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ORIGINAL INVESTIGATION

D. Fiorella · P. A. Palumbo · R. A. Rabin
J. C. Winter

The time-dependent stimulus effects of R(-)-2,5-dimethoxy-4-methamphetamine (DOM): implications for drug-induced stimulus control as a method for the study of hallucinogenic agents

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Abstract The pharmacodynamic characteristics of the stimulus effects of the hallucinogens *d*-LSD and (−)DOM were investigated in the rat. The stimulus control induced by (−)DOM (0.56 mg/kg) was significantly less stable at the 15-min pretreatment time than at the 75-min pretreatment time. In addition, (−)DOM (0.8 mg/kg) produced a time-dependent substitution for the LSD stimulus in LSD trained subjects (0.1 mg/kg, 15-min pretreatment time). As pretreatment times were increased, the substitution of (−)DOM (0.8 mg/kg) for the LSD stimulus increased, culminating in a maximal level of 99.5% LSD-appropriate responding at the 75-min pre-treatment time. A dose-response relationship for the substitution of (−)DOM (75-min pretreatment time) for the LSD stimulus, indicated that 0.2 mg/kg (−)DOM was the minimum dose which elicited greater than 90% LSD-appropriate responding. LSD (0.32 mg/kg, 15-min pretreatment time) fully substituted for (−)DOM in the (−)DOM trained subjects (0.56 mg/kg, 75-min pretreatment time). These findings suggest that the pharmacodynamic parameters of *d*-LSD and (−)DOM-induced stimulus control differ. The time of onset for the stimulus effects of (−)DOM is markedly longer than that of LSD in the rat.

Key words Lysergic acid diethylamide (LSD) · 2,5-Dimethoxy-4-methylamphetamine (DOM) · Drug-induced stimulus control (DISC)

David Fiorella (✉) · Patricia A. Palumbo
Richard A. Rabin · J. C. Winter
Department of Pharmacology and Toxicology School of Medicine and Biomedical Sciences State University of New York at Buffalo, Buffalo, New York 14214 USA

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Introduction

Drug-induced stimulus control (DISC) has been widely used over the past 3 decades to study the interoceptive states created by psychoactive drugs in animal subjects (for reviews see Winter 1978; Balster 1990). Following the initial report of LSD-induced stimulus control in the rat (Hirschhorn and Winter 1971), numerous studies designed to investigate the pharmacologic basis for LSD-induced stimulus control have examined the ability of drugs to substitute for, in tests of generalization, or to block, in tests of antagonism, the stimulus effects of LSD (for review see Colpaert et al. 1982; Glennon et al. 1982, 1984; Cunningham and Appel 1987; Winter 1994].

Binding studies have demonstrated that LSD possesses high affinity for multiple receptor subtypes of both the serotonergic and dopaminergic systems (Burt et al. 1976; Meibach et al. 1980). Predictably, this non-selective pharmacological profile results in the creation of a very complex discriminative stimulus (Appel et al. 1982).

It has been proposed that the more pharmacologically selective phenylalkylamine hallucinogen, 2,5-dimethoxy-4-methamphetamine (DOM), may provide a less complex discriminative stimulus (for review see Glennon 1990), and thereby a more specific model for the study of the pharmacological basis for hallucinogen-induced stimulus control.

While the hallucinogenic effects of LSD and DOM are often assumed to be interchangeable, it must be noted that each compound has a complex spectrum of actions. Among these are additional subjective effects which bestow upon each compound a unique psychotropic profile (Pollard et al. 1960; Jacobsen 1963; Shulgin et al. 1986; Shulgin and Shulgin 1991). Thus, despite their similarities, each member of the class of serotonergic hallucinogens is a distinct pharmacological entity, and as such each would be expected to have distinctive features in both the subjective clinical experience which it induces and in its stimulus

complex. Therefore, conclusions based on the study of any single agent in drug-induced stimulus control (DISC) experiments are necessarily biased toward the particular idiosyncrasies of the training drug, and therefore may not apply to the general class of compounds to which the training drug belongs.

