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Effects of the Phenethylamine Derivatives, BL-3912, Fenfluramine, and Sch-12679, in Rats Trained with LSD as a Discriminative Stimulus

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Abstract. Six rats were trained to discriminate the effects of LSD (100 μg/kg) and saline in a two-lever choice task. They were then tested with each of three phenethylamine derivatives, BL-3912 (2,5-dimethoxy-4-methyl-α-ethyl-phenethylamine), fenfluramine (N-ethyl-α-methyl-m-(trifluoro-methyl)phenethylamine), and Sch-12679 (N-methyl-1-phenyl-7,8-dimethoxy-2,3,4,5-tetra-hydro-3-benzazepine maleate). Fenfluramine and Sch-12679 yielded intermediate results, i.e., responding was not fully appropriate for either training condition while BL-3912 substituted completely for LSD. The LSD-like effects of each of the drugs were antagonized by pretreatment with BC-105, a serotonergic antagonist known to block the stimulus effects of indole and phenethylamine hallucinogens. The present data together with consideration of the known clinical effects of BL-3912, fenfluramine, and Sch-12679 are consistent with the following conclusions: (1) a variety of drugs may substitute in whole or in part for LSD in LSD-trained rats, and (2) even complete substitution of a drug for LSD in the rat is not necessarily associated with the production by that drug of hallucinations in man.

Key words: Drug discrimination – Hallucinogens – LSD – Fenfluramine – Sch-12679 – BL-3912

In 1971 Hirschhorn and Winter reported that mescaline (3,4,5-tri-methoxyphenylethylamine) and lysergic acid diethylamine (LSD) could function as discriminative stimuli in the rat. Furthermore, the fact that mescaline mimicked LSD in rats trained with the latter drug, and vice versa, suggested that the stimulus properties of these representatives of the phenethylamine and indoleamine classes of hallucinogens were quite similar in that species. Subsequent experiments in my laboratory and elsewhere have revealed a remarkable correlation between the stimulus properties of indoleamines and phenethylamines in rats and hallucinogenic activity in human subjects. For example, rats trained with LSD respond in a fashion appropriate for LSD when tested with mescaline (Hirschhorn and Winter, 1971) and psilocybine (Schechter and Rosecrans, 1972) but respond as if treated with saline when tested with nonhallucinogens (*d*-amphetamine – Schechter and Rosecrans, 1972; barbital – Hirschhorn and Winter, 1975; morphine – Hirschhorn and Rosecrans, 1974).

Nonetheless, a limited body of evidence indicates that the correlation between the ability of a drug to mimic the stimulus properties of a known hallucinogen in the rat and its hallucinogenic activity in man is less than perfect. For example, 2,3,4-TMPEA, a purportedly nonhallucinogenic geometric isomer of mescaline, is indistinguishable from mescaline in rats (Winter, 1973); DOET, the 4-ethyl analogue of the known hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM), mimics mescaline (Winter, 1975b) and DOM (Silverman and Ho, 1978) in rats, yet its hallucinogenic activity in man has never been documented (Snyder et al., 1971); quipazine substitutes for LSD (Kuhn et al., 1978; Winter, 1979) and vice versa in rats, (White et al., 1977,1979), yet is nonhallucinogenic in human subjects (J. Villarreal, personal communication). It is of interest to note that the stimulus effects of 2,3,4-TMPEA, DOET, and quipazine are blocked, like those of LSD, mescaline, and DOM, by serotonergic antagonists (Browne and Ho, 1975; Kuhn et al., 1978; White et al., 1977; Winter, 1975a and 1978b).

In the present experiments, rats trained with LSD were tested with three phenethylamine derivatives (Fig. 1) whose clinical pharmacology, particularly with respect to the induction of hallucinations, is reasonably

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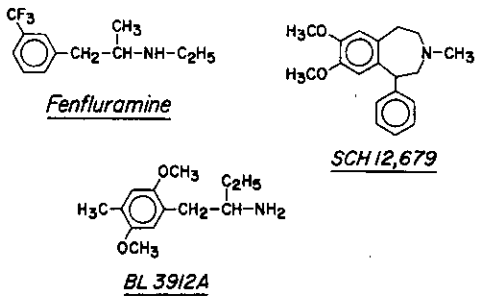

Fig. 1. BL-3912, fenfluramine, and Sch-12679

well established. Each drug was also tested in LSD-trained rats in the presence of BC-105, a serotonergic antagonist. BL-3912 may be regarded as an analogue of the phenethylamine hallucinogen, DOM (2,5-dimethoxy-4-methylamphetamine) in which the α-methyl group is replaced by α-ethyl. Fenfluramine is marketed in the United States as an anorexigenic agent and, although its structure is closely related to amphetamine, its effects seem predominantly on serotonergic systems. The third drug tested in these experiments is Sch-12679 (N-methyl-1-phenyl-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine maleate), which may be viewed as an analogue of 3,4-dimethoxy-N-methylamphetamine in which the side chain is constrained by a two-carbon bridge to the 6-position of the phenyl ring. There are interesting similarities in the animal pharmacology of fenfluramine and Sch-12679 in that both suppress aggressive behavior (Yelnosky and Lawlor, 1970; Barnett et al., 1974) and methamphetamine-induced toxicity in mice (Jesperson and Bonaccorsi, 1969; Barnett et al., 1974).

