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Behavioral characterization of 2-*O*-desmethyl and 5-*O*-desmethyl metabolites of the phenylethylamine hallucinogen DOM

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Abstract

The present investigation was undertaken to test the hypothesis that known metabolites of the phenylethylamine hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) are pharmacologically active. This hypothesis was tested by evaluating the ability of racemic DOM metabolites 2-*O*-desmethyl DOM (2-DM-DOM) and 5-*O*-desmethyl DOM (5-DM-DOM) to substitute for the stimulus properties of (+)lysergic acid diethylamide (LSD). The data indicate that both metabolites are active in LSD-trained subjects and are significantly inhibited by the selective 5-HT_{2A} receptor antagonist M100907. Full generalization of LSD to both 2-DM-DOM and 5-DM-DOM occurred, and 5-DM-DOM was slightly more potent than 2-DM-DOM. Similarly, 5-DM-DOM had a slightly higher affinity than 2-DM-DOM for both 5-HT_{2A} and 5-HT_{2C} receptors. Additionally, it was of interest to determine if the formation of active metabolite(s) resulted in a temporal delay associated with maximal stimulus effects of DOM. We postulated that if metabolite formation resulted in the aforementioned delay, direct administration of the metabolites might result in maximally stable stimulus effects at an earlier pretreatment time. This hypothesis was tested by evaluating (1) the time point at which DOM produces the greatest degree of LSD-appropriate responding, (2) the involvement of 5-HT_{2A} receptor in the stimulus effects of DOM at various pretreatment times by administration of M100907 and (3) the ability of 2-DM-DOM and 5-DM-DOM to substitute for the stimulus properties of LSD using either 15- or 75-min pretreatment time. The data indicate that (a) the DOM stimulus produces the greatest degree of LSD-appropriate responding at the 75-min time point in comparison with earlier pretreatment times and (b) the stimulus effects of DOM are differentially antagonized by M100907 and this effect is a function of DOM pretreatment time prior to testing. Both 2-DM-DOM and 5-DM-DOM were found to be most active, at all doses tested, using a 75-min versus a 15-min pretreatment time. The present data do not permit unequivocal acceptance or rejection of the hypothesis that active metabolites of (−)-DOM provide a full explanation of the observed discrepancy between brain levels of (−)-DOM and maximal stimulus effects.

Keywords: LSD; (−)-DOM; 2-DM-DOM; Rat; 5-DM-DOM; M100907; DOM metabolites

1. Introduction

The discovery in 1943 by Albert Hofmann of the hallucinogenic effects of lysergic acid diethylamide (LSD) continues to influence the course of biological psychiatry. A serotonergic basis for the actions of LSD was proposed nearly a half century ago on the basis of experiments using isolated smooth muscle (Gaddum, 1957; Wooley and Shaw, 1954). LSD and other hallucinogenic agents have been studied in nonverbal species in attempts to mimic naturally occurring psychosis in human.

Following its synthesis by Shulgin (1964), the hallucinogenic effects of the phenylethylamine 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) were reported independently by Hollister et al. (1969) and Snyder et al. (1968). These clinical studies employed racemic DOM, while it has been reported that the (−)-isomer of DOM is considerably more potent than the (+)-isomer or the racemic mixture in both man (Shulgin, 1973) and rat (Benington et al., 1973; Silverman, 1977). Shulgin and Shulgin (1991) state that the (+)-isomer of DOM is inactive in humans up to the doses evaluated and may mediate the unwanted (+)-amphetamine-like effects experienced with ingestion of

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racemic DOM. For these reasons, our experiments have been conducted using (−)-DOM.