One approach to this problem is the simultaneous study of the stimulus effects of both LSD and DOM. By determining the shared interoceptive characteristics of multiple hallucinogenic agents in animals, one increases the probability of studying the pharmacologic interactions which mediate their common effect of hallucinogenesis in humans.

On this basis, a series of parallel studies was designed using both LSD (0.1 mg/kg, 15-min pretreatment time) and (±)DOM (0.5 mg/kg, 15-min pretreatment time)-induced stimulus control (Palumbo and Winter 1992, 1994). The training drugs, doses, route of administration, and pretreatment time used in these studies were consistent with those reported by other investigators studying hallucinogen-induced stimulus control (e.g., Silverman and Ho 1980; Glennon and Hauck 1985). In our laboratory, significant differences in the stability of LSD and (±)DOM-induced stimulus control were observed (Palumbo et al. unpublished observations). Specifically, a greater percentage of the DOM-trained subjects failed to reach criterion levels of performance during any given weekly series of training sessions. While some investigators have reported that racemic DOM serves as a reliable discriminative stimulus under comparable training conditions (Silverman and Ho 1978; Glennon et al. 1982), other investigators have described similar problems with stability of DOM-induced stimulus control (Huang 1972; Tilson et al. 1975). These latter observations suggest the presence of a pharmacodynamic difference between LSD and DOM.

In the present study, the (−)isomer of DOM was employed for three reasons: (1) in human studies (−)DOM, but not (+)DOM, was reported to produce hallucinations (Shulgin 1973; Shulgin and Shulgin 1992); (2) in discrimination studies, (−)DOM has been reported to be more potent than either the racemic mixture or the (+)isomer (Silverman and Ho 1980; Glennon et al. 1982); (3) biochemical studies have demonstrated that, while (+)DOM binds to serotonergic receptor subtypes, it possesses significantly less efficacy with respect to the stimulation of phosphoinositide hydrolysis than (−)DOM, presenting the possibility that the (+)isomer could diminish the effects of the (−)isomer at these receptors (Sanders-Bush et al. 1988).

The present study was designed to characterize selected pharmacodynamic parameters of the (−)DOM and LSD discriminative stimuli. Specifically: (1) the reliability of the stimulus control induced by 0.56 mg/kg (−)DOM administered at the 15- and 75-min pretreatment times was compared; (2) the time courses for the substitution of (−)DOM (0.8 mg/kg) for the LSD stimulus, and the substitution of LSD (0.32 mg/kg) for the (−)DOM stimulus were defined; (3) the dose-response relationship for the substitution of (−)DOM (75-min pretreatment time) for the LSD stimulus was defined.

Materials and methods

Animals

Male Fischer 344 rats were obtained from Harlan Sprague-Dawley (Indianapolis, Ind.). They were housed in pairs under a natural light-dark cycle and allowed free access to water in the home cage. Subjects were fed immediately following experimental sessions. Caloric intake was controlled to yield a mean body weight of 250 g.

Apparatus

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

Procedure

After learning to drink from the dipper, rats were trained to depress one and then the other of two levers. The number of responses for each reinforcement was gradually increased from one to ten, and all subsequent training and testing sessions used a fixed ratio 10 (FR10) schedule of reinforcement. Discrimination training was then begun. Prior to each training session, animals were injected with either saline or the training drug. Following the administration of the training drug, every tenth response on the drug-appropriate lever was reinforced. Similarly, responses on the saline-appropriate lever were reinforced following saline injections. For half of the subjects, the left lever was designated the drug-appropriate lever. During discrimination training, training drug and saline treatments were alternated on a daily basis. 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.

After stimulus control with the training drug was well established, substitution tests (tests of generalization) were conducted once per week in each animal so long as performance during the remainder of the week did not fall below a criterion level of 83% correct responding. During test sessions, no responses were reinforced and the session was terminated after the emission of ten responses on either lever. The distribution of responses between the two levers was expressed as the percentage of total responses emitted on the drug-appropriate lever. Response rate was calculated for each session by dividing the total number of responses emitted prior to lever selection, that is, prior to the emission of ten responses on either lever, by the elapsed time.