Materials and Methods

All subjects were CFN strain rats (Carworth Farms, Wilmington, Massachusetts, USA). They were housed in pairs and had free access to dry food in the home cage. With the exception of weekends, water intake was limited to that obtained during experimental sessions. The rats were trained and tested in standard two-lever operant test chambers equipped with a dipper for delivery of the water reinforcer. Solid state programming equipment and electromechanical counters were used to control and record the sessions.

Six rats were trained with LSD (100 μg/kg) and saline in a two-lever response choice task (Hirschhorn and Winter, 1971; Winter, 1978a) using a fixed-ratio 10 schedule of reinforcement. After the rats learned to drink from the dipper, they were trained to depress first one and then the other of the two levers. After responding was established on both levers, discrimination training was begun. Each ten-minute session was preceded by one of two treatments; following LSD, every tenth response on the LSD-appropriate lever was reinforced and in a similar fashion, responses on the saline-appropriate lever were reinforced following the injection of saline. For three subjects, the left lever was designated as LSD-appropriate and for the remaining subjects, responses on the right lever were reinforced following LSD. During discrimination training, LSD was administered on Monday, Wednesday, and Friday; saline was injected on Tuesday and Thursday. The distribution of the first ten responses between the two levers was recorded each day. LSD-induced stimulus control was presumed to be present when, in five consecutive sessions, eight or more of the initial ten responses were upon the appropriate lever.

To determine the degree of similarity of BL-3912, fenfluramine, and Sch-12679 to LSD, cross tests were conducted in which one of these drugs was administered to LSD-trained subjects. Cross tests as well as tests of antagonism were conducted each Friday as long as previous performance in the same week did not fall below a criterion of 80% correct responding. During cross tests, no responses were reinforced and the cross-test session was terminated after the emission of ten responses. Response distribution during cross tests was compared with the distributions in the immediately preceding LSD and saline sessions (henceforth referred to as control sessions). Sessions in which the ability of BC-105 to antagonize the stimulus properties of BL-3912, fenfluramine, and Sch-12679 are similar to cross tests in that the session is terminated after ten responses and the results are compared with the preceding LSD and saline control sessions. A dose of BC-105 of 3 mg/kg given 60 min before testing has previously been shown to antagonize the stimulus properties of mescaline, LSD, DOET, and quipazine (Winter, 1978b and 1979).

All cross test data were subjected to analysis of variance in a single-factor design with repeated measures (Winer, 1971). Simultaneous comparisons of data from cross tests with LSD and saline control values were made by means of the studentized range test (Winer, 1971). Tests of antagonism were analyzed by means of Wilcoxon's signed ranks tests for paired observations (Goldstein, 1964). Differences were considered to be significant if they would be expected to arise by random sampling alone with $P < 0.05$.

D-LSD tartrate (NIDA, Washington, D.C., USA), BL-3912 (Bristol Laboratories, Syracuse, New York, USA), fenfluramine HCl (A. H. Robins Co., Richmond, Virginia, USA), Sch-12679 (Schering Corporation, Bloomfield, New Jersey, USA), and BC-105 (Sandoz Pharmaceuticals, East Hanover, New Jersey, USA) were dissolved in 0.9% NaCl and injected in a constant volume of 1 ml/kg/body wt.

Results

Figure 2 shows the effects of a range of doses of BL-3912 in rats trained with LSD. At a dose of 10 mg/kg, substitution is complete ($97 \pm 2\%$ LSD-appropriate; LSD control = 97 ± 2). In contrast, when the same group was pretreated with BC-105 and tested with BL-3912, responding was indistinguishable from the saline training condition ($7 \pm 7\%$ LSD-appropriate vs $2 \pm 2\%$ for the saline control).

When compared with BL-3912, neither fenfluramine (Fig. 2) nor Sch-12679 (Fig. 2) substituted as completely for LSD. Nonetheless, each yielded intermediate results, i.e., responding that was not fully appropriate for either training condition (Winter, 1978a). For fenfluramine, 3 mg/kg was followed by $73 \pm 8\%$ LSD-appropriate responses and an upward trend is evident. However, at a dose of 6 mg/kg, only two of six animals responded during the 15-min session. Pretreatment with BC-105 reduced the LSD-appropriate responses to $16 \pm 7\%$ with all animals responding. The data for Sch-12679 are likewise flawed by the fact that not all subjects responded at each dose (4 of 6 at 20 mg/kg; 3 of 6 at 30 mg/kg). At 20 mg/kg, LSD-appropriate responding was reduced by pretreat-

