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Characterization of the discriminative stimulus properties of centrally administered (−)-DOM and LSD

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Abstract

Despite the plausible assumption that the effects of hallucinogens predominantly arise in the central nervous system, most studies of these drugs in intact subjects have been conducted following systemic administration. The objective of the present investigation was to characterize the stimulus effects of (−)2,5-dimethoxy-4-methylamphetamine ((−)-DOM) following intracerebroventricular administration. Chronic indwelling cannulae were implanted into the lateral ventricle of male Fischer 344 rats trained to discriminate systemically administered (−)-DOM or lysergic acid diethylamide (LSD) from saline. Time–course and dose–response relationships for (−)-DOM and LSD administered intracerebroventricularly were established. For both LSD and (−)-DOM, central administration did not change the pretreatment times required for the maximal stimulus effects to occur. However, the onset of the stimulus effect was more rapid following intracerebroventricular administration. Following pretreatment periods that maximize drug-appropriate responding, central administration of (−)-DOM and LSD was approximately 2.4- and 1.5-times more potent, respectively, than systemic administration. The results of this study are consistent with the assumption that the stimulus effects of (−)-DOM and LSD are centrally mediated.

Keywords: Hallucinogen; 2,5-Dimethoxy-4-methyl-amphetamine ((−)-DOM); Lysergic acid diethylamide (LSD); Pirenperone; Intracerebral injection; Microinjection; Intracerebroventricular; Discriminative stimulus

1. Introduction

Phenethylamine and indoleamine hallucinogens, exemplified by 2,5-dimethoxy-4-methyl-amphetamine ((−)-DOM) and lysergic acid diethylamide (LSD), respectively, produce qualitatively similar experiences in humans. These usually consist of alterations in perception such as hallucinations, disrupted awareness of time and so-called out of body sensations. In laboratory animals, drug discrimination procedures are useful for characterizing psychoactive drugs because of the strong correlation between discriminative stimuli in nonverbal species and subjective effects reported by humans (Schuster and Johanson, 1988; Sanger et al., 1994; Brauer et al., 1997). The discriminative stimulus properties of (−)-DOM and LSD have been extensively investigated in several different animal species and it has been shown that, in agreement with studies in humans, these hallucinogens generalize with one another (Winter, 1978; Glennon et al., 1983a,b; Fiorella et al., 1995a). Furthermore, antagonist correlation analysis has determined that the stimulus effects of both classes of drugs are mediated by agonist activity at 5-HT_{2A} receptors and modulated by agonist activity at 5-HT_{2C} receptors (Fiorella et al., 1995b).

The assumption that the effects of hallucinogens in animals arise in the central nervous system is intuitively attractive. Experimental support for this hypothesis comes from the observation that a peripherally acting serotonergic antagonist, xylamidine, blocks the behavioral effects 5-hydroxytryptamine, an agent which does not enter the central nervous system in significant amounts following peripheral administration (Axelrod and Inscoe, 1963), but is without effect on the behavioral actions of the hallucinogenic serotonergic agonists *N*,*N*-diethyltryptamine (Winter, 1969), mescaline (Browne and Ho, 1975) and (±)-DOM (Silverman and Ho, 1980); for low doses of LSD, a minor peripheral component cannot be ruled out (White and

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Appel, 1982). As an alternative to these pharmacological studies, a number of investigators have examined the effects of hallucinogens following direct administration into the central nervous system using operant responding as the behavioral index. For example, Mockler and Rech (1984) compared the response-suppressing effects of intraperitoneal and intracerebroventricular administration of LSD, (−)-DOM, mescaline and lisuride on an FR30 schedule of food reinforcement. While the potency was increased slightly following intracerebroventricular administration of LSD and (−)-DOM (1.3–2.6-fold increase) and more significantly for mescaline (30-fold increase), there was no increase in potency for lisuride. Attempts to localize the central site of action of these drugs have found that infusion of LSD into the dorsal raphe is 1.7-times more potent at disrupting operant behavior than infusion into the cerebral ventricles (Mockler et al., 1986a) and that (−)-DOM is most potent when infused into the median raphe nuclei (Mockler et al., 1986b). Alternatively, in a study using prepulse inhibition (PPI) as the behavioral index, greater disruption occurred when DOI was infused into the ventral pallidum than into the nucleus accumbens (Sipes and Geyer, 1997).

While a limited number of studies have examined the discriminative stimulus effects elicited by administration of LSD and (−)-DOM into discrete neuroanatomical sites, none have characterized the effects of central administration into the cerebral ventricles. Minnema et al. (1980) found that, in rats trained to discriminate LSD (0.096 mg/kg ip) from saline, infusion into the dorsal raphe nucleus of half the training dose fully substituted for the full training dose. Furthermore, in animals trained to discriminate 0.16 mg/kg ip LSD from saline, microinjection of 1 μg LSD into the nucleus accumbens produced 84±8% LSD-lever responding (Nielsen and Scheel-Kruger, 1986).