Evaluation of (−)DOM-induced stimulus control

Stimulus control was established in 15 subjects with (−)DOM [0.56 mg/kg, 15 min pretreatment, intraperitoneal injection (IP)]. Following the establishment of stimulus control, subjects were trained under these conditions for 20 weeks. During the final 12 weeks of this 20-week period, percent drug-appropriate responding was calculated for each animal following both drug and saline

training sessions. Each week, the percent drug-appropriate responding for each animal was averaged for both saline and drug training sessions to yield weekly individual mean performance (IMP) values for each animal, for both drug (IMP-D) and saline (IMP-S) training sessions, respectively. IMP-D and IMP-S values were averaged weekly to yield group mean performance (GMP) values for both drug and saline sessions, GMP-D and GMP-S, respectively. This calculation results in two weekly values, one GMP-D and one GMP-S, representing the performance of the entire group during that week's drug and saline training sessions, respectively. In addition, weekly IMP-D and IMP-S values for each subject were averaged over the 12-week period. This calculation results in 15 individual pairs of values, i.e., average IMP-D and IMP-S values for each of the 15 subjects, representing the average performance of each subject during drug and saline training sessions over the 12-week trial. Following this trial, the pretreatment time was changed from 15 to 75 min. Subjects were then trained under these conditions, i.e., (−) DOM (0.56 mg/kg, 75-min pretreatment time, IP injection) for 22 weeks. During the final 12 weeks of this 22-week period, IMP-D and IMP-S values were calculated as described above, for each subject during drug and saline training sessions, respectively. IMP-D and IMP-S values were averaged for the 15 subjects to yield weekly GMP-D and GMP-S values, respectively. In addition, weekly IMP-D and IMP-S values for each subject were averaged over the 12-week period.

Time course and dose-response substitution experiments

Stimulus control was established in 45 subjects with 0.1 mg/kg LSD. LSD was administered by IP injection 15-min prior to the initiation of training sessions. After stimulus control was well established, substitution experiments were begun.

In (−)DOM time course experiments, 0.8 mg/kg (−)DOM, a dose which produced substantial rate suppression but was still compatible with test completion, was administered by IP injection to the LSD-trained subjects at pre-treatment times ranging from 15 to 480 min. During preliminary studies in which a range of (−)DOM doses were tested at the 15-min pretreatment time, 0.8 mg/kg (−)DOM elicited the highest level of LSD-appropriate responding. Percent LSD-appropriate responding and response rates were recorded.

In (−)DOM dose-response experiments, varying doses of (−)DOM were administered to the LSD-trained animals 75 min prior to initiation of test sessions. Percent LSD-appropriate responding and response rates were recorded.

In the LSD time course experiments, 0.32 mg/kg LSD was administered by IP injection to (−)DOM trained subjects (0.56 mg/kg, 75-min pretreatment time) at pretreatment times ranging from 15 to 180 min. Percent (−)DOM-appropriate responding and response rates were recorded. These data were generated in the (−)DOM trained subjects during the second 12-week trial period described above.

Drugs

LSD and (−)DOM were obtained from NIDA. Both drugs were dissolved in 0.9% saline, and injected IP in a volume of 1.0 ml/kg body weight.

Results

Evaluation of (−)DOM-induced stimulus control

Figure 1a represents the weekly GMP-D and GMP-S values determined for the (−)DOM-trained subjects during the two 12-week trials. Over the 12-week trials, GMP-D values were greater in subjects trained with (−)DOM (0.56 mg/kg) at the 75 min pretreatment time then in those same subjects when trained with (−)DOM (0.56 mg/kg) at the 15-min pretreatment time. During the first trial (15-min pretreatment time) GMP-D values fell below the criterion level for acceptable performance, 83% drug-appropriate responding,

