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The Stimulus Properties of Para-Methoxyamphetamine: A Nonessential Serotonergic Component

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WINTER, J. C. *The stimulus properties of para-methoxyamphetamine: A nonessential serotonergic component.* PHARMACOL BIOCHEM BEHAV 20(2) 201–203, 1984.—A group of six rats was trained to discriminate the effects of para-methoxyamphetamine (PMA; 3 mg/kg, 15 min pretreatment time) and saline in a two-lever choice task using a fixed ratio 10 schedule of water reinforcement. Stimulus control was assumed to be present when 80% or more of the first ten responses were appropriate for the treatment condition on each of five consecutive days. PMA established stimulus control in each of the subjects. The mean number of sessions prior to the onset of criterion performance was 19 (SE=2, range=14–24). A second group of ten rats was similarly trained with lysergic acid diethylamide (LSD; 0.1 mg/kg, 15 min pretreatment time) and saline. In rats trained with PMA, LSD yielded intermediate results, i.e., significantly different from both training conditions. Likewise, the response distribution was intermediate in nature when LSD-trained subjects were tested with PMA. Pizotyline did not antagonize PMA-induced stimulus control in rats trained with PMA and saline but did antagonize the intermediate responding produced by PMA in LSD-trained subjects. It is concluded that PMA-induced stimulus control does not depend upon activation of serotonergic receptors but that PMA does possess some LSD-like effects which are mediated serotonergically.

Stimulus control Para-methoxyamphetamine 5-Hydroxytryptamine Pizotyline

THE synthesis of para-methoxyamphetamine (alpha-methyl-4-methoxyphenylethylamine; PMA) was reported by Alles in 1932 [1] and its sympathomimetic properties were subsequently studied [6]. More recent investigations have emphasized the effects of PMA upon the central nervous system both in the rat [3, 5, 13] and in man [12]. The pharmacological classification of PMA is uncertain. It is often cited as being hallucinogenic but the clinical evidence for such activity is unconvincing (see Discussion). PMA produces a prolonged increase in blood pressure both in man (Angrist, personal communication) and in the dog. In the latter species, this effect has been attributed to alpha and beta-adrenergic receptor activation [4]. A significant effect of PMA upon both uptake and release of 5-hydroxytryptamine (5-HT, serotonin) is suggested by the results of serveral studies in the rat [7, 11, 15, 16], and a direct stimulatory action of PMA on serotonergic neurons has also been proposed [2]. Based on an extensive series of experiments in the chronic spinal dog in which the effects of lysergic acid diethylamide (LSD) and d-amphetamine were compared with those of PMA, it was concluded that PMA may possess a "liminal degree of LSD-like activity" but is predominantly amphetamine-like [10].

In the present experiments, PMA is evaluated in terms of its ability to establish stimulus control, a phenomenon in which the dimensions of an antecedent stimulus determine the probability of occurrence of a conditioned response [18] and by comparison of its stimulus properties with those of LSD, a drug believed to induce stimulus control by effects at serotonergic receptor sites [9,19]. In the only previous study of the stimulus properties of PMA, the drug was administered to rats previously trained with d-amphetamine and it was concluded that PMA was similar to amphetamine [18]. Finally, the ability of pizotyline, a serotonergic antagonist, to block PMA-induced stimulus control was determined. Pizotyline was previously shown to antagonize the stimulus properties of LSD and mescaline but not those of d-amphetamine [19].

METHOD

Animals

A total of 16 female Wistar strain rats were used in these experiments. They were housed in pairs in quarters exposed to a natural light cycle. Body weight was maintained at about 80% of normal by restriction of water intake. Rat chow was freely available in the home cage. Prior to these experiments, the rats had received neither drugs nor behavioral training.

Apparatus

Two standard small animal test chambers (Coulbourn Instruments model E10-10) housed in larger light-proof sound-insulated boxes were used for all experiments. The chamber contained two levers mounted at opposite ends of one wall. Centered between the levers was a dipper which delivered 0.1 ml of tap water.

TABLE 1

EFFECTS OF LSD IN RATS TRAINED WITH PMA (3 mg/kg)

Dose of LSD (mg/kg)	N*	% PMA Choice
0.03	6	28
0.1	6	51
0.3	6	45

*Six animals tested at each dose; N designates the number which emitted ten responses during the test session.

TABLE 2

EFFECTS OF PMA IN RATS TRAINED WITH LSD (0.1 mg/kg)

Dose of PMA (mg/kg)	N*	% LSD Choice
0.03	10	11
1	10	48
3	5	75

*Ten animals were tested at each dose; N designates the number which emitted ten responses during the test session.

TABLE 3

EFFECTS OF PMA ALONE AND IN COMBINATION WITH PIZOTYLINE IN RATS TRAINED WITH EITHER PMA OR LSD

Training Drug (mg/kg)	Dose of PMA (mg/kg)	Dose of Pizotyline (mg/kg)	N*	Cross Test †
PMA	3	0	6	98
(3)	3	3	6	96
	3	10	6	90
LSD	1	0	6	52
(0.1)	1	3	6	16

*Six animals were tested at each dose; N designates the number which emitted ten responses during the test session.

†Percentage of responses on the training drug-appropriate lever.