The absence of a comprehensive characterization of the discriminative stimulus properties of centrally (intracerebroventricularly) administered LSD or (−)-DOM is in contrast to other psychoactive drugs. For example, Locke and Holtzman (1985) characterized the discriminative stimulus effects of morphine administered intracerebroventricularly in rats trained to discriminate 3.0 mg/kg sc morphine from saline. Intracerebroventricular morphine was found to be 1000-times more potent than subcutaneous morphine but the onset of the discriminative stimulus effects was delayed 60 min, approximating the time–course following systemic administration. In rats trained to discriminate intraperitoneal cathinone from saline, intracerebroventricular infusion was 15-times more potent then intraperitoneal (Schecter et al., 1992). Similarly, Sannerud et al. (1991) found the stimulus effects of midazolam to be 2.4–4.3-times more potent following intracerebroventricular infusion than following subcutaneous or intraperitoneal injection and Slifer and Balster (1985) found that intracerebroventricular infusion of PCP was seven times more potent than intraperitoneal. Interestingly, central administration does not always increase the potency of psychoactive drugs. For example, in rats trained to discriminate systemically administered ethanol (intraperitoneally) from saline, intracerebroventricular infusion of ethanol produced only partial generalization (Hodge, 1994) and in rats trained to discriminate subcutaneous nicotine from saline, administration of nicotine into the fourth ventricle produced motor effects but did not result in generalization (Shoaib and Stolerman, 1996).

Although (−)-DOM and LSD produce a qualitatively similar psychoactive experience in humans and are both thought to produce stimulus control through agonist activity at 5-HT_2 receptors, the onset of the psychoactive or stimulus effects occurs much more rapidly for LSD than (−)-DOM. In the initial report of the discriminative stimulus properties of LSD, Hirschhorn and Winter (1971) used a 5-min pretreatment period. In subsequent studies, a 15-min pretreatment period has been employed. Stimulus control by (−)-DOM, however, was shown by Fiorella et al. (1995a) to be most stable following a 75-min pretreatment period. Furthermore, in comparison to LSD (Kulig, 1990; Shulgin and Shulgin, 1991), (−)-DOM requires a significantly longer time, 90–120 min, for the onset of hallucinogenic activity in humans than does LSD (Snyder et al., 1968; Hollister et al., 1969; Shulgin and Shulgin, 1991). One explanation for the disparity in time to maximal effect is that (−)-DOM is absorbed or distributed to the brain more slowly than LSD, a phenomenon that might be eliminated by intracerebroventricular administration.

The objective of the present investigation was to characterize the stimulus effects of (−)-DOM following intracerebroventricular administration. Time–course and dose–response relationships for (−)-DOM administered intracerebroventricularly were established in animals trained to discriminate systemically administered (−)-DOM from saline. In addition, a comparison was made of the time–course and potency of (−)-DOM and LSD administered intracerebroventricularly.

2. Materials and methods

2.1. Animals

Male Fischer 344 rats were obtained from Harlan Sprague–Dawley (Indianapolis, IN, USA), housed in pairs under a 12-h light–dark cycle beginning at 6:00 a.m. and allowed free access to water in their home cages. All training and testing took place during the light cycle. Caloric intake was controlled to maintain a mean body weight of 250 g. Subjects were fed following experimental sessions. Caloric control has been shown to lengthen the life span and decrease the incidence of a variety of pathologies in Fischer 344 rats (Keenan et al., 1994). Animals used in these studies were maintained in accordance with the ‘Guide for Care and Use of Laboratory Animals’ of the Institute of Laboratory Animals Resources, National Research Council.

2.2. Apparatus

Animal test chambers (Coulbourn Instruments Model E10-10) housed in larger light-proof, sound-insulated boxes were used for all experiments. Each box had a house light and exhaust fan. Chambers contained two levers mounted on opposite ends of one wall. Centered between the levers was a dipper that delivered 0.1 ml of sweetened condensed milk diluted 2:1 with tap water.

2.3. Discrimination training

Subjects were trained to discriminate either LSD (0.1 mg/kg ip, 15-min pretreatment time) or (−)-DOM (0.6 mg/kg ip, 75-min pretreatment time) from saline as described previously (Fiorella et al., 1995b). A fixed ratio 10 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 reinforcement were on the appropriate lever. Experiments were conducted in each animal so long as performance did not fall below 83% correct on any one of the previous three training sessions. Time–course experiments were performed by conducting consecutive test sessions at 5, 15, 30 and 75 min following the start of the infusion procedure. During test sessions, no responses were reinforced and the session was terminated after the emission of 10 responses on either lever. The distribution of responses on the drug-appropriate lever was expressed as a percentage of the total responses emitted. Response rate was calculated for each session by dividing the total number of responses emitted prior to the emission of 10 responses on both levers by the elapsed time. While the intention was to test every dose two times in each animal, in several cases, the subjects died or their cannulae became obstructed prior to replication of the data point. Thus, each data point represents the mean of one to two trials in each animal. The second determinations were conducted following the completion of the first dose–response curve. A group of 10 rats was trained with LSD and a group of 14 rats was trained with (−)-DOM. However, not all rats completed cannulation and subsequent behavioral testing hence the numbers in any given experiment are as indicated in the figure legends.