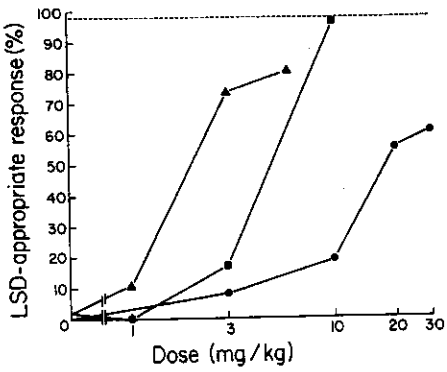

Fig. 2. The effects of fenfluramine (▲), BL-3912 (■), and Sch-12679 (●) in rats trained with LSD as a discriminative stimulus. All drugs were injected 15 min before testing. The dotted line indicates mean LSD control performance. Each point represents the mean of two determinations in each of six subjects. *Ordinate:* Mean percentage of responses on the LSD-appropriate lever. *Abscissa:* Dose plotted on a log scale

nt with BC-105 from 55 ± 16 to 5 ± 5 with all animals responding.

Discussion

Of the three phenethylamines chosen for comparison with LSD, only BL-3912 was able to substitute completely (Fig. 2). However, both fenfluramine and Sch-12679 gave intermediate results, i.e., responding was not fully appropriate for either training condition (Fig. 2). A parsimonious explanation of these data is that the training drug, LSD, functions as a compound stimulus and that fenfluramine and Sch-12679 produce one or more of the elements of that stimulus but less than the full spectrum of LSD's activity. The behavioral consequence is intermediate responding (Winter, 1978a). The antagonism of each of the three drugs by BC-105 suggests, in agreement with earlier studies (Winter, 1978b and 1979), that the common factor ared with LSD is serotonergic in nature.

The effects of Sch-12679 in normal human subjects has not been reported, but the results of investigations in a variety of patient populations provide no substantial evidence of hallucinogenic activity. In a study of chronic schizophrenics (Keskiner et al., 1971; maximum dose: 405 mg/day) an increase in 'psychotic symptoms, such as hallucinations and delusions' was noted, but in other investigations no such effects were reported in patients diagnosed as suffering anxiety neurosis (LaPierre, 1978; max. dose: 75 mg/day), behaviorally disturbed adolescents (Itil et al., 1972; max. dose: 225 mg/day), aggressive mental retardates (Albert et al., 1977; max. dose: 400 mg/day), or acute schizophrenics (Park et al., 1972; mean max. dose: 2,060 mg/day).

The data of Fig. 2 suggest that fenfluramine shares a significant portion of the stimulus properties of LSD in the rat. This finding is consonant with the observation by Appel and his associates (1978) that fenfluramine yields quipazine-appropriate responding in rats trained with the latter drug and with the failure of Goudie (1977) to detect similarities in the stimulus properties of fenfluramine and *d*-amphetamine. Fenfluramine is not generally regarded as an hallucinogenic agent but doses two to four times that recommended for weight loss may produce a state of intoxication, which includes visual hallucinations (Levin, 1975) and which has been characterized as LSD-like (Griffith et al., 1975). In addition, Mullen and her colleagues (1977) reported increased dreaming and nightmares, and expressed concern that the drug might induce or exacerbate mental disorder.

The most interesting finding of the present investigation is that BL-3912 substitutes completely for LSD and, like LSD, is antagonized by BC-105 (Fig. 2). Earlier studies in rats found differences between BL-3912 and both *d*-amphetamine and DOM (Tilson et al., 1977a; 1977b) but in the chronic spinal dog (Martin et al., 1978), BL-3912 and LSD were indistinguishable in terms of behavioral effects, cross tolerance, and antagonism by cyproheptadine (Jasinski et al., 1978). However, clinical trials of BL-3912 conducted by Bristol Laboratories, Inc. failed to reveal hallucinogenic activity (Clinical Files, Bristol Laboratories, cited by Tilson et al., 1977a; J. A. Gylys, personal communication). In unpublished studies conducted at the NIDA Addiction Research Center, Lexington, Kentucky, USA, doses of BL-3912 up to 270 mg in normal human subjects produced euphoria and other LSD-like effects but neither perceptual changes nor hallucinations were noted (D. B. Vaupel, personal communication).

The data presented in Fig. 2, together with those cited earlier with respect to 2,3,4-TMPEA, DOET, and quipazine, suggest that a variety of drugs may substitute in whole or in part for LSD in LSD-trained rats. Consideration of the clinical data with respect to BL-3912 and the data of Fig. 2 indicate that the ability to mimic LSD in rats is poorly correlated with the ability to produce overt hallucinations of the LSD or phenethylamine type in man. The present data further support a conclusion reached earlier (Winter, 1975b; Kuhn et al., 1977) that mimicry of the stimulus properties of LSD in the rat represents a necessary but not a sufficient condition for prediction of hallucinogenic activity of the indole/phenethylamine type in man.

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