Despite their structural differences, a number of observations suggested that the phenylethylamines and the indoleamines act via a common mechanism. In human subjects (Balistrieri and Fontanari, 1959; Wolbach et al., 1962) as well as in animals (Appel and Freedman, 1968; Winter, 1972), cross-tolerance develops between LSD and mescaline (2-(3,4,5-trimethoxyphenyl)-1-aminoethane), a naturally occurring phenylethylamine hallucinogen. In humans, the syndrome produced by LSD is similar to that of both mescaline (Hoch et al., 1952) and DOM (Hollister et al., 1969). In addition, both groups of hallucinogens produce similar effects on the firing rate of serotonergic neurons (Aghajanian et al., 1970) and on the level and rate of turnover of serotonin in the brain (Tonge and Leonard, 1969). Finally, it was known that serotonergic antagonists block some of the nonbehavioral effects of phenylethylamine hallucinogens in animals (Cheng et al., 1973; Horita and Hamilton, 1972; Huang and Ho, 1972). This observation was later extended to the behavioral effects of both indoleamine and phenylethylamine hallucinogens when trained as discriminative stimuli in the rat (Winter, 1978; Glennon et al., 1982). The relevance of these observations to man was demonstrated by Vollenweider et al. (1998) in their report that in normal subjects the hallucinogenic effects of psilocybin, an indoleamine hallucinogen, are antagonized by the 5-HT_2 antagonists ketanserin and risperidone.

During the mid-1960s, DOM was introduced as a hallucinogenic street drug said to be LSD like while possessing a lengthened duration of action (Stafford, 1992). Individuals who ingested DOM commonly had prior experience with LSD and were expecting a similar onset of the hallucinogenic effect. Unlike LSD, the onset of DOM required a longer time period for its hallucinogenic properties to emerge. As a result, many users ingested multiple doses, thinking that the original dose was insufficient to induce the desired psychotomimetic effect (Shulgin and Shulgin, 1991). The difference in time of hallucinogenic onset represents a differentiating property of LSD and DOM that ultimately resulted in emergency room visits due to overdose (Smith, 1969a,b).

Studies using drug-induced stimulus control in the rat suggest that pretreatment times of 1 h or greater for (−)-DOM result in more stable LSD-like stimulus effects than at earlier times (Fiorella et al., 1995). For this reason, subsequent experimentation in our laboratory has employed a 75-min pretreatment time when (−)-DOM has served as the training agent. In contrast, the stimulus effects of LSD and mescaline are fully present after 15 min (Fiorella et al., 1996; Winter, 1978; Winter and Rabin, 1988). This difference is not explained by a delay in uptake to the brain because maximum levels of (−)-DOM in rat brain occur between 15 and 30 min (Eckler et al., 2001). This discrepancy between behavioral data and maximal brain levels is consistent with the formation of an active metabolite. In the presence of active metabolites, predictions of a drug's profile based on receptor binding properties of the parent drug may be inappropriate because the receptor binding properties and the relative contribution of active metabolites may be quite different.

Heffter (1896) isolated mescaline by fractioning the alkaloids from *Anhalonium lewinii* (peyote cactus) in order to identify the active hallucinogenic agent. Mescaline inactivation has been associated with the loss of a methoxy group (Shulgin and Shulgin, 1991; Daly et al., 1962). In contrast, Shulgin and Shulgin (1991) state that "with DOM this loss may be associated with the formation of an active metabolite." Zweig and Castagnoli (1977) identified 2-*O*-desmethyl and 5-*O*-desmethyl metabolites of DOM [1-(2-hydroxy-5-methoxy-4-methylphenyl)-2-aminopropane (2-DM-DOM) and 1-(5-hydroxy-2-methoxy-4-methylphenyl)-2-aminopropane (5-DM-DOM), respectively] using a stable isotope dilution assay using rabbit liver homogenates. We then were interested in determining if either metabolite would mimic the stimulus effects of either LSD or (−)-DOM when cross tested. Additionally, it was of interest to determine if the formation of active metabolite(s) resulted in a temporal delay associated with maximal stimulus effects of (−)-DOM. We postulated that if metabolite formation resulted in the aforementioned delay, direct administration of the metabolites might result in maximally stable stimulus effects at an earlier pretreatment time. To test this hypothesis, the stimulus effects of the 2-*O*-desmethyl and 5-*O*-desmethyl metabolites of DOM were examined in rats trained to discriminate LSD or (−)-DOM from saline.

