Available online at www.sciencedirect.com

SCIENCE DIRECT

Pharmacology, Biochemistry and Behavior 81 (2005) 830 – 837

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

The stimulus properties of LSD in C57BL/6 mice☆

J.C. Winter [a,*], A.K. Kieres [b], M.D. Zimmerman [b], C.J. Reissig [a], J.R. Eckler [a], T. Ullrich [c], K.C. Rice [c], R.A. Rabin [a], J.B. Richards [b]

[a] *Department of Pharmacology and Toxicology, School of Medicine and Biomedical Sciences, University at Buffalo, 102 Farber Hall, Buffalo, NY 14214-3000, USA*

[b] *Research Institute on Addictions and Department of Pediatrics, School of Medicine and Biomedical Sciences, University at Buffalo, 102 Farber Hall, Buffalo, NY 14214-3000, USA*

[c] *Laboratory of Medicinal Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD 20892, United States*

Received 6 October 2004; received in revised form 7 February 2005; accepted 19 May 2005
Available online 11 July 2005

Abstract

Rationale: Drug-induced stimulus control has proven to be a powerful tool for the assessment of a wide range of psychoactive drugs. Although a variety of species has 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

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

☆ A preliminary report was presented at the Society for Neuroscience Annual Meeting, San Diego, CA, 27 October 2004 (Winter et al., 2004a).

* Corresponding author. Tel.: +1 716 829 3239; fax: +1 716 829 2801.
E-mail address: jcwinter@buffalo.edu (J.C. Winter).

0091-3057/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2005.05.014

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 et al. (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 D_2 (Chausmer et al., 2002), D_4 (Katz et al., 2003), or D_5 (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 lever.

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 manipulandum. 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).

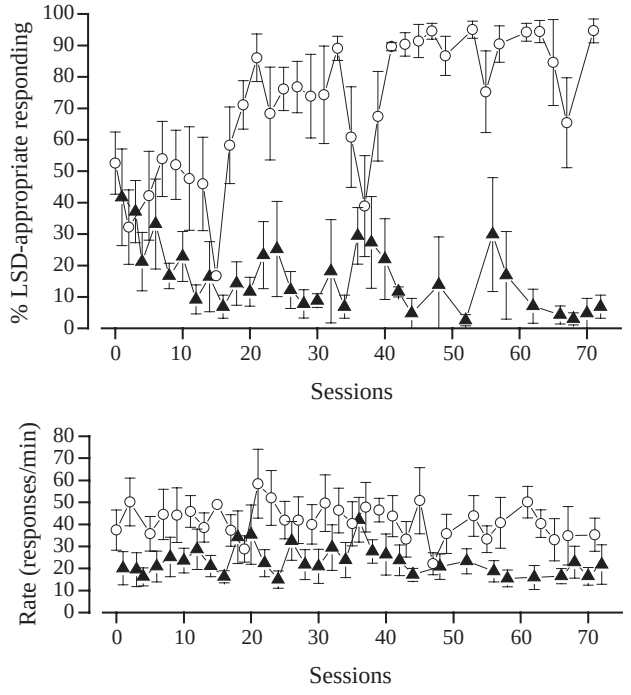

Fig. 1. LSD-induced stimulus control at a training dose of 0.17 mg/kg. Data shown are for the 6 subjects in which criterion performance was achieved. (▲) Experiments in which saline was injected SC 15 min before the session. (>) Identical experiments in which LSD was administered. Standard errors of 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.

2.5. Statistical analysis

Behavioral data were assessed for statistical significance using individual applications of paired Student's *t*-test and one-way repeated measures analysis of variance [ANOVA] followed by pair-wise 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, Fig. 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; $P=0.004$; Fig. 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 (Fig. 2, upper panel). Although less pronounced than that seen in Fig. 1, the rate differential between LSD and vehicle treatments remained (control: 20 rpm; LSD: 30 rpm; $P=0.038$; Fig. 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 (Fig. 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 [$P<0.02$; Fig. 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