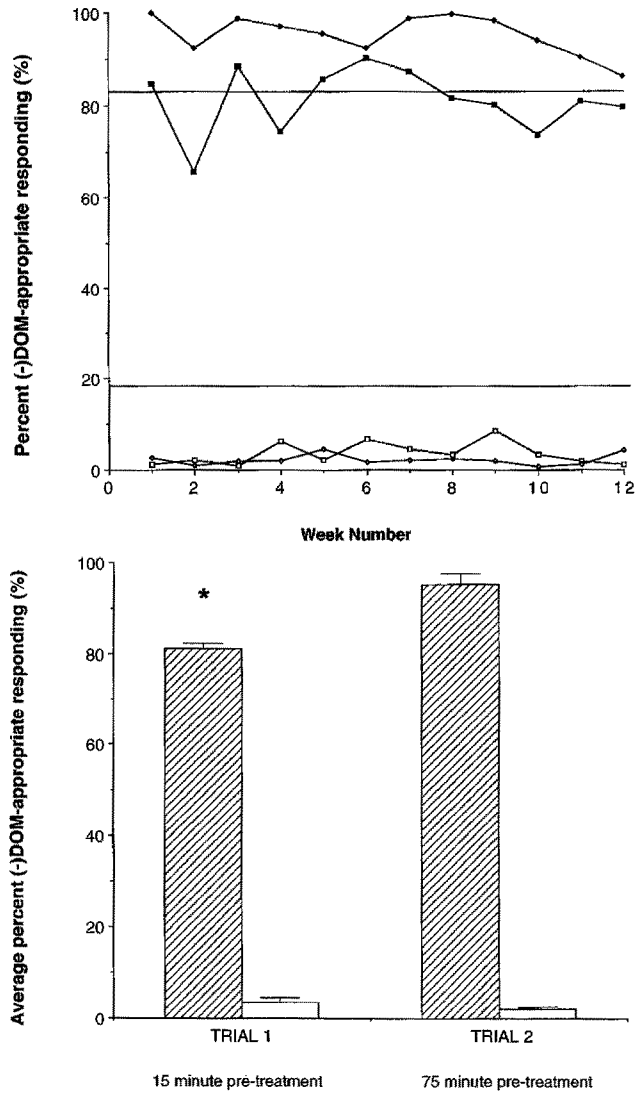

Fig. 1a Weekly GMP-D (*closed figures*) and GMP-S (*open figures*) values for the two 12 week trials. *Squares* represent values from the first trial (15-min pretreatment time), while *diamonds* represent results from the second 12-week trial (75-min pretreatment time). *Horizontal lines* at 83% and 17% percent drug-appropriate responding indicate criterion levels of performance during drug and saline training sessions, respectively. *Ordinate:* GMP values expressed as percent (−)DOM-appropriate responding *Abscissa:* week number. **b** 12 week average IMP-D (*hatched bars*) and IMP-S (*open bars*) for the two 12-week trials. *Ordinate:* Average % (−)DOM-appropriate responding, *Abscissa:* trial number (first or second) and pretreatment time (15 or 75 minutes). *Asterisk* indicates a significant difference ($P < 0.01$) between the 12-week average IMP-D values for the subjects during the first (15-min pretreatment) and second (75-min pretreatment) trials as determined by a Wilcoxon's signed ranks test for paired observations

during 7 of the 12 weeks. In contrast during the second trial (75-min pretreatment time), GMP-D values never fell below 83% drug-appropriate responding. GMP-S values were similar during both trials. Twelve-week average IMP-D and IMP-S values are displayed in Fig. 1b. Twelve week average IMP values obtained during the first 12-week trial were compared with 12-week average IMP values obtained during the second 12-week trial using a paired Wilcoxon's signed ranks test. Average IMP-D values were significantly greater ($T_s = 1$, $P < 0.01$) in the subjects during the second 12-week trial (75-min pretreatment time) than in the same subjects during the first 12-week trial (15-min pretreatment time). In addition, the average IMP-D value during the first trial was 81.3 (2.3)%, a value slightly below the established criterion level of 83% (−)DOM-appropriate responding. Average IMP-S values were not different ($T_s = 36$, $P > 0.05$) during the two trials.