2. Materials and methods

2.1. Materials

(−)-DOM and (+)-LSD were supplied by the National Institute on Drug Abuse (Rockville, MD, USA). The two DOM metabolites were prepared by the method of Zweig and Castagnoli (1977) and used as their hydrochloride salts. All drugs used in the behavioral experiments were dissolved in 0.9% saline solution and were intraperitoneally (ip) injected in a volume of 1.0 ml/kg body weight.

2.2. Animals

Adult male Fischer 344 rats were obtained from Harlan Sprague–Dawley (Indianapolis, IN, USA) and were housed with free access to food and water in a temperature-controlled room under a constant 12:12 h light/dark cycle. All experiments were conducted during the light phase. Subjects were fed following experimental sessions. Caloric intake was controlled to yield a mean body weight of about 250 g. Animals used in these studies were maintained in accordance with the Guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources,

National Research Council. The present study was approved by the Institutional Animal Care and Use Committee of the University at Buffalo.

2.3. Drug-induced stimulus control

Five 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 of sweetened condensed milk diluted 2:1 with tap water.

Twelve subjects were trained to discriminate LSD (0.1 mg/kg, 15-min pretreatment time) from saline and an additional 12 subjects were trained using (−)-DOM (0.6 mg/kg ip, 75 min pretreatment time) as described previously (Fiorella et al., 1995). 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. LSD- and (−)-DOM-induced stimulus control were established after 25–30 training sessions. The (−)-DOM training dose produced 99.3% drug-appropriate responding, while the training dose of LSD yielded 99.5% drug-appropriate responding. 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. Half of the test sessions were conducted the day after saline training sessions with the remainder following either LSD or (−)-DOM training sessions. 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 between the two levers was expressed as a 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 on both levers by the elapsed time prior to 10 responses on either lever.

For purposes of discussion of these data, complete generalization of a training drug to a test drug is said to be present when (a) a mean of 80% or more of all test responses occurs on the drug-appropriate lever, (b) there is no statistically significant difference between the response distributions of the training drug and the test drug and (c) there is a statistically significant difference between the response distributions of the test drug and saline control sessions. An intermediate degree of generalization is defined as being present when response distributions after a test drug are less than 80% drug appropriate and are significantly different from both training conditions. Finally, when the response distribution after a test drug is not statistically significantly different from that in saline control sessions, an absence of generalization of the training drug to the test drug is assumed. Similar criteria are applied to the definitions of full, partial and no antagonism. Thus, full antagonism is assumed to be present when (a) less than 20% of all test responses are on the training drug-appropriate lever, (b) there is no significant difference between the response distributions in the test of antagonism and the saline control and (c) there is a statistically significant difference between the response distributions of the test drug alone and in combination with the antagonist.

2.4. Binding

Radioligand binding assays were carried out as previously described using membranes from either COS-7 cells stably expressing the human 5-HT_{2A} receptor or NIH3T3 cells stably transfected with the human 5-HT_{2C} INI receptor (Chang-Fong et al., 2002). For binding to the COS-7 cell membranes, assays were carried out at room temperature for 30 min in a final volume of 1 ml containing 0.4 nM [^{3}H]ketanserin. A 30-min incubation at 37 °C in the presence of 1 nM [^{3}H]mesulergine was used with the NIH3T3 cell membranes. Nonspecific binding was defined with 10 μM mianserin. Reactions were terminated by vacuum filtration through glass fiber filters (presoaked with 0.3% polyethyleneimine) using a Brandel cell harvester. Data were analyzed using Prism software (GraphPad, San Diego CA).