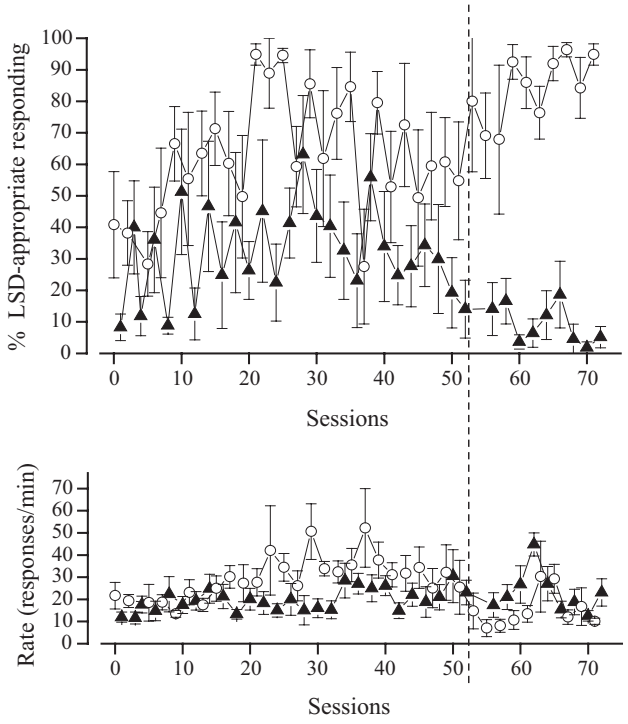

Fig. 2. LSD-induced stimulus control at a dose of 0.30 mg/kg. Data shown are for the 5 subjects in which stimulus control was not induced at a dose of 0.17 mg/kg but did occur when the dose was increased to 0.30 mg/kg [as indicated by the dotted line]. All other details are as in Fig. 1.

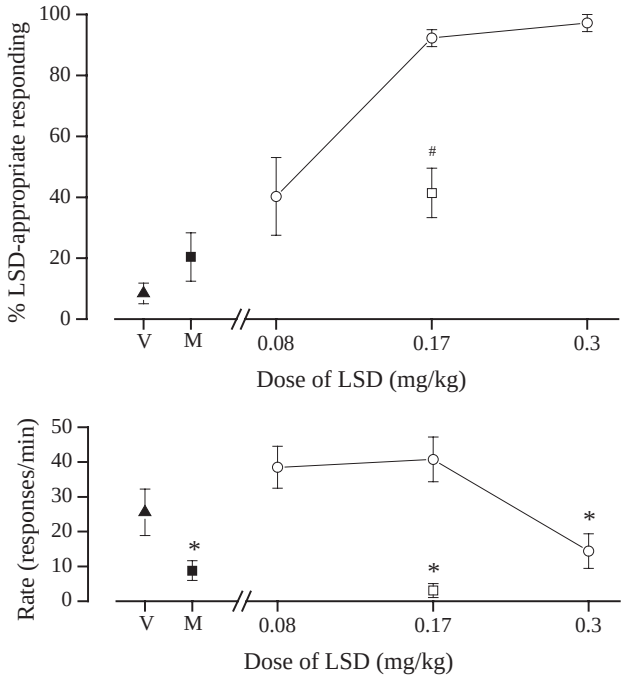

Fig. 3. Dose–effect relationship for LSD alone and in combination with M100907. (>) Effects of LSD alone in mice trained with LSD as a discriminative stimulus [0.17 mg/kg]. (□) Effects of LSD in combination with M100907 [0.08 mg/kg]. M100907 and LSD were administered SC 30 min and 15 min, respectively, 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.

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 (Fig. 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 Fig. 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 Fig. 6. In contrast with the data shown in Figs. 3–5, in which tests were conducted in mice trained with a dose of LSD of 0.17 mg/kg, the tests represented in Fig. 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 Figs. 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 6 mice trained at a dose of 0.17 mg/kg (Fig. 1), the number of sessions required to reach criterion performance [39 rpm] and the rate of emission of the nose-poke operant [44 rpm] may be

