with the selective 5-HT_{2A} antagonist, M100907. Whereas complete blockade of LSD without suppression of the rate of responding has been observed in rats, the present data show only partial antagonism of LSD by M100907 and significant suppression of rates of responding both by M100907 alone and in combination with LSD. These observations suggest that certain non-5-HT_{2A}-mediated elements in the compound stimulus induced by LSD may be more salient in the mouse than in the rat.

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Figure 1.

LSD-induced stimulus control at a training dose of 0.17 mg/kg. Data shown are for the 6 subjects in which criterion performance was achieved. *Triangles* represent experiments in which saline was injected SC 15 min before the session. *Circles* represent identical experiments in which LSD was administered. Standard errors of the mean are indicated. Response rates were significantly higher following LSD as compared with saline [$p < 0.05$; see text for details]. *Ordinate: upper panel: percent LSD-appropriate responding; lower panel: rate expressed as responses per minute. Abscissa: sessions.*

Figure 2.

LSD-induced stimulus control at a dose of 0.30 mg/kg. Data shown are for the 5 subjects in which stimulus control was not induced at a dose of 0.17 mg/kg but did occur when the dose was increased to 0.30 mg/kg [as indicated by the dotted line]. All other details are as in figure 1.

Figure 3.

Dose-effect relationship for LSD alone and in combination with M100907. Circles represent the effects of LSD alone in mice trained with LSD as a discriminative stimulus [0.17 mg/kg]. Squares represent the effects of LSD in combination with M100907 [0.08 mg/kg]. M100907 and LSD were administered SC 30 min and 15 min, respectively, before testing. Each point represents the mean of one determination in each of 6 mice. Standard errors of the mean are indicated. The points at V and M on the *abscissa* are for vehicle and M100907 alone, respectively. # significantly different from both training conditions; * significantly different from vehicle control. *Ordinate: upper panel:* percent LSD-appropriate responding; *lower panel:* rate expressed as responses per minute. *Abscissa:* dose plotted on a log scale.

Figure 4.

Dose-effect relationship for M100907 in mice trained with LSD [0.17 mg/kg]. Squares represent the effects of M100907 alone [30 min pretreatment time]. Circles represent the effects of a range of doses of M100907 in combination with the training dose of LSD. The points at V and TD on the *abscissa* are for vehicle and LSD training conditions, respectively. In the event that not all subjects completed the test, the number of animals which did complete are indicated by a number adjacent to a given data point. * significantly different from LSD-induced stimulus control. # significantly different from LSD control rate. All other details are as in figure 3.

Figure 5.

Time course of stimulus control by LSD [circles] in mice trained with LSD [0.17 mg/kg; 15 min] as a discriminative stimulus. The triangle represents the effects following the administration of vehicle. Each point is the mean of one determination in each of 6 mice. Standard errors of the mean are indicated. * significantly different from 15 min pretreatment time. *Ordinate: upper panel: percent LSD-appropriate responding; lower panel: rate expressed as responses per minute. Abscissa: time in min.*

Figure 6.

Tests of generalization of LSD to [-]-DOM [open triangles] in mice trained with LSD [0.3 mg/kg, 15 min] as a discriminative stimulus. Each point represents the mean of one determination in each of 5 mice. Standard errors of the mean are indicated. The points at V and TD represent results following the vehicle and LSD training conditions, respectively. All other details are as in figures 3 and 4.