Time course: substitution of (−)DOM for the LSD stimulus

0.8 mg/kg (−)DOM was administered to the LSD-trained subjects at pretreatment times ranging from 15 to 480 min (Fig. 2). LSD-appropriate responding ranged from 55%, at the 15-min pretreatment time, to 99% at the 75-min pretreatment time. In addition, LSD-appropriate responding remained greater than 90% at the 180-min pretreatment time. The 0.8 mg/kg dose of (−)DOM was substantially rate depressing at pretreatment times up to 240 min. At the 15-min pretreatment time, 8 of 25 subjects failed to complete the test session.

Dose-response relationship for the substitution of (−)DOM for the LSD stimulus

Doses of (−)DOM (75-min pretreatment time) ranging from 0.066 to 0.8 mg/kg were administered to the LSD-trained subjects (Fig. 3). (−)DOM 0.2 mg/kg was the lowest dose which elicited greater than 90% LSD-appropriate responding.

Time course: substitution of LSD for the (−)DOM stimulus

Figure 4 represents the time course for the substitution of 0.32 mg/kg LSD for the (−)DOM stimulus (0.56 mg/kg, 75-min pretreatment time). The results of the (-)DOM dose-response experiments in the LSD-trained subjects demonstrated that LSD was approximately twice as potent as (−)DOM (Fig. 3). For this reason, a 0.32 mg/kg dose of LSD was chosen for the LSD time course experiment, i.e., slightly greater than one-half of the (−)DOM training dose (0.56 mg/kg). LSD was administered in test sessions at pretreatment times ranging from 15 to 180 min. Full substitution of 0.32 mg/kg LSD for the (−)DOM stimulus was observed at the 15-min pretreatment time. (−)DOM-appropriate responding remained at levels greater than 95% for pretreatment times of up to 90 min.

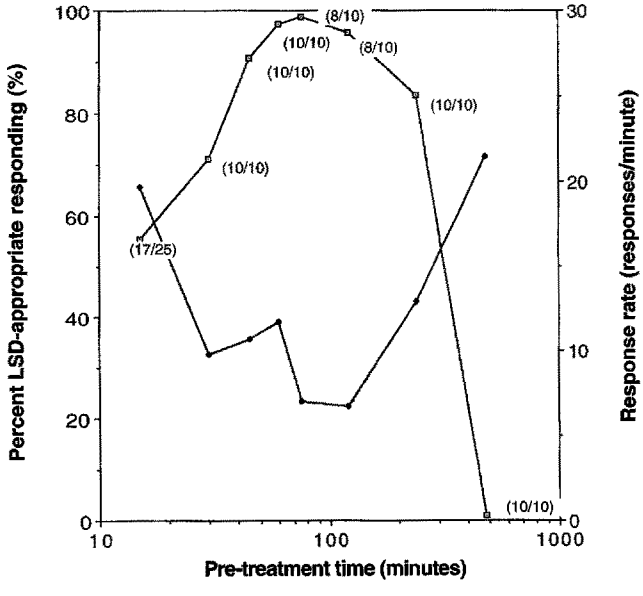

Fig. 2 Time course of (−)DOM (0.8 mg/kg) in LSD-trained animals. *Abscissa*: pretreatment time. *Left ordinate*: % LSD-appropriate responding (*open squares*). *Right ordinate*: response rate (responses per minute; *closed squares*). The fraction of participating subjects that completed each test session is indicated as a ratio in parentheses adjacent to each time point