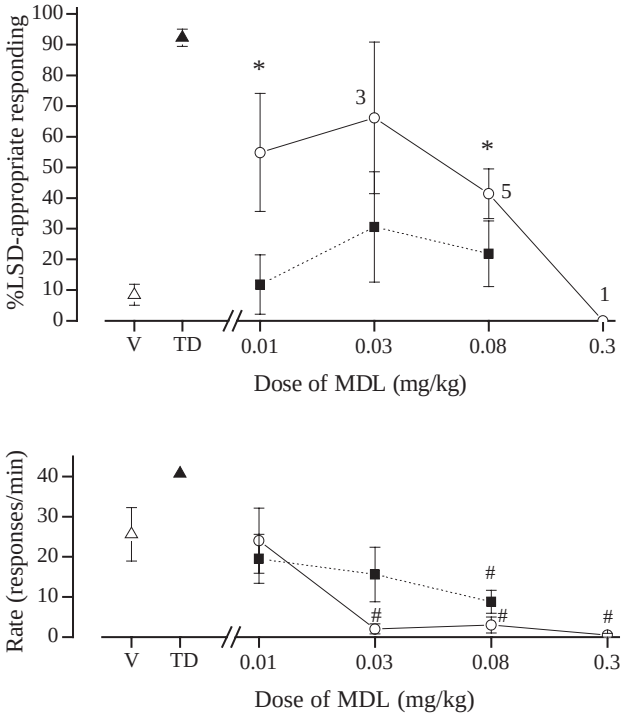

Fig. 4. Dose–effect relationship for M100907 in mice trained with LSD [0.17 mg/kg]. (■) Effects of M100907 alone [30 min pretreatment time]. (>) Effects of a range of doses of M100907 in combination with the training dose of LSD. The points at V and TD on the abscissa are for vehicle and LSD training 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.

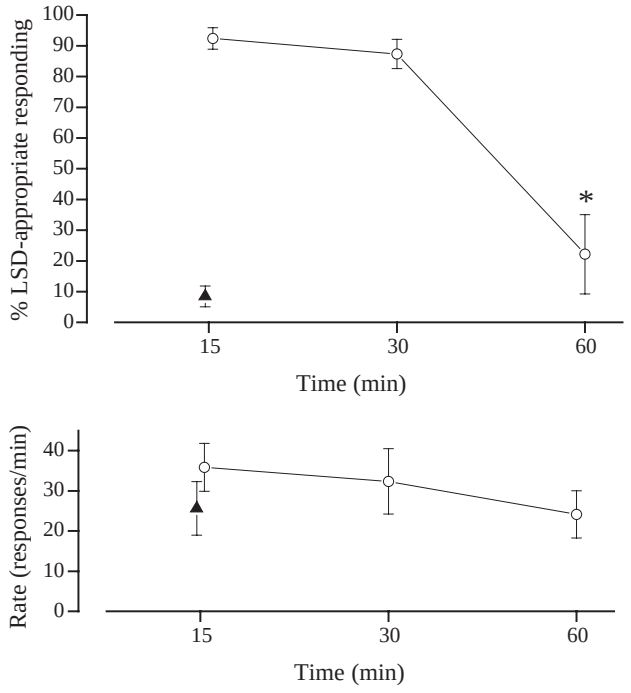

Fig. 5. Time course of stimulus control by LSD (>) in mice trained with LSD [0.17 mg/kg; 15 min] as a discriminative stimulus. (▲) Effects following the administration of vehicle. Each point is the mean of one determination in each of 6 mice. Standard errors of the mean are indicated. *Significantly 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.

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 [S.E.M.=1] sessions was required to reach criterion performance with a rate of lever-press responding of 27 [S.E.M.=6] per minute [unpublished observations] which was not significantly different from the rate following vehicle [20±3]. The fact that when the dose was increased to 0.30 mg/kg, an additional 5 mice quickly reached criterion performance (Fig. 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. FR10], the operant utilized [lever press versus nose-poke], and the basis for determining response rates.

The dose–effect relationship for LSD shown in Fig. 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 Fig. 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., 2004a,b) 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

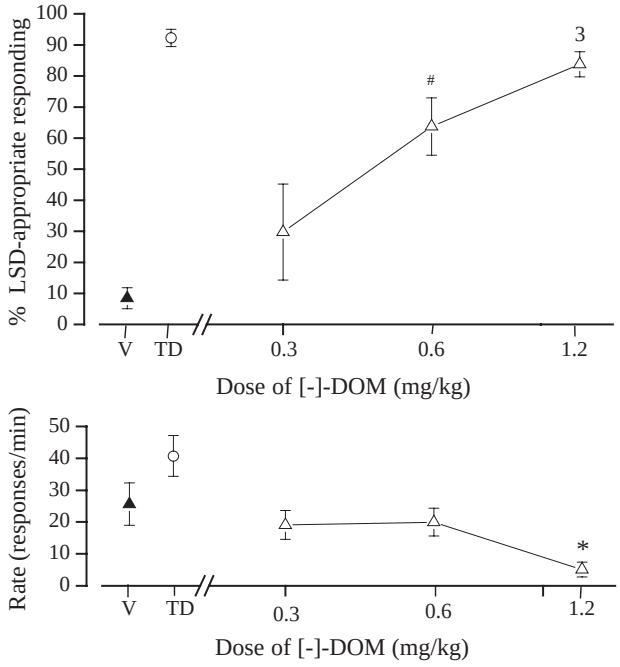

Fig. 6. Tests of generalization of LSD to [−]-DOM (△) in mice trained with LSD [0.3 mg/kg, 15 min] as a discriminative stimulus. Each point represents the mean of one determination in each of 5 mice. Standard errors of the mean are indicated. The points at V and TD represent results following the vehicle and LSD training conditions, respectively. *Significantly different from vehicle control. #Significantly different from both training conditions.

