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Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 1998, Vol. 22, pp. 649–663

0278-5846/98 $19.00 + .00

PII S0278-5846(98)00031-1

A COMPARISON OF N,N-DIMETHYLTRYPTAMINE, HARMALINE, AND SELECTED CONGENERS IN RATS TRAINED WITH LSD AS A DISCRIMINATIVE STIMULUS

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(Final form, February 1998)

Abstract

Helsley, Scott, David Fiorella, Richard A. Rabin, and J.C. Winter: A Comparison of N,N-dimethyltryptamine, Harmaline, and Selected Congeners in Rats Trained with LSD as a Discriminative Stimulus. Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 1998.22 pp. 649–663. © 1998 Elsevier Science Inc.

1. A series of N-substituted tryptamines was compared with a series of beta-carbolines in rats trained to discriminate LSD (0.1 mg/kg) from saline.
2. Intermediate levels of substitution were elicited by MDMT (76.4%), DMT (77.9%), and DET (48.7%). 6-F-DET produced 41.3% LSD-appropriate responding at a dose of 6.0 mg/kg but only 4 of 8 subjects completed the test session thus precluding statistical analysis. Bufotenine (25.8%) also failed to substitute. Although none of the tryptamines substituted completely for LSD, the pattern of substitution is consonant with what is known of their activity in humans. MDMT, DMT, and DET are well established in the literature as hallucinogens but the same cannot be said for 6-F-DET and bufotenine.
3. Of the beta-carbolines tested, none substituted for LSD completely and only harmane elicited intermediate substitution (49.5%). No significant generalization of the LSD stimulus to 6-methoxyharmalan, harmaline, or THBC was observed. Thus, in contrast to the tryptamines, scant ability to substitute for LSD was observed in the beta-carbolines tested.
4. Taken together, the present data indicate that the representative tryptamines employed in the present study exhibit greater similarity to the LSD stimulus than do representative beta-carbolines. The receptor interactions responsible for these differences remain to be determined.

Keywords: beta-carbolines, drug-induced stimulus control, hallucinogens, tryptamines

Abbreviations: N,N-diethyltryptamine (DET), 6-fluoro-N,N-diethyltryptamine (6-F-DET), N,N-dimethyltryptamine (DMT), (-)-2,5-dimethoxy-4-methylamphetamine (DOM), 5-hydroxytryptamine (5-HT), D-lysergic acid diethylamide (LSD), 5-methoxy-N,N-dimethyltryptamine (MDMT), tetrahydro-beta-carboline (THBC)

Introduction

The discovery and use of naturally occurring hallucinogenic compounds by mankind predates written history (Schultes and Hoffman, 1980). Certain of these substances, whose chemical identity is now known, remain in use today, and are variously labeled as recreational drugs or as drugs of abuse. Examples include N,N-dimethyltryptamine (DMT), mescaline, and psilocybin. To these must now be added synthetic or semi-synthetic hallucinogens such as LSD, 2,5-dimethoxy-4-methylamphetamine (DOM), and a variety of so-called designer drugs. Despite the illicit nature of the hallucinogens, recent data indicate increased use of LSD especially among high school and college students (Johnston et al., 1993; Schwartz, 1995).

Following the initial report of stimulus control induced by LSD and by mescaline in rats (Hirschhorn and Winter, 1971), the phenomenon of drug-induced stimulus control has often been used to characterize the effects of hallucinogens (Glennon, 1994; Winter, 1994). The venerable hypothesis that serotonergic receptors are crucial to the action of hallucinogenic drugs in general (Gaddum, 1957) led to the demonstration in our laboratory (Winter, 1975), and independently by Browne and Ho (1975), that the stimulus effects of mescaline, a phenethylamine hallucinogen, are blocked by serotonergic antagonists. This observation was then extended to include other antagonists of serotonin and other hallucinogens including LSD, DOM, and DMT (Kuhn et al., 1977; Winter, 1978a; Glennon et al., 1983a). With the identification of subtypes of the serotonergic receptor, Glennon and his colleagues observed blockade of the stimulus effects of DOM, LSD, and mescaline by serotonergic antagonists which are relatively specific for the 5-HT_2 subtype and they hypothesized that classical hallucinogens act as 5-HT_2 agonists (Glennon et al., 1983b, 1985; Lyon et al., 1988). The discovery of the 5-HT_{2C} receptor subtype (Pazos et al., 1984) and the realization that there is often a close correlation between affinities for undifferentiated 5-HT_{2A} and 5-HT_{2C} sites (Sanders-Bush and Breeding, 1988; Teitler et al., 1988; Glennon, 1990) led to speculation that the 5-HT_{2C} receptor may play an independent or complementary role in hallucinogenic activity (Teitler et al., 1988; Sanders-Bush and Breeding, 1991). However, Schreiber et al. (1994), demonstrated that the stimulus effects of the hallucinogen DOI are mediated primarily via 5-HT_{2A} receptors. Recent studies in our laboratory using antagonist correlation analysis have extended these findings by providing evidence that the

5-HT_{2A} receptor is the primary mediator of DOM- and LSD-induced stimulus control and that the 5-HT_{2C} receptor plays at most a modulatory role (Fiorella et al., 1995a, 1995b, 1995c).

