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EFFECT OF SEROTONIN DEPLETION BY *p*-CHLOROPHENYLALANINE UPON DISCRIMINATIVE BEHAVIOURS

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Abstract—1. *Para*-chlorophenylalanine (*p*-CPA), a competitive inhibitor of the serotonin (5-HT) synthesis enzyme tryptophan hydroxylase, was administered to rats at a dosage (100 mg/kg daily for 3 days) that depletes 5-HT.

2. Different groups of these rats were previously trained to discriminate the interoceptive stimuli produced by amphetamine, cathinone, 3,4-methylenedioxymethamphetamine (MDMA), N-ethyl-3,4-methylenedioxyamphetamine (MDE), fenfluramine or yohimbine, and the effect of *p*-CPA pretreatment upon their discriminative performance was compared with the effect of saline (control) pretreatment.

3. *p*-CPA was shown to have no effect upon the dopaminergically-mediated stimuli produced by the stimulants amphetamine and cathinone or upon yohimbine performance.

4. *p*-CPA significantly decreased discriminative performance with the serotonergic releasing drugs MDMA, MDE and fenfluramine. This decrease in discriminative performance returned to pre-*p*-CPA (criterion) levels at a time (9–12 days) when 5-HT has been reported to replete to normal brain concentrations.

5. It is concluded that *p*-CPA pretreatment lowers brain 5-HT and, in turn, significantly decreases the ability of rats to discriminate centrally active drugs whose interoceptive cueing stimuli are mediated by 5-HT neurons.

INTRODUCTION

Serotonin (5-HT) has been shown to mediate various biological processes, including sleep (Mouret *et al.*, 1968), locomotor activity (Fibiger and Campbell, 1971), the recognition of pain (Harvey and Lints, 1971) and the level of sexual activity (Shillito, 1970). In the context of the present work, the role of 5-HT in mediating the discrimination of the interoceptive cueing properties of various centrally active drugs has been investigated. One method to determine the role of 5-HT in the expression of the discriminative stimulus properties of a specific drug is to observe the effect of its depletion on that discrimination. To this end, there are various methods to produce a depletion of 5-HT in the brain, including mid-brain raphé lesions and the administration of 5,6- or 5,7-dihydroxytryptamine or *para*-chloroamphetamine (see review by Lorens, 1978). An alternative method, one that is unique in the sense that the levels of 5-HT in the brain decrease and then replete, is the administration of *para*-chlorophenylalanine (*p*-CPA). As early as 1966, Koe and Weissman showed that *p*-CPA *in vitro* acts as a weak competitive inhibitor of the 5-HT synthesis enzyme tryptophan hydroxylase. This depletion of central 5-HT appears to be maximal by the third day post-administration with a gradual return to normal levels by approximately day 9–11 (Jequier *et al.*, 1967; Tenen, 1967).

The recent discovery of multiple populations of central 5-HT binding sites has renewed interest in finding specific receptor ligands (Glennon, 1987). Although this area of research is fraught with controversy (Fozard, 1987), many of the specific ligands have been used to investigate the 5-HT mediation of drugs considered to be hallucinogenic (Glennon, 1985). Perusal of an extensive bibliography of the drug discrimination literature (Stolerman *et al.*, 1982) indicates that pretreatment with *p*-CPA before drugs used to control discriminative behavior has led to divergent results, i.e. *p*-CPA was observed to have no effect upon phencyclidine (Järbe *et al.*, 1975), fentanyl (Colpaert *et al.*, 1977) and nicotine (Schechter and Rosecrans, 1972) discrimination but to increase the discriminative sensitivity to low doses of other drugs, such as LSD (Cameron and Appel, 1973), mescaline (Browne and Ho, 1975) and quipazine (White *et al.*, 1979). Lastly, *p*-CPA pretreatment was shown to decrease the discriminative performance of both ethanol (Schechter, 1979) and morphine (Rosecrans *et al.*, 1973); although these findings were not replicated (Winter, 1977). The purpose of the present study was to extend the list of drugs that may be affected by pretreatment with the reversible serotonin depletor *p*-CPA and to investigate the time-course of depletion and repletion of 5-HT as it may alter discriminative performance.

METHODS

Male Sprague–Dawley rats, purchased from Zivic–Miller Laboratories (Allison Park, PA), weighing 260–350 g at the beginning of these experiments, were the subjects used. The rats were individually housed in galvanized cages with free access to water except during experimental sessions and they were maintained at 80–85% of their free-feeding body weight as determined by a growth chart from the supplier. The rats

were trained 5 days/week at the same time every day and, when not being trained or tested, they were kept in a room on a 12 hr (0600–1800 hr) light/dark cycle and relatively constant temperature and humidity.

All of the rats used in the present study had previously been trained to discriminate various drugs using the same behavioral procedures. This is indicated by the following (as drug; dose; publication reference; number of rats): The central nervous system stimulants amphetamine (0.8 mg/kg; Schechter and Boja, 1988; nine rats) and cathinone (0.8 mg/kg; Schechter, 1989b; nine rats); the "designer" drugs MDMA (1.5 mg/kg; Schechter, 1989a; six rats) and MDE (2.0 mg/kg; Boja and Schechter, 1987; six rats) and the other drugs, fenfluramine (2.0 mg/kg; Schechter, 1990; 10 rats) and yohimbine (3.0 mg/kg; unpublished data; six rats). The detailed training procedure may be found in any of these cited publications and the present research constituted the last series of experiments, before the rats were killed, in each group of trained animals. The rats were approximately the same age at the time of this experimentation and the duration of these experiments in each group was similar.