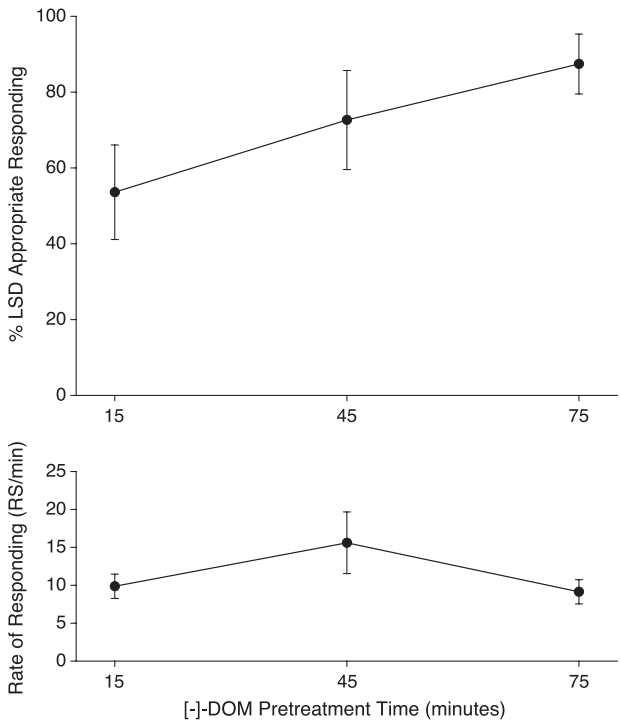

Fig. 1. Time course for the substitution of (−)-DOM (0.6 mg/kg) for the stimulus effects of LSD in rats trained with the latter drug (0.1 mg/ml, 15 min). Each point represents the mean of one determination in 12–15 rats. Ordinate top panel: %LSD-appropriate responding. Ordinate bottom panel: Rate of responding (responses/min). Abscissa: Pretreatment time (min). Data are presented as means ± S.E.M.

2.5. Statistics

The degree of generalization of LSD to (−)-DOM was assessed by individual applications of one-way analysis of variance (ANOVA) of the results following (−)-DOM and both training conditions. Subsequent multiple comparisons were made by the method of Student's–Newman–Keuls' for each pretreatment time of (−)-DOM tested.

The degree of generalization of LSD to 2-DM-DOM and 5-DM-DOM was assessed using two-way ANOVA using both dose and pretreatment as factors. In tests of antagonism of the stimulus effects of (−)-DOM, 2-DM-DOM and 5-DM-DOM by M100907, significance was assessed by individual applications of Student's *t* test for each dose of M100907 tested. Differences were considered statistically significant if the probability of their having arisen by chance was $<.05$. All analyses were conducted using SigmaStat for Windows (Jandel Scientific Software, San Rafael, CA, USA).

3. Results

The training agents (−)-DOM and LSD both elicited >98% drug-appropriate responding during training sessions conducted throughout the course of this study. In contrast, <3% drug-appropriate responding was observed in training sessions that were preceded by saline treatment.