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. Although 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., 2004a,b) or the decreases in rate produced by M100907 when given alone to mice (Figs. 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 (Fig. 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 Fig. 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 Fig. 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 min. 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 Fig. 5, suggests 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 min (Lanz et al., 1955; Stoll et al., 1955; Haley and Rutschmann, 1957) as compared with 100 min in monkeys (Axelrod et al., 1957), and 175 min 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 Fig. 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.

Acknowledgements

This study was supported in part by U.S. Public Health Service Grants DA 03385 (J.C.W.; R.A.R.) and DA 14183 (A.K.K., M.D.Z., J.B.R.) and by National Research Service Awards DA 13920 (J.R.E.) and DA 16457 (C.J.R).

References

Aghajanian GK, Bing OHL. Persistence of lysergic acid diethylamide in the plasma of human subjects. Clin Pharmacol Ther 1964;5:611–4.

Ator NA. Interrelationships between drug self-administration and drug discrimination. Problems of drug dependence. NIDA Monograph, vol. 140. Rockville (MD): USGPO; 1994. p. 99–117.

Ator NA, Grant KA, Purdy RH, Paul SM, Griffiths RR. Drug discrimination analysis of endogenous neuroactive steroids in rats. Eur J Pharmacol 1993;241:237–43.

Axelrod J, Brody RO, Witkop B, Evarts EV. The distribution and metabolism of lysergic acid diethylamide. Ann N Y Acad Sci 1957;66:435–44.

Balster RL. Perception of drug effects. In: Berkeley MA, Stebbens WG, editors. Comparative Perception, vol. 1. New York: Wiley; 1990. p. 127–54.

Balster RL, Moser VC. Pentobarbital discrimination in the mouse. Alcohol Drug Res 1987;7:233–42.

Borlongan CV, Watanabe S. Footshock facilitates discrimination of stimulus properties of morphine. Life Sci 1997;61:1045–9.

Brauer LH, Goudie AJ, deWit H. Dopamine ligands and the stimulus effects of amphetamine: animal models versus human laboratory data. Psychopharmacology 1997;130:2–13.

Browne RG, Ho BT. The role of serotonin in the discriminative stimulus properties of mescaline. Pharmacol Biochem Behav 1975;3:429–35.

Bucan M, Abel T. The mouse: genetics meets behavior. Nat Rev Genet 2002;3:114–23.

Chausmer AL, Elmer GI, Rubinstein M, Low MJ, Grandy DK, Katz JL. Cocaine-induced locomotor activity and cocaine discrimination in dopamine D2 receptor mutant mice. Psychopharmacology 2002; 163:54–61.

Comer SA, France CP, Woods JH. Training dose: influences in opioid drug discrimination. In: Glennon RA, Jarbe TUC, Frankenheim J, editors. Drug discrimination: applications to drug abuse research. Research Monograph, vol. 116. Rockville (MD): USGPO; 1991. p. 145–61.

Cunningham KA, Appel JB. Neuropharmacological reassessment of the discriminative stimulus properties of D-lysergic acid diethylamide [LSD]. Psychopharmacology 1987;91:67–73.

Dykstra LA, Preston KL, Bigelow GE. Discriminative stimulus and subjective effects of opioids with mu and kappa activity: data from laboratory animals and human subjects. Psychopharmacology 1997;130:14–27.

Elliot EE, Sibley DR, Katz JL. Locomotor and discriminative stimulus effects of cocaine in dopamine D5 receptor knockout mice. Psychopharmacology 2003;169:161–8.

English JA, Bruce KH, Paul IA. Increased discriminative stimulus potency of PCP in C57BL/6 mice infected with the LP-BM5 retrovirus. Eur J Pharmacol 1999;367:1–5.

Evans EB, Balster RL. Effects of methosyflurane and flurothyl in mice trained to discriminate pentylenetetrazol from saline. Behav Pharmacol 1992;3:465–73.