Procedure

Subjects were assigned randomly either to a group (N=6) to be trained with PMA (3 mg/kg; 15 min pretreatment) or to a group (N=10) to be trained with LSD (0.1 mg/kg; 15 min pretreatment). After learning to drink from the dipper, subjects were trained to depress first one and then other of the two levers. The number of responses for each reinforcement was gradually increased from one to ten and all subsequent training and testing employed a fixed ratio 10 (FR10) schedule of reinforcement. Discrimination training was then begun. Each ten-minute session was preceded by the injection of either drug or saline. Following the administration of PMA (Group II) or LSD (Group II), every tenth response on the drug-appropriate lever was reinforced. Similarly, responses on the saline-appropriate lever were reinforced in both groups following the injection of saline. For half of the subjects in each group, the left lever was designated as drug-appropriate and for the remaining subjects responses on the right lever were reinforced following drug. During discrimination training, drug and saline were alternated on a daily basis. Drug-induced stimulus control was assumed to be present when, in five consecutive sessions, eight or more of the initial ten responses were on the appropriate lever.

To determine the degree of similarity of the stimulus properties of PMA to those of LSD and vice versa, cross tests were conducted in which PMA and LSD were administered to subjects trained with LSD and PMA, respectively. Cross tests as well as tests of antagonism (vide infra) were conducted each Friday so long as performance during the remainder of the 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 or after 10 minutes. Distribution of the responses between the two levers during cross tests was compared with the distributions of the immediately preceding training-drug and saline sessions (henceforth referred to as control sessions). The ability of pizotyline to antagonize PMA was tested in subjects trained with either PMA or LSD. Pizotyline was injected 60 min before testing, i.e., 45 min before the administration of PMA. Sessions were terminated after the first 10 responses were emitted. Sessions in which pizotyline is given in combination with PMA are compared with sessions in the absence of the antagonist. All cross test and antagonism data were compared with control data by means of individual applications of Wilcoxon's signed ranks test (one-tailed). Differences were considered to be significant if they would be expected to arise by random sampling alone with a probability less than 0.025.

Drugs

Pizotyline (Sandoz Pharmaceuticals, East Hanover, NJ), D-LSD tartrate (National Institute on Drug Abuse, Rockville, MD), and PMA hydrochloride (Fox Chemical Co., Los Angeles, CA) were dissolved in 0.9% saline solution and injected intraperitonealy in a constant volume of 1 ml/kg body weight.

RESULTS

PMA-induced stimulus control was observed in each of the six subjects trained. The mean number of sessions prior to the onset of criterion performance was 19 (SE=2, range=14–24). Cross tests conducted in PMA-trained rats (Table 1) with LSD yielded intermediate results, i.e., the

distribution of responses on the two levers at doses of 0.1 and 0.3 mg/kg was significantly different from that observed following either the PMA or saline training conditions. The results of cross tests of PMA in rats trained with LSD are presented in Table 2. At a dose of PMA of 1 mg/kg, intermediate results were obtained. At 3 mg/kg, the proportion of responses on the LSD-appropriate lever increased to 75% but it must be noted that of the 10 LSD-trained subjects, only 5 responded.

Following the cross tests of LSD in PMA-trained subjects and vice versa, a separate series of experiments was conducted in which the ability of pizotyline to antagonize the effects of PMA was determined (Table 3). No significant antagonism of PMA in subjects trained with PMA by doses of pizotyline of 3 and 10 mg/kg was observed. In contrast, the intermediate results produced by PMA in subjects trained with LSD were antagonized significantly by a dose of pizotyline of 3 mg/kg.

DISCUSSION

The present data are most readily interpreted by assuming that the effects of a drug constitute a compound stimulus and that, in establishing stimulus control, the relative importance of the component stimuli may vary with the circumstances of training and testing [18]. Thus, the intermediate results obtained with LSD in rats trained with PMA (Table 1) and with PMA in rats trained with LSD (Table 2) indicate a common stimulus component. The fact that the intermediate effects of PMA in LSD-trained subjects is antagonized by pizotyline (Table 3) indicates that the effect shared by LSD and PMA is serotonergic in nature. Nonetheless, the failure of pizotyline to antagonize PMA-induced stimulus control in rats trained with the drug (Table 3) suggests that the serotonergic component of the action of PMA is not essential for the induction of stimulus control and that the serotonergic effect of PMA is manifest only when PMA is cross tested in subjects trained with a drug such as LSD whose major stimulus effects are mediated by 5-HT [19].

It has been suggested that studies of the stimulus properties of known hallucinogens of various classes may provide a means for identifying, prior to their use in man, those drugs which are likely to be hallucinogenic [17]. In studies by Smythies *et al.* [13,14] in which the effects of hallucinogens were characterized in terms of the latencies and appropriateness of avoidance and escape responses, it was found that of the drugs tested, PMA was "the most potent hallucinogen...with the exception of LSD" and that it "produces a typical hallucinogenic profile". These findings are at odds with the present data and with the results of Martin *et al.* [10] in the chronic spinal dog which suggest that LSD-like serotonergic activity is but a minor part of the spectrum of PMA's pharmacological effects. The obvious resolution of this disparity lies in a careful analysis of the available clinical data regarding PMA. The only published report of which I am aware is the frequently cited study by Shulgin *et al.* [12] in which PMA is said to be five times as potent as mescaline. Unfortunately, details of the objective and subjective effects of PMA are not provided. Furthermore, Shulgin has stated (personal communication) that the effects of PMA at a dose of 1 mg/kg in man "are not particularly similar to mescaline." Instead, PMA produced an "extremely simple intoxication with pleasant and desirable aspects without complication." In the absence of clinical evidence to the contrary and in view of the present data and those of Martin *et al.* [10], it seems inappropriate to continue to assume that PMA is a hallucinogen of the indole/phenethylamine type.

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