Although LSD is often regarded as the prototypic indoleamine hallucinogen, it is a complex molecule with high affinity for many receptor subtypes (Burt et al., 1976; Creese et al., 1976; U'Pritchard et al., 1977; Meibach et al., 1980; Leysen, 1985; Hoyer, 1988). This promiscuity makes more difficult the elucidation of those receptor interactions crucial to its stimulus effects in animals, and by extension, crucial to its hallucinogenic activity in humans. Thus, the study of simpler molecules bearing some structural similarity to LSD and for which there is reasonably good evidence of hallucinogenic activity may contribute to our understanding of hallucinogenesis in more general terms. Certain substituted tryptamines and beta-carbolines fulfill both of these criteria and, in the present investigation, selected tryptamines and beta-carbolines were examined in rats trained with LSD as a discriminative stimulus. The behavioral data thus obtained might then begin to answer the question as to whether a common mechanism of action joins these diverse chemicals.

Methods

Animals

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

Apparatus

Six small 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. 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.

Experimental Procedure

12 subjects were trained to discriminate LSD (0.1 mg/kg, 15 minute pre-treatment time, intraperitoneal injection) from saline as described previously (Fiorella et al., 1995a). 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-induced stimulus control was established after 25-35 training sessions. The LSD training dose (0.1 mg/kg, 15 min. pre-treatment time) produced 99.3% drug-appropriate responding whereas saline treatment elicited less than 5% LSD-appropriate responding. After stimulus control was established with LSD, 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.

Tests were conducted in such a fashion that approximately half of the test sessions fell on days following saline training sessions and the remainder occurred the day after LSD training sessions. Dose-response relationships were determined for the substitution of beta-carboline and tryptaminergic agents for the LSD-trained stimulus. 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 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 prior to lever selection, that is, prior to the emission of 10 responses on either lever, by the elapsed time. The data for subjects failing to emit 10 responses within the constraints of the ten minute test session were not considered in the calculation of percent drug-appropriate responding but were included in the calculation of response rates.

Drug Administration

Pre-treatment times were 15 minutes for LSD (Fiorella et al., 1995a), THBC (Nielsen et al., 1982), MDMT, DMT, DET (Glennon et al., 1983b), and 6-F-DET; 25 min for harmaline; and 30 min for harmane, 6-methoxyharmalan, and bufotenine. (+)-LSD-(+)-tartrate, DET HCl,

bufotenine monoxalate, and DMT HCl were provided by the National Institute on Drug Abuse. 6-F-DET HCl was provided by the Upjohn Company (Kalamazoo, MI). MDMT oxalate was purchased from Research Biochemicals Inc. (Natick, MA). Harmaline HCl, 6-methoxyharmalan, harmane, and THBC were purchased from Sigma Chemical Company (St. Louis, MO). All drugs were dissolved in 0.9% NaCl and solutions were injected i.p. in a volume of 1.0 ml/kg bodyweight.