2.4. Drugs

The negative isomer of DOM, (−)-DOM, was employed in all experiments. (−)-DOM hydrochloride and (+)-LSD (+)-tartrate (2:1) were provided by the National Institute on Drug Abuse. Doses are expressed as milligrams per kilogram of the respective salts. For intraperitoneal injections, (−)-DOM was dissolved in water and LSD was dissolved in 0.9% NaCl. For intracerebroventricular injections, both LSD and (−)-DOM were dissolved in sterile 0.9% NaCl solution. Pirenperone and angiotensin II were purchased from Sigma-Aldrich, USA. A stock solution of pirenperone was made in a minimal volume of a 45% w/v aqueous solution of 2-hydroxy-propyl-β-cyclodextrin and 8.5% lactic acid and solutions for intraperitoneal and intracerebroventricular injections were made by diluting the stock with sterile 0.9% NaCl. Angiotensin II was dissolved in sterile 0.9% NaCl solution. For intraperitoneal and intracerebroventricular injections, all drugs were injected in a volume of 0.25 ml and 2.0 μl, respectively.

2.5. Stereotaxic procedure

Following successful discrimination training and the establishment of a complete dose–response relationship to systemic administration of the training drug, subjects were implanted with 10-mm 26-gauge stainless steel guide cannulae. Rats were anesthetized (pre-anesthesia: 0.05 mg/kg atropine and 0.05 mg/kg buprenorphine administered intraperitoneally 5 min prior to anesthesia; anesthesia: 70 mg/kg ketamine and 5 mg/kg xylazine administered intraperitoneally) and placed in a standard Kopf stereotaxic apparatus. In order to minimize gliosis at the target, guide cannulae (Plastics One, Ronanoke, VA, USA) were placed 1 mm above the right lateral ventricle according to coordinates established by Paxinos and Watson (1986) (AP = −1.3, ML = +2, DV = −4.2, relative to bregma) and 36-gauge infusion cannula (Plastics One) extending 1 mm beyond the guide were used to deliver the drugs to the target area. The guide cannulae were secured to the skull via dental cement and three small stainless steel screws. Removable 36-gauge dummy cannulae (Plastics One) of the same length as the guide were placed within the guide cannulae following surgery and between infusions to prevent occlusion by tissue growth or foreign material. Animals were allowed to recover for at least 7 days following surgery after which behavioral training resumed. Cannulae placement was confirmed by positive drinking response (consumption of at least 10 ml of water) within 10 min following the infusion of 1.5-μg/kg angiotensin II (Severs and Summy-Long, 1976).

2.6. Infusion procedure

Following recovery from surgery, discrimination training resumed until subjects performed with 83% accuracy on five consecutive training sessions. The intracerebroventricular injections were administered via injectors connected to a 10-μl syringe in a BAS Busy Bee pump via plastic tubing. The syringe and tubing were filled with distilled H_2O and backfilled with the drug solution, which was separated from the water by a small air bubble. Drugs were administered in a volume of 2 μl over 2 min and the cannulae were left in place for an additional minute to minimize removal of drug with the injector. In addition, complete delivery of the intended volume was confirmed by (1) inspecting the tips of the injectors for droplets of solution and (2) assessing the patency of the injector by resuming the flow of solution.