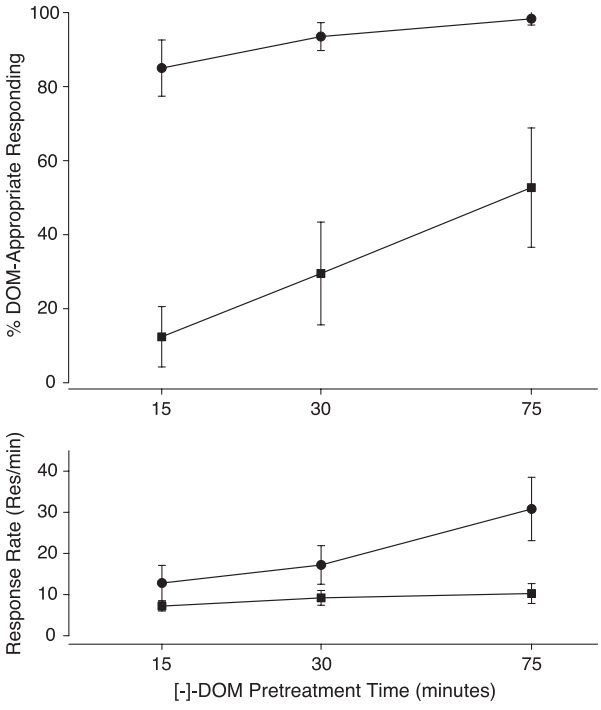

Fig. 2. The effect of pretreatment time on the stimulus effects of (−)-DOM administered either alone (circles) or in combination with M100907 (0.05 mg/kg, 30 min, squares) in rats trained with (−)-DOM (0.6 mg/kg, 75 min). Each point represents the mean of one determination in each of 11 rats. Ordinate top panel: %(−)-DOM-appropriate responding. Ordinate bottom panel: Rate of responding (responses/min). Abscissa: Pretreatment time (min). Data are presented as means ± S.E.M.

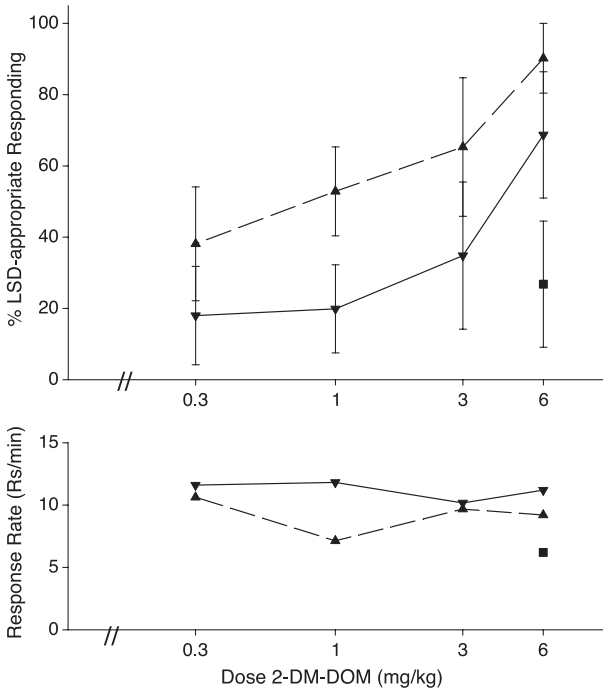

Fig. 3. The substitution of 2-DM-DOM for the stimulus effects of LSD using a pretreatment time of either 15 min (solid line; triangle down) or 75 min (dashed line; triangle up). Antagonism by M100907 (0.05 mg/kg, 30 min) of the maximum effect of 2-DM-DOM (6 mg/kg, 75 min) is indicated by the square. Each point represents the mean of one determination in six to eight rats. Ordinate top panel: %(−)-DOM-appropriate responding. Ordinate bottom panel: Rate of responding (responses/min). Abscissa: Dose of 2-DM-DOM administered (mg/kg). Data are presented as means ± S.E.M.

Preliminary experiments were conducted in (−)-DOM-trained subjects (data not shown). Full generalization of (−)-DOM to both metabolites was observed. A dose of 3.0 mg/kg 2-DM-DOM (75 min) resulted in 99% (−)-DOM-appropriate responding ($n=9$). A dose of 0.3 mg/kg 5-DM-DOM (75 min) resulted in 87.5% (−)-DOM-appropriate responding ($n=8$). The stimulus effects of both metabolites were inhibited by 0.05 mg/kg M100907. The administration of 3.0 mg/kg 5-DM-DOM resulted in 32.3% (−)-DOM-appropriate responding 24 h following its administration ($n=9$).

LSD-trained subjects were tested using 0.6 mg/kg (−)-DOM at various pretreatment times (Fig. 1). LSD-appropriate responding ranged from 53% at the 15-min pretreatment time to 87% at the 75-min pretreatment time. Statistical analysis revealed that the (−)-DOM stimulus produced an intermediate degree of generalization at both 15- and 45-min pretreatment times. In contrast, full generalization of LSD to (−)-DOM is present at the 75-min pretreatment time.