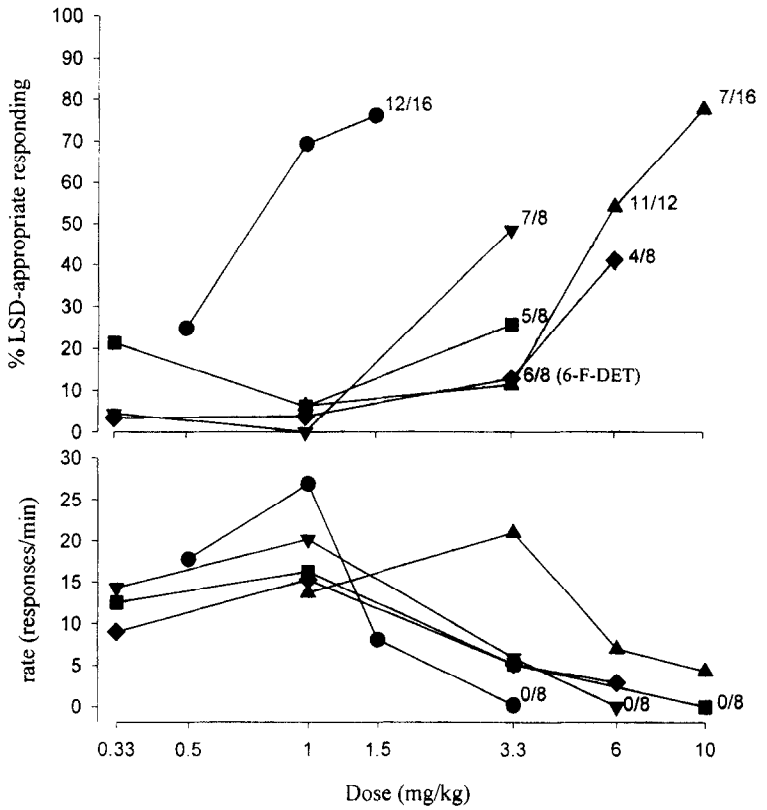
Data Analysis

Complete generalization of a training drug to a test drug is said to be present when [i] a mean of 83% or more of all test responses are on the drug-appropriate lever (this value reflects two or fewer responses on the incorrect lever prior to the completion of ten responses on the correct lever), [ii] there is no statistically significant difference between training-drug and test-drug response distributions, and [iii] there is a statistically significant difference between test-drug and saline-control response distributions (Winter and Rabin, 1992). An intermediate degree of generalization is here defined as being present when mean response distributions following a test-drug show a statistically significant difference from distributions following both training conditions. Finally, when response distributions following a test-drug are not significantly different from saline-control response distributions, an absence of generalization is assumed. Comparisons of data are by means of individual applications of Wilcoxon's signed ranks test. Thus, data obtained with a given drug at a given dose are compared with the immediately preceding training sessions for saline and training drug, respectively. Differences are considered to be significant if they would be expected to arise by random sampling alone with a probability < 0.05.

Results

None of the agents tested produced full substitution for the LSD-trained stimulus. However, among the tryptamines, an intermediate level of generalization was observed with MDMT (76.4%), DMT (77.9%), and DET (48.7%) but not to bufotenine (25.8%) or 6-F-DET (41.3%) (Fig 1). In contrast, of the beta-carbolines, only harmane (49.5%) produced intermediate substitution for the LSD-trained stimulus while harmaline (20.6%), 6-methoxyharmalan (14.5%),

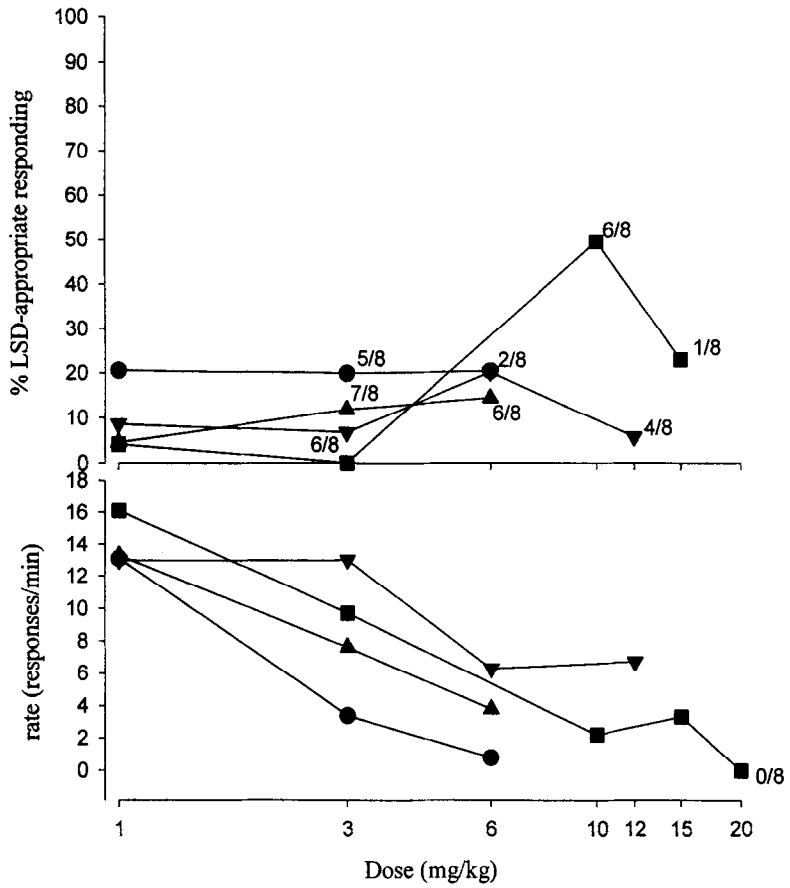
and THBC (20.3%) failed to substitute (Fig 2). All of the drugs tested produced a dose-related suppression of response rate.