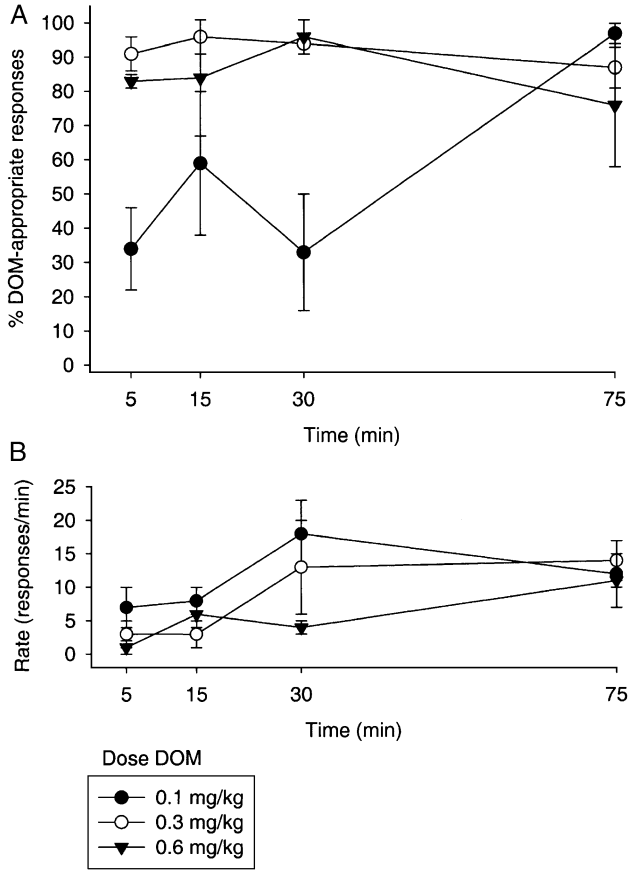

Fig. 1. Percent (−)-DOM-appropriate responding (Panel A) and response rates (Panel B) at 5, 15, 30 and 75 min following intracerebroventricular injection of either 0.1, 0.3 or 0.6 mg/kg (−)-DOM in rats trained to discriminate 0.6 mg/kg ip (−)-DOM (75-min pretreatment time) from saline. Each point represents the mean ± S.E.M. of one to two trials in five to eight subjects.

2.7. Statistics

The data are expressed as the percent drug-appropriate responses, which is the number of responses emitted on the drug-appropriate lever as a percentage of the total number of responses emitted. Response rates are expressed as the number of responses per minute. These were calculated for each session by dividing the total number of responses emitted prior to the emission of 10 responses on either lever by elapsed time. Data for any subjects failing to emit 10 responses within the constraints of the 10-min test session were not considered in the calculation of the percent drug-appropriate responding but were included in the analysis of response rates. Generalization was said to occur if 83% or more of the responses were on the drug-appropriate lever.

ED_{50} values were determined by fitting a regression line to the ascending portion of the dose–response curve. Prior to analysis, percentage data were normalized using an arc-sine-square root transformation. Comparisons between two groups were made using Student's *t*-test and when more then two groups were compared one-way analysis of variance was employed. Dunnett's method of multiple comparisons was used for individual comparisons. Differences were considered statistically significant if the probability of their having arisen by chance was $<.05$. All analyses were conducted using SigmaStat 2.03 for Windows.

3. Results

In preliminary experiments, drug-appropriate responding following intraperitoneal injections of 0.3 mg/kg (−)-DOM alone or accompanied by microinfusion of 2 μl of saline into the lateral ventricles was compared in animals trained to discriminate intraperitoneal (−)-DOM (0.6 mg/kg) from saline. When administered alone, intraperitoneal injection of 0.3 mg/kg (−)-DOM elicited 72 ± 11% (mean ± S.E.M., $n=6$) drug-appropriate responding at an average response rate of 16 ± 5 responses/min (mean ± SEM) and when accompanied by intracerebroventricular infusion of saline the same dose of (−)-DOM yielded 70 ± 12% drug-appro-

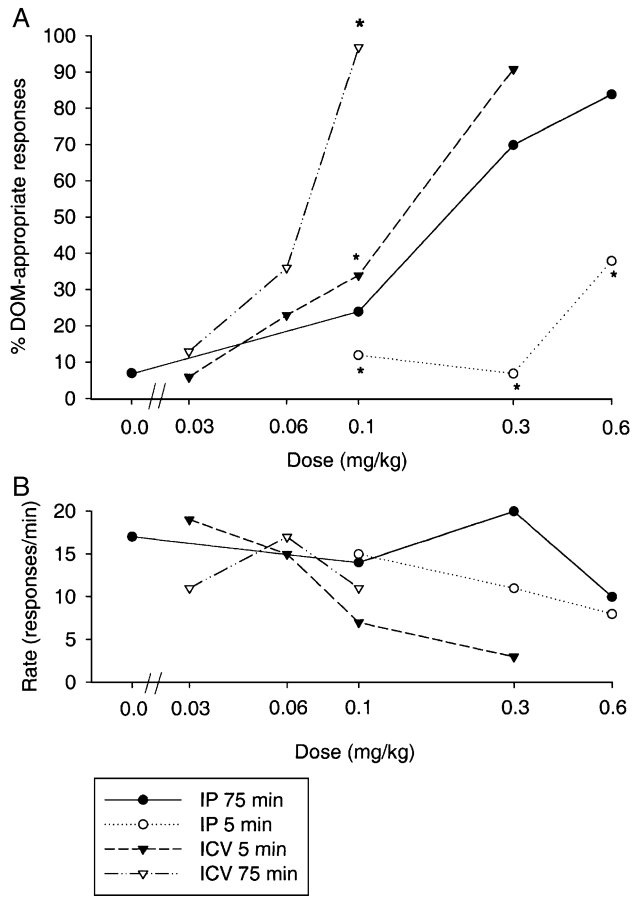

Fig. 2. Dose–response relationship (Panel A) and response rates (Panel B) of (−)-DOM at 5 and 75 min following either intracerebroventricular or intraperitoneal administration in rats trained to discriminate 0.6 mg/kg ip (−)-DOM (75-min pretreatment time) from saline. Each point represents the mean of one to two trials in five to eight subjects. Asterisks represent data points that are statistically significant from the training condition intraperitoneal injection, 75-min pretreatment time.

priate responding (mean ± S.E.M., $n = 7$) at 20 ± 7 (mean ± S.E.M.) responses/min. There was no significant difference in either the percent drug-appropriate responding or the response rate.