The training dose of (−)-DOM alone was administered at various pretreatment times in rats trained to discriminate (−)-DOM from saline (Fig. 2). Although the substitution of (−)-DOM at all three time points met our criteria for full generalization, the degree of substitution at 75 min (99%)

was statistically significantly greater than at 15 min (85%). Furthermore, when (−)-DOM was administered in combination with the selective 5-HT_{2A} receptor antagonist, M100907, stimulus control was significantly reduced at all three time points. However, analysis of the degree of antagonism reveals significant differences as a function of pretreatment time. Thus, full antagonism is seen at 15 min but only intermediate antagonism at 75 min.

The stimulus effects of racemic 2-DM-DOM were determined in LSD-trained subjects (Fig. 3). The dose–effect relationship for 2-DM-DOM was evaluated using 15- and 75-min pretreatment times. At each dose tested, the %LSD-appropriate responding was greatest at the later pretreatment time, with a maximum of 90% (6.0 mg/kg, 75 min), representative of full generalization. Two-way ANOVA with dose of 2-DM-DOM and pretreatment time as factors revealed a significant effect of both pretreatment time ($F=5.7$, $P=.021$) and dose ($F=4.1$, $P=.012$). The maximal effect of 2-DM-DOM was significantly antagonized by M100907 and fulfilled the criteria for partial antagonism.

The stimulus effects of racemic 5-DM-DOM were determined in LSD-trained subjects (Fig. 4). The dose–effect relationship for 5-DM-DOM was evaluated using either a 15-min or a 75-min pretreatment time. At each dose tested, the %LSD-appropriate responding was greatest at the later time point, with a maximum of 94% (3.0 mg/kg, 75 min), representative of full generalization. Two-way ANOVA with dose of 5-DM-DOM and pretreatment time as factors revealed a significant effect of both pretreatment time ($F=25.6$, $P=.001$) and dose ($F=2.5$, $P=.05$). No animal tested at a dose of 3.0 mg/kg and a 15-min pretreatment time was able to complete the test session. A dose of 1.0 mg/kg of 5-DM-DOM (75 min) was significantly reduced by M100907 and fulfilled the criteria for full antagonism.

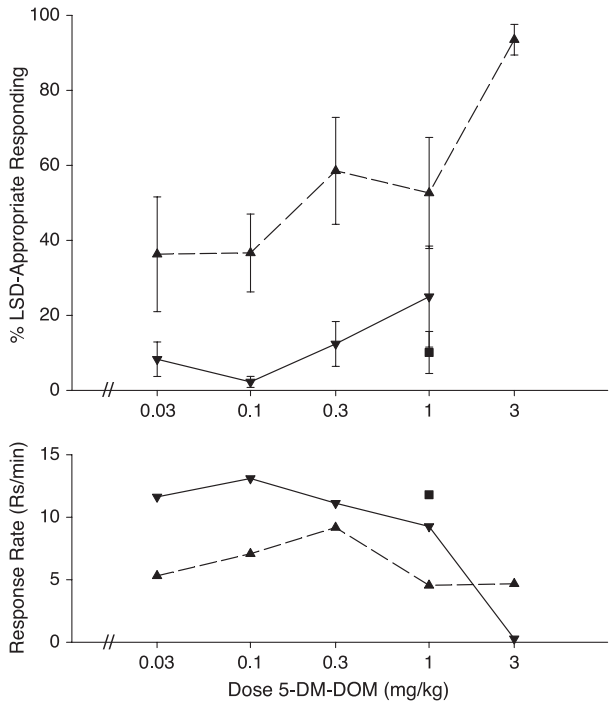

Fig. 4. The substitution of 5-DM-DOM for the stimulus effects of LSD using a pretreatment time of either 15 min (triangle down; solid line) or 75 min (triangle up; dashed line). Antagonism by M100907 (0.05 mg/kg, 30 min) of 5-DM-DOM (1.0 mg/kg, 75 min) is indicated by the square. Each point represents the mean of one determination in 7–10 rats. Ordinate top panel: %(−)-DOM-appropriate responding. Ordinate bottom panel: Rate of responding (responses/min). Abscissa: Dose of 5-DM-DOM administered (mg/kg). Data are presented as means ± S.E.M.