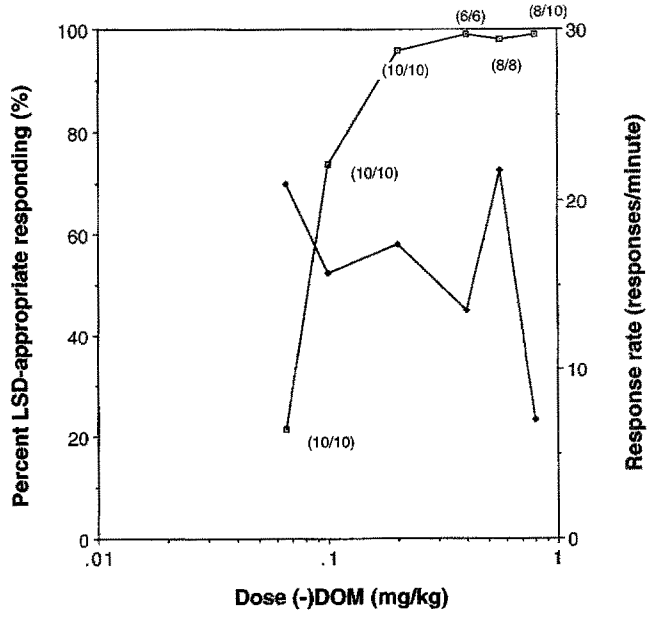

Fig. 3 Dose-response for (−)DOM (75-min pretreatment time) in LSD-trained animals. *Left ordinate*: % of LSD-appropriate responses (*open squares*). *Right ordinate*: response rate (responses per minute; *closed squares*). *Abscissa:* dose of (−)DOM. The fraction of participating subjects that completed each test session is indicated as a ratio in parentheses adjacent to each time point

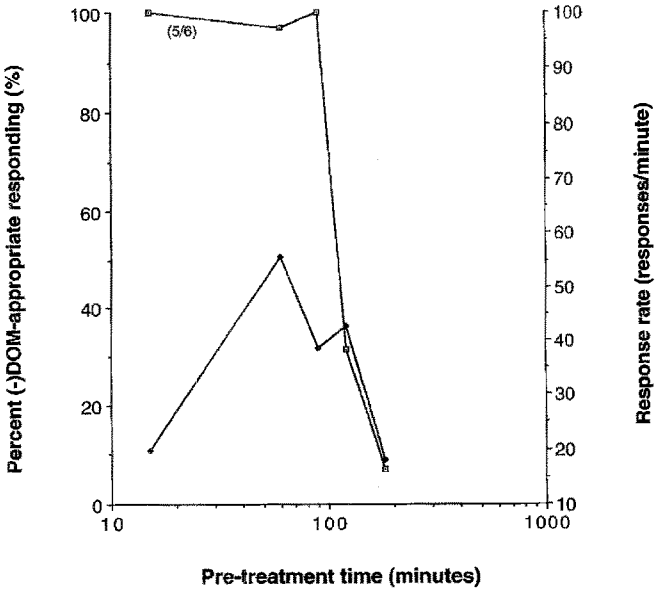

Fig. 4 Time course for LSD (0.32 mg/kg) in (−)DOM trained subjects (0.56 mg/kg; 75-min pretreatment time). *Abscissa:* pretreatment time. *Left ordinate*: % (−)DOM-appropriate responding (*open figures*). *Right ordinate*: response rate (responses per minute; *closed figures*). The fraction of tested subjects thatcompleted each test session is indicated as a ratio in parentheses adjacent to each time point. Where no ratio is indicated, 6 of 6 tested subjects completed the test session

Discussion

Drug-induced stimulus control (DISC) has been proposed as an animal model for the subjective effects of psychoactive drugs in humans (Brady et al. 1990). DISC has been applied to the study of hallucinogenic drugs in an attempt to understand the pharmacological basis for drug-induced hallucinations (Appel et al. 1982). The ability of humans to report verbally the characteristics of the subjective effects of psychoactive substances allows verification that a given substance does, in fact, induce hallucinations. In contrast, while hallucinogens readily establish stimulus control in non-verbal species, the true qualitative nature of the interoceptive state governing stimulus control is not accessible. Thus, although a hallucinogenic agent is trained, the investigator cannot absolutely determine that the interactions which are responsible for the induction of hallucinations in humans are identical or even related to those which mediate the interoceptive state, and thus stimulus control, in trained animal subjects. This potential problem is further complicated by the non-selective pharmacological profile of hallucinogenic substances, particularly LSD (Burt et al. 1976; Pazos et al. 1985).