Dose-response relationships for tryptamines.

Fig 1. The dose response relationships for MDMT (●), DMT (▲), DET (▼), bufotenine (■), and 6-F-DET (◆) in rats trained to discriminate LSD (0.1 mg/kg, i.p., 15 min pre-session) from saline. The number of subjects completing the test session and the number of subjects participating in each test session is expressed as a ratio adjacent to each of the points. Where no ratio is indicated, 8 of 8 subjects completed the test. Ordinate: Upper panel: mean percentage of

responses on the LSD-appropriate lever. Lower panel: response rate expressed as responses per minute. Abscissa: dose of test agent (mg/kg).



Dose-response relationships for beta-carbolines.

Fig 2. The dose response relationship for harmaline (●), 6-methoxyharmalan (▲), THBC (▼), and harmane (■) in rats trained to discriminate LSD (0.1 mg/kg, i.p., 15 min pre-session) from saline. Other details are as described for Fig. 1.

Discussion

During the course of this investigation, data was generated comparing representative tryptamines and beta-carbolines on the basis of the level of LSD-appropriate responding elicited during drug-discrimination studies.

Tryptamines in LSD Trained Rats

Of the drugs tested in the present investigation, DMT and MDMT substituted to the greatest extent for LSD. However neither drug fully met our criteria for complete generalization. With respect to MDMT, the present data are in agreement with previous experiments in our laboratory (Winter and Rabin, 1988) which found a maximum of 76% LSD-appropriate responding at a dose of 3 mg/kg. Studies by others have also yielded less than complete generalization of LSD to MDMT (Rosecrans and Glennon, 1979). In contrast, White and Appel (1982) observed complete generalization of LSD to MDMT but this was seen at a dose of 4 mg/kg which is higher than the doses tested in the present study. Differences between the present study and that of White and Appel include the use of a different rat strain (Sprague-Dawley vs. Fischer-344) and different training doses. In addition these authors demonstrated that the LSD discriminative stimulus varies depending on the training dose (White and Appel, 1982). Thus the results of the present study may not extrapolate to studies where LSD training doses higher or lower than 0.1mg/kg are used.

While the data for both MDMT and DMT suggest that these agents are similar to LSD in regard to their stimulus properties, our results with DET and 6-F-DET are more difficult to interpret. Indeed, while DET produced an intermediate level of substitution for LSD in the present study (48.7%), it was not nearly as effective as either DMT (77.9) or MDMT (76.4%). In humans, DET is hallucinogenic whereas 6-F-DET is not (Faillace et al., 1967). Despite the fact that 6-F-DET elicited 41.6% LSD-appropriate responding, this does not fulfill our criteria for intermediate responding as the number of subjects completing this task was less than that required for statistical analysis.

Bufotenine also failed to substitute for LSD; this may be attributable to the fact that bufotenine is metabolized extensively in the periphery and does not cross the blood-brain barrier to any significant extent (Fuller et al., 1995). Evidence for the hallucinogenicity of bufotenine in man is equivocal (Turner and Merlis, 1959; Weil and Davis, 1994). Interestingly, although clinical data exist in support of the hallucinogenic effects of both DET (Faillace et al., 1967; Boszormenyi et al., 1959) and DMT (Turner and Merlis, 1959; Strassman et al., 1994; Strassman and Qualls, 1994), the only reports of MDMT hallucinogenesis of which we are aware are of an anecdotal nature. Indeed, MDMT is not a controlled substance in the U.S.A. at present despite the fact that it is used for recreational purposes (Weil and Davis, 1994).

It has been well documented that classical hallucinogens such as LSD and DOM elicit their stimulus effects through interactions with 5-HT_2 receptors (Winter, 1978b; Appel et al., 1982; Glennon et al., 1984). Subsequent investigations suggest that the 5-HT_{2A} subtype plays a major role (Fiorella et al., 1995a,1995b,1995c). Thus it is not surprising that hallucinogenic tryptamines such as DMT and MDMT possess appreciable affinity for the 5-HT_{2A} receptor (Spencer et al., 1987; Lyon et al., 1988; Sadzot et al., 1989; Deliganis et al., 1991). Indeed, a plausible explanation of the present data for DMT and MDMT is that these drugs interact in a functionally significant manner with 5-HT_{2A} receptors in the production of their stimulus effects. However, the fact that antagonists at 5-HT_{2A} receptors produce only a partial blockade of the MDMT discriminative cue in both LSD (Winter and Rabin, 1988) and MDMT-trained rats (Young et al., 1983, 1986; Spencer et al., 1987) suggests that other receptors are also involved. The most likely candidate is the 5-HT_{1A} receptor in that the hallucinogenic tryptamines display much higher affinity for 5-HT_{1A} receptors than for 5-HT_{2A} receptors (Peroutka, 1985; Spencer et al., 1987; Deliganis et al., 1991) and the MDMT cue is blocked by metitepin and pindolol, agents with significant antagonist properties at the 5-HT_{1A} receptor. In light of these observations it appears that these tryptamine derivatives produce complex discriminative cues involving at least 5-HT_{1A} and 5-HT_{2A} receptors.