The affinities of these metabolites at the human 5-HT_{2A} and 5-HT_{2C} receptors were also determined. In COS-7 cells expressing the 5-HT_{2A} receptor, a KI of 589 ± 70 and 210 ± 15 nM was observed for 2-DM-DOM and 5-DM-DOM, respectively. For comparison, the KI for DOM at the 5-HT_{2A} receptor in this system was 120 ± 20 nM. In NIH3T3 cells expressing the 5-HT_{2C} receptor, the KI for 2-DM-DOM was 770 ± 50 nM, while the KI for 5-DM-DOM was 500 ± 100 nM.

4. Discussion

To the extent that the stimulus effects of hallucinogens in the rat reflect hallucinogenic activity in man (Winter, 1974; Glennon et al., 1982), animals trained with a known hallucinogen may be used to predict the activity in humans of novel agents. However, if active metabolites of (−)-DOM are formed and contribute to a compound discriminative stimulus in the rat, substitution of a given metabolite for (−)-DOM in rats trained with (−)-DOM may not be reflective of hallucinogenic potential. For this reason, the metabolites of (−)-DOM were evaluated in rats trained with LSD.

The data of Fig. 1 confirm previous observations made by Fiorella et al. (1995) that the (−)-DOM stimulus produces the greatest degree of LSD-appropriate responding at pretreatment times of greater than 60 min. These data are compatible with the formation of an active metabolite, and the data of Fig. 2 support this possibility. Using M100907, at a dose that fully antagonizes the stimulus effects of the training dose of LSD, the stimulus effects of (−)-DOM were reduced to 50% at the 75-min pretreatment time, while full antagonism was observed at the 15-min pretreatment time. It is important to note that maximal brain levels of (−)-DOM occur between 15 and 30 min in the rat (Eckler et al., 2001). If the stimulus effects of (−)-DOM are 5-HT_{2A} receptor mediated, the administration of M100907, one of the most selective 5-HT_{2A} receptor antagonists available (Sorensen et al., 1993; Kehne et al., 1996; Schmidt et al., 1997), should completely block the stimulus effects of (−)-DOM. This did not occur (Fig. 2) and again is suggestive of active metabolites of DOM. However, pirenpirone (60-min pretreatment time), a less selective serotonergic antagonist, fully blocked the stimulus effects of (−)-DOM (data not shown), indicating that active metabolites would act within the 5-HT_2 serotonergic receptor system.

Biochemical data suggest that indoleamine and phenylethylamine hallucinogens differ in binding selectivity. LSD has been reported to bind with high affinity to serotonergic 5-HT_{1A} (Pauwels et al., 1993a; Rabin and Winter, 1993), 5-HT_{1B} (Titeler et al., 1988), 5-HT_{1D} (Titeler et al., 1988; Pauwels et al., 1993b), 5-HT_{2A} (Glennon, 1996), 5-HT_{2C} (Titeler et al., 1988; Sanders-Bush et al., 1988), 5-HT_5 (Waeber et al., 1998), 5-HT_6 (Sleight et al., 1998; Bourson et al., 1998; Hirst et al., 2000; Stean et al., 2002), 5-HT_7 (Hemedah et al., 1999), dopaminergic (D_2) (Burt et al., 1976) and adrenergic (α_1 and α_2) receptors (Arvanov et al., 1999; Rabin and Winter, 1993). In contrast, DOM binds with some selectivity for 5-HT_{2A} and 5-HT_{2C} receptors, possessing $\sim$2 orders of magnitude lower affinity for other serotonergic and nonserotonergic receptors (Leyson et al., 1989; Rabin et al., 2000). Given the greater receptor selectivity of DOM as compared with LSD, the former drug appears to present advantages when used as a discriminative stimulus in that receptor-based interpretation of results are simplified (for review, see Glennon, 1990). However, this assumption is challenged by the observation that brain levels of (−)-DOM in the rat are not well correlated with stimulus control. Thus, maximal brain levels of (−)-DOM are present 15–30 min after administration (Eckler et al., 2001), but efficacy of the (−)-DOM stimulus, when tested in LSD-trained subjects, occurs at pretreatment times greater than 60 min (Fiorella et al., 1995); a replication of this behavioral finding is seen in the present Fig. 1.