The time–courses for various doses of intracerebroventricular (−)-DOM in animals trained to discriminate intraperitoneal (−)-DOM (0.6 mg/kg, 75-min pretreatment) from saline are presented in Fig. 1. There is no significant difference between the percent drug-appropriate responding following intracerebroventricular infusion of 0.1, 0.3 and 0.6 mg/kg at 75 min. Five minutes following intracerebroventricular microinjection, complete generalization (>83% drug-appropriate responding) was elicited by 0.3 and 0.6 mg/kg, while 0.1 mg/kg produced only 34% drug-appropriate responding. However, by 75 min 0.1 mg/kg engendered 97% drug-appropriate responding suggesting that the stimulus effects of centrally administered (−)-DOM increase with time.

Fig. 2 compares the dose–response curves for (−)-DOM at 5 and 75 min following either central (intracerebroventricular) or systemic (intraperitoneal) administration in animals trained to discriminate intraperitoneal (−)-DOM (0.6 mg/kg, 75-min pretreatment) from saline. The discriminative

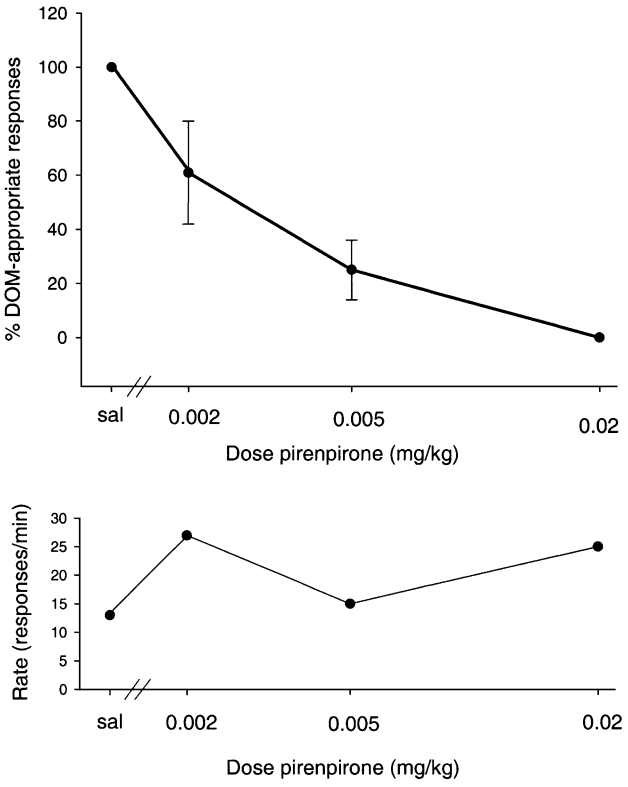

Fig. 3. Dose–response relationship for blockade of (−)-DOM-induced stimulus control by pirenperone infused into the lateral ventricle (intracerebroventricular) in animals trained to discriminate (−)-DOM (0.6 mg/kg ip, 75-min pretreatment period) from saline. (−)-DOM (0.6 mg/kg ip) was administered 75 min prior to testing. Pirenperone was administered intracerebroventricularly 60 min prior to testing. Each point represents the mean ± S.E.M. of one to two trials in five to eight subjects.