Beta-Carbolines in LSD-Trained Rats

Of the beta-carbolines tested in the present investigation, none substituted completely for LSD and, indeed, only harmane yielded intermediate results. The present results stand in contrast with

those of Nielsen et al. (1982) who observed in LSD-trained rats what would be, by the criteria employed in the present study, an intermediate degree of generalization to harmaline (54% LSD-appropriate responding) and to THBC (69% LSD-appropriate responding). Correspondingly Schechter (1986) observed intermediate substitution by LSD in THBC-trained subjects. Furthermore, harmane, the beta-carboline which the authors found to be most active (49.5%) was observed to be inactive by Nielsen et al. (1982). Several explanations may be offered for these discrepant results. Of perhaps the greatest significance, different rat strains were used (Fischer-344 vs. Sprague-Dawley) and different testing doses were used (i.e., the highest dose of harmaline that could be tested in the present study was 6.0 mg/kg whereas Nielsen et al used 8.0 mg/kg). Although different rat strains are seldom directly compared in drug discrimination studies, strain differences in receptor properties have been documented. For example, in a comparison of Fawn-hooded rats with Wistar and Sprague-Dawley strains, Hulihan-Giblin et al. (1993) observed significant differences in 5-HT_{2C} receptors with respect to ligand affinity and receptor density.

Unlike the tryptamines, for which there is abundant evidence of functionally significant interactions with serotonergic receptors, the beta-carboline hallucinogens are enigmatic agents. The fact that they resemble 5-HT in structure taken together with the hallucinogenic effects of some derivatives such as harmaline and 6-methoxyharmalan (Naranjo, 1967) strongly suggests that these agents, like LSD, exert their psychotropic effects through serotonergic mechanisms. However, the affinities of these agents for 5-HT receptors are quite low compared to those of traditional hallucinogens such as LSD or DOM (Deecher et al., 1992). In spite of this, a recent study in our laboratory demonstrated that harmaline occupies 5-HT_{2A} receptors (Helsley et al., 1997). Thus, it is possible that beta-carboline agents such as harmaline produce their psychotropic effects through interactions with 5-HT_2 receptors but higher drug concentrations are required. Indeed 100-300 mg of harmaline is required to produce hallucinations in man (Naranjo, 1967) whereas as little as 0.1 mg of LSD (Sankar, 1975) or 3.0 mg of DOM (Shulgin and Shulgin, 1991) is effective. However, based upon our hypothesis that LSD-induced stimulus control is primarily mediated by 5-HT_{2A} receptors (Fiorella et al., 1995a, 1995b, 1995c), the present results suggest that beta-carbolines do not produce their stimulus effects through interactions with 5-HT_{2A} receptors at the doses tested.

It could be argued that because LSD binds to a variety of receptors, the lack of generalization to beta-carbolines in the present study may be due to differences in binding to receptors other than 5-HT_{2A}. However, the fact that symmetrical generalization occurs between LSD and DOM, which differ from one another in their receptor binding profiles argues against this (Glennon et al., 1983b; Winter and Rabin, 1988; Fiorella et al., 1995a, 1995d).

Conclusion

In conclusion, it appears that while the hallucinogenic tryptamines appear to mediate their stimulus effects in part through interactions with 5-HT_{2A} receptors, these receptors do not play a major role in the stimulus effects of the hallucinogenic beta-carbolines. Because relatively little is known about the mechanisms of action of these beta-carbolines, further studies with these agents may greatly enhance our understanding of the mechanisms of hallucinogenesis.

Acknowledgments

This study was supported in part by U.S. Public Health service grant DA 03385 [JCW, RAR], by National Research Service Awards MH 10567 [DF] and DA 05735 [SH], by a fellowship from Schering-Plough Research Institute [DF], and by a grant from Schering-Plough Research Institute [SH]. We thank Ms. Deborah Petti for technical assistance.

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