In order to test the hypothesis that the time delay associated with maximal (−)-DOM stimulus effects is the result of the time required for the formation of active metabolite(s), we determined the dose–effect relationship for racemic 2-DM-DOM and 5-DM-DOM at both 15- and 75-min pretreatment times in LSD-trained subjects. Both metabolites were found to be more active at the later pretreatment time. One possible explanation is that when the 2-DM-DOM and 5-DM-DOM are administered intraperitoneally, a delay associated with crossing the blood–brain barrier is present, i.e., the increased polar nature of the hydroxy groups should decrease the lipophilicity of the metabolites. Nonetheless, the data of Figs. 3 and 4 indicate that racemic 2-DM-DOM and 5-DM-DOM are active in LSD-trained subjects. LSD-trained subjects produced greater than 90% LSD-appropriate responding at a dose of 6.0 mg/kg 2-DM-DOM (75 min). The same group of LSD-trained subjects indicated that a dose of 3.0 mg/kg 5-DM-DOM (75 min) resulted in 98% LSD-appropriate responding. This would indicate that while both generalize fully 5-DM-DOM is slightly more potent than 2-DM-DOM and is consistent with the binding data. The stimulus effects of both metabolites were inhibited by M100907, consistent with 5-HT_{2A} receptor mediation.

The data of Fig. 2 indicate a time-related decrease in the efficacy of M100907 in blocking the stimulus effects of (−)-DOM. Although full antagonism was seen using a pretreatment time for (−)-DOM of 15 min, this decreased to an intermediate degree of antagonism when a 75-min pretreatment time was used. This observation is not explicable on the basis of differing levels of M100907 at the time of testing because the antagonist was administered in all cases 30 min prior to testing with (−)-DOM. The plausible hypothesis that intermediate antagonism of (−)-DOM-induced stimulus control after 75 min is due to the formation of 2-DM-DOM and 5-DM-DOM is not supported by the data of Figs. 3 and 4 in which it is seen that the effects of both following a 75-min pretreatment time are fully blocked by M100907. However, it must be noted that, for reasons stated above, these tests were conducted in rats trained with LSD. Though no definitive explanation for these results can be given at this time, they may simply reflect distinctive stimulus properties for (−)-DOM (Fig. 2) and LSD (Figs. 3 and 4) when used as reference.

In conclusion, we should be reminded that in vitro binding data often fails to take into account the formation of active metabolites that may have very different binding characteristics than the parent compound. The present study has addressed this issue. Nonetheless, both metabolites of DOM are active in LSD-trained subjects, and their stimulus effects are inhibited by the selective 5-HT_{2A} receptor antagonist M100907. Future evaluations of the underlying mechanism of hallucinogenesis may be aided by the behavioral characterization of individual isomers of both 2-DM-DOM and 5-DM-DOM. Additionally, behavioral data must always be evaluated in context of the training agent. Using active DOM metabolites as training agents for drug-induced stimulus control may yield a more thorough understanding of interactions at specific receptor sites. The hypothesis that metabolites of DOM are pharmacologically active in terms of mimicking the stimulus effects of LSD was answered in the affirmative. However, the present data do not permit unequivocal acceptance or rejection of the hypothesis that active metabolites of (−)-DOM provide a full explanation of the observed discrepancy between brain levels of (−)-DOM and maximal stimulus effects. The two hydroxy metabolites of DOM certainly possess DOM-like stimulus character, and the most parsimonious explanation is that the metabolites contribute to the actions of DOM and contribute particularly to the long-lasting nature of DOM-like effects.

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