For this reason, it is of paramount importance to design experiments which increase the probability that the pharmacological basis for the interoceptive state studied in animals is related to the pharmacological basis for human hallucinosis. One approach is the simultaneous study of stimulus control by two or more hallucinogenic agents. By considering the shared interoceptive characteristics of multiple hallucinogenic agents in animals, one increases the probability of studying the interactions which mediate their common effect of hallucinogenesis in humans. On this basis, the simultaneous study of DOM and LSD (Palumbo and Winter 1992, 1994) is a potentially effective method by which to unravel the pharmacological basis for drug-induced hallucinogenesis.

In the present study, (−)DOM was studied as a training stimulus. Initially (−)DOM was administered using a 15-min pretreatment time based on previous reports in the literature describing the induction of stimulus control with phenylalkylamine hallucinogens (e.g., Silverman and Ho 1980; Glennon and Hauck 1985 for review see Glennon et al. 1982). As was previously observed in experiments employing the racemate (Palumbo and Winter, unpublished observations), the criterion for stimulus control could be achieved with (−)DOM (0.56 mg/kg, 15-min pretreatment time); however, levels of drug-appropriate responding during drug training sessions indicated instability (Fig. 1a). Average levels of drug-appropriate responding during drug training sessions over the first 12 week trial (81.2%) were slightly below established level for criterion performance (83%). Similar observations were made by Tilson et al. (1975), who reported an average of 74% (−)DOM-appropriate responding during drug training sessions [0.75 mg/kg (−)DOM, 15-min pretreatment time], and reported that 0.5 mg/kg (−)DOM (15-min pretreatment time) was not sufficient to serve as a discriminative stimulus. Because a single sub-criterion training session disqualifies a subject from any subsequent testing sessions during that week, often 8 or more of the 15 subjects were not eligible for test sessions each week. On this basis, it was concluded that (−)DOM (0.56 mg/kg, 15-min pretreatment time) was an insufficient training stimulus.

Figure 2 represents the time course for the substitution of 0.8 mg/kg (−)DOM for LSD in LSD-trained animals (0.1 mg/kg, 15-min pretreatment). Although the 0.8 mg/kg dose of (−)DOM was observed to be substantially rate depressing, this dose still allowed most subjects to complete the test sessions. At the 15-min pretreatment time, (−)DOM elicited only 55% LSD-appropriate responding. LSD-appropriate responding increased with increasing pre-treatment times, culminating in 99.5% LSD-appropriate responding at the 75-min pretreatment time. LSD-appropriate responding remained stable at a level above 90% for pretreatment times of up to 180 min, and subsequently declined at later time points. These data demonstrate that pretreatment times of 1 h or greater are required for (−)DOM to produce its maximal and stable LSD-like stimulus effects. Correspondingly, these data indicate that DOM, when administered at pretreatment times of less than 60 min, may 1) induce an

interoceptive state mediated by interactions unrelated to those which mediate the interoceptive state of LSD or 2) induce an unstable interoceptive state which may qualitatively change over short periods of time.

Although caution must be exercised when extrapolating studies in animals to the human condition, an interesting correlate to these observations has been reported in humans. In comparison to LSD (Kulig 1990; Shulgin and Shulgin 1992), DOM requires a significantly longer time, 90–120 min, for the onset of hallucinogenic activity (Snyder et al. 1968; Hollister et al. 1969; Shulgin and Shulgin 1992). This pharmacodynamic phenomenon is thought responsible for the high incidence of DOM overdose in naive users: persons consume multiple doses of DOM after experiencing no hallucinogenic effects 30 min after the ingestion of a single dose (Shulgin and Shulgin, 1992).

The dose-response relationship for the substitution of DOM (Snyder et al., 1968) (75-min pretreatment time) for the LSD stimulus demonstrates that 0.2 mg/kg (−)DOM was the lowest dose which elicits full substitution (Fig. 3). Interestingly, the typical street dose of LSD ranges between 100 and 250 μg (Kulig 1990). Approximately twice that dose, 500 μg, of (−)DOM was observed to produce LSD-like effects in humans (Shulgin and Shulgin 1991).