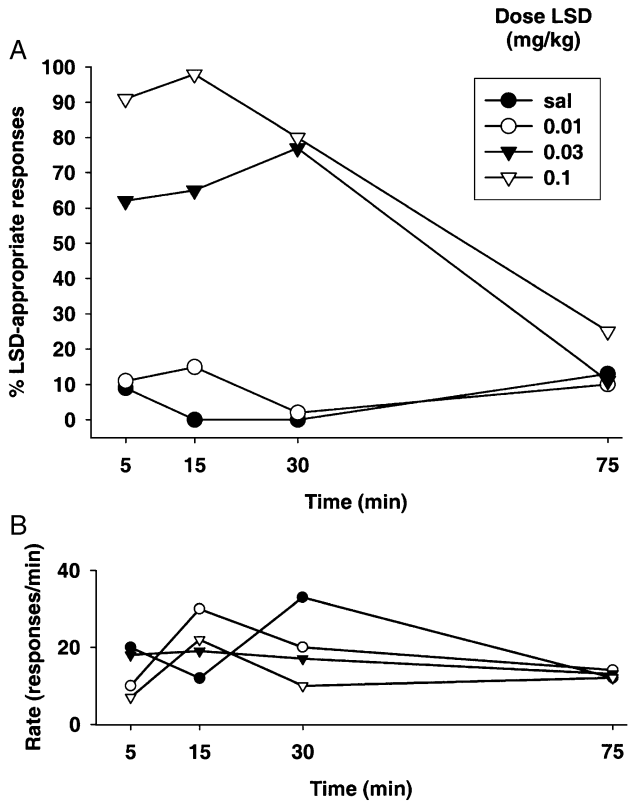

Fig. 4. Percent (−)-LSD-appropriate responding (Panel A) and response rates (Panel B) at 5, 15, 30 and 75 min following intracerebroventricular injection of either saline, 0.01, 0.03 or 0.1 mg/kg LSD in rats trained to discriminate 0.1 mg/kg ip LSD (15-min pretreatment period) from saline. Each point represents the mean of one to two trials in four to six subjects.

training regimen employs a 75-min pretreatment period following intraperitoneal injection. This pretreatment time was that found in our earlier studies (Fiorella et al., 1995a) to be most stable in maintaining stimulus control following systemic administration of (−)-DOM. The mean ED_{50} value ± S.E.M. for the drug-appropriate responding following intraperitoneal (−)-DOM at 75 min (the training regimen) was 0.20 ± .01 mg/kg. The mean ED_{50} value at 5 min following intraperitoneal administration was not determined because a complete dose–response relationship could not be established at the doses tested. At 5 and 75 min following intracerebroventricular injection, the mean ED_{50} values ± S.E.M. were 0.14 ± 0.02 and 0.08 ± 0.02 mg/kg, respectively, indicating an increase in potency with time. Furthermore, the dose–response curve for (−)-DOM at 5 min following intracerebroventricular administration is shifted to the left of the dose–response curve of (−)-DOM at 5 min following intraperitoneal injection indicating a more rapid onset of the stimulus with intracerebroventricular administration. The dose–response curves at 75 min following intracerebroventricular injection (ED_{50} ± S.E.M. = 0.08 ± 0.02 mg/kg) and at 5 min following intracerebroventricular infusion (ED_{50} ± S.E.M. = 0.14 ± 0.02 mg/kg) are shifted to the left of the dose–response curve for intraperitoneal (−)-DOM (ED_{50} ± S.E.M. = 0.2 ± 0.01 mg/kg) at the same time thus

indicating a 2.4-fold and a 1.5-fold increase in potency with intracerebroventricular administration respectively. One-way analysis of variance using Dunnett's method for multiple comparison versus a control (intraperitoneal administration, 75-min pretreatment time) indicates that these differences in potency are statistically significant ($P < .05$).

Fig. 3 shows the dose–response relationship for blockade of the (−)-DOM stimulus by the 5-$HT_{2A/2C}$ antagonist, pirenperone, administered into the lateral cerebral ventricle (intracerebroventricularly). The (−)-DOM stimulus was completely antagonized by microinfusion of 0.02-mg/kg pirenperone and the ID_{50} value was 0.003 ± 0.001 mg/kg. Following systemic (intraperitoneal) administration of pirenperone (data not shown), the ID_{50} value for the blockade of the stimulus effects of (−)-DOM by was 0.005 ± 0.006 mg/kg. The difference in these ID_{50} values is not statistically significant. In an earlier study, an ID_{50} of approximately 0.01 for intraperitoneal pirenperone was observed (Glennon et al., 1983a,b), but it must be noted that a racemic mixture of DOM was employed in that study and hence is not directly comparable to our results.

Fig. 4 shows the time–course for various doses of intracerebroventricular LSD in animals trained to discriminate intraperitoneal LSD (0.1 mg/kg, 15-min pretreatment time) from saline. A dose–response relationship was established as early as 5 min following intracerebroventricular infusion, maximal stimulus effects were observed at 15 min and, by 75 min, the stimulus effects of LSD had diminished. Full generalization occurred at 5 and 15 min following the intracerebroventricular microinjection of 0.1 mg/kg (−)-DOM.