Fiorella D, Palumbo PA, Rabin RA, Winter JC. The time-dependent stimulus effects of 1-[2,5-dimethoxy-4-methylphenyl]-2-aminopropane [DOM]: implications for drug-induced stimulus control as a method for the study of hallucinogenic agents. Psychopharmacology 1995;11:239–45.

Geter-Douglas B, Witkin JM. Behavioral effects and anticonvulsant efficacies of low-affinity, uncompetitive NMDA antagonists in mice. Psychopharmacology 1999;146:280–9.

Gingrich JA, Hen R. Dissecting the role of the serotonin system in neuropsychiatric disorders using knockout mice. Psychopharmacology 2001;155:1–10.

Glennon RA, Rosecrans JA, Young R. The use of the drug discrimination paradigm for studying hallucinogenic agents. In: Colpaert FC, Slangen JL, editors. Drug discrimination: applications in CNS pharmacology. Amsterdam: Elsevier; 1982. p. 69–96.

Gommans J, Bouwknecht JA, Hijzen TH, Berendsen HH, Broekkamp CL, Maes RA, et al. Stimulus properties of fluvoxamine in a conditioned taste aversion procedure. Psychopharmacology 1998;140:496–502.

Grant KA, Knisely JS, Tabakoff B, Barrett JE, Balster RL. Ethanol-like discriminative stimulus effects of non-competitive NMDA antagonists. Behav Pharmacol 1991;2:87–95.

Haley TB, Rutschmann J. Brain concentrations of LSD-25 [Delysid] after intracerebral or intravenous administration in conscious animals. Experientia 1957;13:199–202.

Harris RT, Balster RL. An analysis of the function of drugs in the stimulus control of operant behavior. In: Thompson T, Pickens R, editors. Stimulus properties of drugs. New York: Appleton-Century-Crofts; 1971. p. 111–32.

Hirschhorn I, Winter JC. Mescaline and LSD as discriminative stimuli. Psychopharmacologia 1971;22:64–71.

Kamien J, Bickel W, Hughes J, Higgins S, Smith B. Drug discrimination by humans compared to nonhumans: current status and future directions. Psychopharmacology 1993;111:259–70.

Katz JL, Chausmer AL, Elmer GI, Rubenstein M, Low MJ, Grandy DK. Cocaine-induced locomotor activity and cocaine discrimination in dopamine D_4 receptor mutant mice. Psychopharmacology 2003; 170:108–14.

Lanz U, Cerletti A, Rothlin E. Distribution of lysergic acid diethylamide in the organism. Helv Physiol Pharmacol Acta 1955;13:207–16.

Middaugh LD, Favara JP, Boggan WO, Stringer AJ. Discriminative properties of phencyclidine in mice: generalization to ketamine and monohydroxy metabolites. Psychopharmacology 1988;96:381–4.

Middaugh LD, Bao K, Becker HC, Daniel SS. Effects of Ro 15-4513 on ethanol discrimination in C57BL/6 mice. Pharmacol Biochem Behav 1991;38:763–7.

Middaugh LD, McGroarty KK, Groseclose CH, Adinoff B. Cocaine discrimination: relationship to local anesthetics and monoamine uptake inhibitors in C57BL/6 mice. Psychopharmacology 1998;136:44–9.

Mumford GK, Holtzman SG. Qualitative differences in the discriminative stimulus effects of low and high dose caffeine in the rat. J Pharmacol Exp Ther 1991;258:857–65.

Overton DA. Discriminative control of behavior by drug states. In: Thompson T, Pickens R, editors. Stimulus properties of drugs. New York: Appleton-Century-Crofts; 1971. p. 87–110.

Philibin SD, Prus AJ, Pehrson AL, Porter JH. Serotonin receptor mechanisms mediate the discriminative stimulus properties of the atypical antipsychotic clozapine in C57BL/6 mice. Psychopharmacology 2005;180:49–56.

Rees DC, Balster RL. Attenuation of the discriminative stimulus properties of ethanol and oxazepam but not of pentobarbital by Ro 15-4513 in mice. J Pharmacol Exp Ther 1988;244:592–8.

Sanger DJ, Benavides J, Perrault G, Morel E, Cohen C, Joly D, et al. Recent developments in the behavioral pharmacology of benzodiazepine [omega] receptors: evidence for functional significance of receptor subtypes. Neurosci Biobehav Rev 1994;18:355–72.

Sankar DVS, 1975. LSD—a total study. Westbury (NY): PJD Publications Ltd; 1975. p. 255–65.