These findings describing the pharmacodynamics of the (−)DOM stimulus in LSD-trained subjects formed the basis for the second 12 week trial in the (−)DOM-trained subjects. The pretreatment time for the (−)DOM training stimulus was changed from 15 to 75 min. After 10 weeks of training under these conditions, i.e., 0.56 mg/kg (−)DOM, 75-min pretreatment time, the second 12-week trial was initiated. The elongation of the pretreatment interval substantially improved the stability of (−)DOM-induced stimulus control. GMP-D values were greater than the criterion level for acceptable performance (83% drug-appropriate responding) during all 12 weeks of the study (Fig. 1a). Twelve week average IMP-D values were significantly greater for the subjects during the second trial (75-min pretreatment) than during the first trial (15-min pretreatment, Fig. 1b). Thus, as was observed in the substitution experiments, the (−)DOM stimulus requires over 1 h to reach maximal salience and stability.

Following these observations, the time course for the substitution of LSD for this stable (−)DOM stimulus (0.56 mg/kg, 75 min pretreatment time) was determined. LSD 0.32 mg/kg fully substituted for the (−)DOM stimulus within 15 min of administration (Fig. 4). This result is consistent with the more rapid onset of LSD-induced hallucinations reported in humans.

The findings in the present study form the basis for future novel applications of DISC to study hallucinogenic drugs. First, the substitution of (−)DOM for the LSD stimulus offers the opportunity to study specifically an interoceptive state common to both (−)DOM and LSD. The selective study of the receptor interactions required for (−)DOM to substitute for LSD can eliminate some of the idiosyncratic aspects of the pharmacological profiles and the stimulus effects of each compound. This method could potentially facilitate the selective study of the shared aspects of the discriminative cues of each drug, thereby increasing the probability of studying an interoceptive state more closely related to the induction of hallucinations in humans, i.e., the hallucinogenic discriminative cue, rather than either the DOM or LSD-discriminative cue. The method of antagonist correlation analysis described by Friedman et al. (1984), is well suited for the determination of the pharmacological basis for this hallucinogenic cue.

Second, the use of the 75-min pretreatment time, and the (−) isomer of DOM to establish stimulus control may provide a pharmacologically more selective discriminative stimulus than either racemic DOM or LSD. (−)DOM-induced stimulus control offers the potential to complement and clarify previous and future studies of LSD-induced stimulus control. For example, it is of particular interest to determine whether the non-hallucinogenic compounds which fully substitute for LSD, i.e., quipazine (Colpaert et al. 1979; Winter 1979; Parati et al. 1980), MK-212 (White and Appel 1982; Lowy and Meltzer 1988), lisuride (Freedman and Boggan 1982; White and Appel 1982) and yohimbine (Holmberg et al. 1961; Colpaert 1984), fully substitute for the (−)DOM stimulus. If these "false positive" agents do not substitute for (−)DOM, their ability to substitute for LSD may be attributable to receptor interactions shared with LSD, but extraneous to those required for LSD-induced hallucinosis. Conversely, if these agents do substitute for (−)DOM, their ability to substitute for LSD may be attributable to receptor interactions shared with LSD and (−)DOM which may be required, but not sufficient to induce hallucinations in humans. Presently, this question is being investigated in our laboratory.

In conclusion, the pharmacodynamic characteristics of the DOM and LSD stimuli differ markedly. Although stimulus control can be established with (−)DOM using standard 15-min pretreatment time, stimulus control is unstable and thus inadequate. This instability can be attributed to the delayed onset of the stable and LSD-like stimulus effects of (−)DOM. This time dependent nature of the DOM stimulus is evidenced by 1) the time course for the substitution of (−)DOM for LSD and 2) the marked improvement in (−)DOM-induced stimulus control observed after the elongation of the pretreatment interval.

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