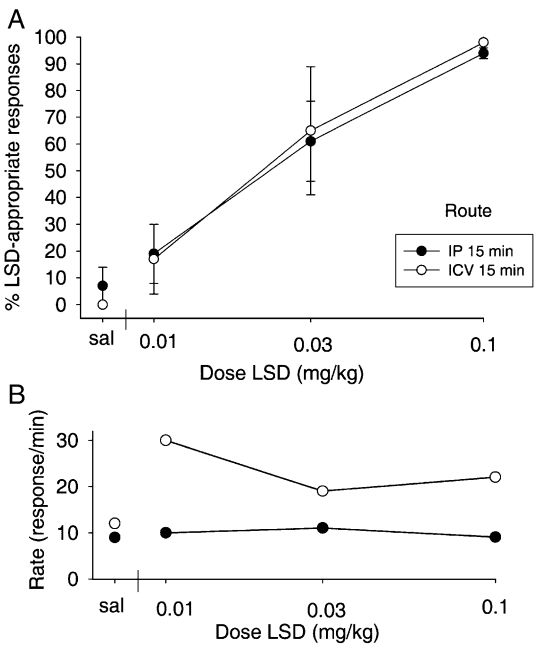

Fig. 5. Dose–response relationship (Panel A) and response rates (Panel B) for LSD 15 min following either intracerebroventricular or intraperitoneal administration in rats trained to discriminate 0.1 mg/kg ip LSD (15-min pretreatment period) from saline. Each point represents the mean ± S.E.M. of one to two trials in five to eight subjects.

Fig. 5 compares the dose–response relationship for LSD at 15 min following either central (intracerebroventricular) or systemic (intraperitoneal) administration. Intraperitoneal LSD (0.1 mg/kg ip) produced 95% drug-appropriate responding at 15 min following intraperitoneal injection. The ED_{50} values ± S.E.M. for LSD at 15 min following intraperitoneal and intracerebroventricular injection were 0.03 ± 0.01 and 0.02 ± 0.005 mg/kg, respectively. The difference in these values is not statistically significant indicating that intracerebroventricular injection does not increase the potency of LSD.

4. Discussion

Initial control experiments assessed the effects of surgically implanting cannulae into the lateral ventricle and the microinfusion procedure on the (−)-DOM stimulus in animals trained to discriminate (−)-DOM from saline. Neither the level of drug-appropriate responding nor the rate of responding following a submaximal dose of intraperitoneal (−)-DOM (0.3 mg/kg) was altered by intracerebroventricular microinfusion of saline. Thus, it is concluded that cannula implantation and microinjection of an inert solution into the lateral ventricle does not affect drug discrimination performance.

Previously, it was shown that the stimulus effects of (−)-DOM administered intraperitoneally are most stable following a 75-min pretreatment period (Fiorella et al., 1995a). In the present study, although generalization occurred as early as 5 min following intracerebroventricular administration for the two highest doses (0.3 and 0.6 mg/kg), percent drug-appropriate responding elicited by the lower dose (0.1 mg/kg) increased with time and by 75 min produced full substitution (Fig. 1). Similarly, the maximal stimulus effect of centrally administered LSD was observed at 15 min (Fig. 2), the pretreatment time used in discrimination training. Thus, for both LSD and (−)-DOM, central administration did not change the pretreatment times required for the maximal stimulus effects to occur.

While it might be expected that the stimulus effects of a centrally acting drug would occur immediately following central administration, the findings of this investigation are in accord with studies examining the time–course of the stimulus effects of other psychoactive drugs. For example, in animals trained to discriminate subcutaneously administered morphine with a 60-min pretreatment time, the peak effects following intracerebroventricular administration also occurred at 60 min (Easterling and Holtzman, 1998). Furthermore, our results are consistent with a nonperiventricular site of action for (−)-DOM and LSD.

While the pretreatment time required to produce the maximal stimulus effect is the same for both systemic and central administration, the onset of the stimulus effect

occurs more rapidly following intracerebroventricular administration. The dose–response curve at 5 min following intracerebroventricular administration of (−)-DOM is shifted to the left of the dose–response curve for intraperitoneal (−)-DOM at 5 min (Fig. 2). Indeed, at the intraperitoneal doses tested, a complete dose–response relationship was not obtained for the 5-min pretreatment time due to decreased rates of responding.

It is puzzling that, while the onset of the stimulus is more rapid following intracerebroventricular infusion, the pretreatment times resulting in maximal effects are not significantly shorter than following systemic administration. The presence of a dose–response relationship to (−)-DOM at 5 min following intracerebroventricular administration but not at 5 min following systemic administration indicates that intracerebroventricular administration does increase delivery of (−)-DOM to central sites. It is possible that the maximal effects of (−)-DOM and LSD result from activity of these drugs at several anatomically distinct areas that are not periventricular. Thus, if (−)-DOM were distributed through cerebral tissue more slowly than LSD, a longer delay prior to maximal effects would be observed for (−)-DOM regardless of whether it was administered centrally or systemically. Support for this possibility comes from the respective lipid solubilities of LSD and racemic DOM, with LSD being approximately five times as lipid soluble (Nichols et al., 1977). Alternatively, the persistence of the 75-min delay prior to maximal effects of (−)-DOM is also consistent with the existence of active (−)-DOM metabolites as suggested by Shulgin and Shulgin (1991) and Eckler et al. (2001). For example, it is possible that the stimulus effects resulting from systemically administered (−)-DOM are the result of interactions with serotonergic receptors in the brain not only by the parent compound but also by the 2-desmethyl and 5-desmethyl metabolites.