Schuster C, Johanson C. Relationship between the discriminative stimulus properties and subjective effects of drugs. In: Colpaert F, Balster R, editors. Transduction mechanisms of drug stimuli. Berlin: Springer; 1988. p. 161–75.

Seong E, Seasholtz AF, Burmeister M. Mouse models of psychiatric disorders. Trends Genet 2002;18:643–50.

Shannon HE, Holtzman SG. Morphine training dose: a determinant of stimulus generalization to narcotic antagonists in the rat. Psychopharmacology 1979;61:239–44.

Shannon EE, Shelton KL, Vivian JA, Yount I, Morgan AR, Homanics GE, et al. Discriminative stimulus effects of ethanol in mice lacking the gamma-aminobutyric acid type A receptor delta subunit. Alcohol Clin Exp Res 2004;28:906–13.

Shulgin AT, Shulgin A, 1991. PiHKAL: a chemical love story. Berkley: Transform Press; 1991. p. 633–7.

Smith RL, Barrett RJ, Sanders-Bush E. Discriminative stimulus properties of 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane [(+/−)DOI] in C57BL/6 mice. Psychopharmacology 2003;166:61–8.

Snoddy AM, Tessel RE. Nisoxetine and amphetamine share discriminative stimulus properties in mice. Pharmacol Biochem Behav 1983;19:205–10.

Spencer DG, Glaser T, Traber J. Serotonin receptor subtypes mediation of the interoceptive discriminative stimuli induced by 5-methoxy-*N*,*N*-dimethyltryptamine. Psychopharmacology 1987;93:158–66.

Stolerman IP, Kamien JB. Drug Discrimination Bibliographic Database 2004; http://www.dd-database.org/.

Stolerman IP, Naylor C, Elmer GI, Goldberg SR. Discrimination and self-administration of nicotine by inbred strains of mice. Psychopharmacology 1999;141:297–306.

Stolerman IP, Chamberlain S, Bizarro L, Fernandes C, Schalkwyk. The role of nicotinic alpha7 subunits in nicotine discrimination. Neuropharmacology 2004;46:363–71.

Stoll A, Rothkin E, Rutschmann V, Schalch WR. Distribution and fate of C^{14}-labeled lysergic acid diethylamide [LSD-25] in the animal body. Experientia 1955;11:396–9.

Ullrich T, Rice KC. A practical synthesis of the serotonin 5-HT_{2A} receptor antagonist MDL 100907, its enantiomers and their 3-phenolic derivatives as precursors for [11C]labeled PET ligands. Bioorg Med Chem 2000;8:2427–32.

Varvel SA, James JR, Bowen S, Rosecrans JA, Karan LD. Discriminative stimulus properties of nicotine in the C57BL/6 mouse. Pharmacol Biochem Behav 1999;63:27–32.

Winter JC. Hallucinogens as discriminative stimuli. Fed Proc 1974; 33:1825–32.

Winter JC. Blockade of the stimulus properties of mescaline by a serotonin antagonist. Arch Int Pharmacodyn Ther 1975;214:250–3.

Winter JC. Drug-induced stimulus control. In: Blackman DE, Sanger DJ, editors. Contemporary research in behavioral pharmacology. New York: Plenum Press; 1978a. p. 209–37.

Winter JC. Stimulus properties of phenethylamine hallucinogens and lysergic acid diethylamide: the role of 5-hydroxytryptamine. J Pharmacol Exp Ther 1978b;204:416–23.

Winter JC, Rabin RA. Interactions between serotonergic agonists and antagonists in rats trained with LSD as a discriminative stimulus. Pharmacol Biochem Behav 1988;30:617–24.

Winter JC, Filipink RF, Timineri D, Helsley SE, Rabin RA. The paradox of 5-methoxy-*N*,*N*-dimethyltryptamine: a hallucinogen which induces stimulus control via 5-HT_{1A} receptors. Pharmacol Biochem Behav 2000;65:75–82.

Winter JC, Kieres AK, Hausknecht KA, Farrar AM, Acheson A, Choi S, et al. Discriminative stimulus effects of lysergic acid diethylamide [LSD] in mice. 34th Annu Meet Soc Neurosci, session #130, poster #15, Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience; 2004a. Online.

Winter JC, Eckler JR, Rabin RA. Serotonergic/glutamatergic interactions: the effects of mGlu2/3 receptor ligands in rats trained with phencyclidine and LSD as discriminative stimuli. Psychopharmacology 2004b;172:233–40.