Following pretreatment periods that maximize drug-appropriate responding, central administration of (−)-DOM and LSD are 2.4- and 1.5-times more potent, respectively, than systemic administration. Intuitively, it might be expected that, if the stimulus properties of these hallucinogens were centrally mediated, intracerebroventricular infusion would show a much greater potency than systemic administration. Several explanations are possible. The brain areas mediating the stimulus effects of (−)-DOM and LSD may not be periventricular thus resulting in a significant reduction in drug concentration following diffusion to the relevant areas. In this situation, it would be predicted that a highly lipophilic drug would more rapidly exit the CNS following intraventricular administration thus diminishing potency differences as compared with systemic administration. The present data are compatible with this hypothesis in that LSD is more lipid soluble than is racemic DOM (Nichols et al., 1977) and LSD was observed to have a lesser enhancement of potency (a factor of 1.5) following intracerebroventricular administration as compared with (−)-DOM (a factor of 2.4). Alternatively, if (−)-DOM and LSD reach the relevant brain areas via the blood stream and not the CSF, each drug would be diluted in the total blood volume, similar to following systemic administration, and a significant increase in potency would not be expected. Finally, as mentioned previously, active metabolite formation might also be responsible (Shulgin and Shulgin, 1991; Eckler et al., 2001). However, it should be noted that complete generalization observed following intracerebroventricular administration of (−)-DOM suggests that these purported metabolites are either formed locally in the brain or, if they are formed peripherally, that they play only an ancillary role in the (−)-DOM stimulus.

The effects of intracerebroventricular administration on the discriminative stimulus effects of other psychoactive drugs are varied. For example, morphine is approximately 1000-times more potent when administered intracerebroventricularly (Locke and Holtzman, 1985), while complete substitution is not achieved at any dose of centrally administered EtOH (Hodge, 1994). The potencies of centrally administered (−)-DOM and LSD to disrupt bar pressing were increased 3- and 1.3-times, respectively (Mockler and Rech, 1984). Thus, the effects of intracerebroventricular infusion on the potencies of the (−)-DOM and LSD stimulus in the present study are consistent with investigations of central administration of these drugs using different behavioral paradigms and are plausible in the context of discrimination studies following central infusion of other drugs.

In characterizing the discriminative stimulus properties of phenethylamine and indoleamine hallucinogens, it is important to evaluate the blockade of their effects by 5-$HT_{2A/2c}$ antagonists. Pirenperone is an antagonist with nanomolar affinity for 5-HT_{2A} receptors ($K_i \pm$ S.E.M. = 1.91 nM ± 0.40) and 5-HT_{2C} receptors ($K_i \pm$ S.E.M. = 58.9 nM ± 10.5) (Fiorella et al., 1995b). In the present study (Fig. 3), both intracerebroventricular and intraperitoneal administration of pirenperone dose-dependently and fully blocked the stimulus effects of systemically (intraperitoneally) administered (−)-DOM (0.6 mg/kg); however, the potency of pirenperone was not significantly increased by central administration. These results are consistent with the hypothesis that the small increase in potency with central administration of (−)-DOM and LSD is due to a non-perventricular site of action. For example, it is plausible that the concentration of pirenperone decreases as it diffuses to the site of action.

In conclusion, the findings that (1) in animals trained to discriminate systemically administered LSD or (−)-DOM from saline, generalization occurs with central administration of (−)-DOM and LSD, respectively, and (2) central administration of pirenperone fully blocks the stimulus effects of systemically administered (−)-DOM are consistent with the assumption that the stimulus effects of (−)-DOM and LSD are centrally mediated. However, the data in Fig. 1 suggest that, although a complete dose–response relationship was established at 5 min following

intracerebroventricular but not intraperitoneal administration of (−)-DOM, the differences in the time–course for maximal effects following systemic administration were not reduced by central infusion. In addition, the data in Figs. 2 and 3 indicate that following optimum pretreatment times there is only a small increase in potency is associated with intracerebroventricular administration of LSD and (−)-DOM (1.2- and 2.4-fold increase, respectively). The persistence of a 15- and 75-min delay to the onset of maximal stimulus effects for LSD and (−)-DOM, respectively, and the small increase in potency following intracerebroventricular administration of these drugs suggest that intracerebroventricular administration may increase central delivery of these drugs but that perhaps some metabolic activity, neuroanatomical interaction or diffusion to the relevant brain areas occurs during the pretreatment period to maximize the stimulus effect. This could be due to (1) the relevant brain areas being far from the ventricles or (2) poor absorption of LSD and (−)-DOM from the ventricles.

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