As indicated in the majority of drug discrimination studies employing *p*-CPA pretreatment, the most efficacious regimen of administration consists of 3 days of daily i.p. injection of 100 mg/kg *p*-CPA. As the rats were not scheduled to continue to receive maintenance (reinforced training) sessions during the nine testing days after *p*-CPA treatments, it was necessary to investigate if this extended time of non-reinforcement would affect the animals' discriminative performance. To this end, the animals in all groups were first administered a daily injection of 1 ml/kg saline for 3 consecutive days. On the third day after the last of these non-contingent saline administrations, the rats of all groups were tested at 0930 hr with the vehicle used in their training and, upon making 10 responses on either lever, they were immediately removed (without receiving reinforcement) from the operant chamber. On the same day, at approximately 1500 hr, the rats were injected with the drug used in their training and, likewise, tested and removed upon making 10 responses on either lever. This procedure was repeated on days 5 and 9 following the last of the 3 days of saline administrations.

Starting on the next day (day 10), the animals were each retrained, over a 4-day period, with two alternating administrations of vehicle and trained drug. Each session was conducted using a reinforced FR10 schedule to ensure that discriminative performance returned. In all cases, discriminative performance was at pre-saline levels. At this time, 100 mg/kg *p*-CPA (i.p.) was administered once a day for 3 consecutive days. On the third day after the last of these multiple *p*-CPA administrations, the animals were again tested with non-reinforced trials after vehicle in the morning and non-reinforced trials with the drug used for training in the afternoon. They were allowed to press one lever 10 times and immediately removed from the chamber. All animals were tested through a 9 days post-*p*-CPA period except for the fenfluramine-trained rats which had one additional test on day 12 post-administration.

The first lever on which 10 presses accumulated was designated the "selected" lever. The percentage of rats selecting the lever appropriate for the drug state was the quantal measurement of discrimination and quantal data are presented as per cent first choices on the drug-appropriate lever. In addition, the number of lever presses on the drug-appropriate lever divided by the total number of responses on both levers before 10 responses on either lever, times 100, constitutes the quantitative measurement. Unlike the all-or-none quantal measurement, the quantitative measurement allows for the magnitude as well as the direction of lever choice. An animal's quantitative measurement after drug or vehicle testing on any given post *p*-CPA treatment day was compared with the same animal's post-saline treatment day using a paired Student's *t*-test with $P > 0.05$ chosen as the level of significance.

The drugs (abbreviations; suppliers) used in the study were: D-amphetamine sulfate (AMPH; Sigma Chemical Co., St Louis, MO), cathinone hydrochloride (CATH; National Institute of Drug Abuse), yohimbine hydrochloride (YOH; Sigma Chemical Co.), 3,4-methylenedioxymethamphetamine (MDMA; NIDA), N-ethyl-methylenedioxyamphetamine (MDE; NIDA) and D,L-fenfluramine hydrochloride (FEN; A. H. Robins Co., Richmond, VA). All drugs were dissolved in deionized water (vehicle) and injected intraperitoneally in a constant volume of 1 ml/kg as free-base.

RESULTS

The quantal and quantitative measurements generated by testing the drugs and their vehicle on day 3, 5, or 9 after multiple treatments with either saline or *p*-CPA appear in Table 1. The first column labeled "after 3 × saline", when read vertically, indicates that at no time within 9 days after multiple saline administrations was the rats' ability to discriminate the vehicle condition compromised. The most "disruption" occurred when two of either the nine cathionine- or 10 fenfluramine-trained rats selected the drug-appropriate lever after vehicle injection on day 9 post-saline. Likewise, the discrimination of the drug state was unaffected by 9 days of non-reinforcement.

The rightmost columns indicate the effects of testing vehicle (in the morning) or drug (in the afternoon) "after 3 × *p*-CPA" treatments. Again, vehicle was not greatly compromised, with a maximum of two of the nine cathinone-trained animals choosing the drug lever after vehicle on day 3 after saline and two of the 10 fenfluramine-trained rats incorrect on days 9 and 12. The rightmost column indicates the quantal and quantitative measurements after drug testing post-*p*-CPA administration. Perusal of the amphetamine, cathionine and yohimbine data at 3, 5 and 9 days post-*p*-CPA indicates no significant changes. In contrast, on day 3 and 5 post-*p*-CPA, the testing of MDMA resulted in significantly diminished discriminative performance with a return to criterion level (i.e. over 80%) at 9 days post-administration. Likewise, at 3 days post-*p*-CPA the five rats (one of the six rats died after the second *p*-CPA administration) trained with MDE exhibited significantly decreased discriminative performance which, by day 9, returned to criterion level. Lastly, the fenfluramine-trained rats displayed a 50% quantal discrimination on both and days 5 and 9 post *p*-CPA. An additional test day was, therefore, conducted on day 12 with a resulting return to criterion level drug discrimination.

DISCUSSION

The drug discrimination paradigm has proven to be useful in the study of centrally active drugs in that the stimulus (interoceptive cue) produced by a drug is specific and, once learned, can be affected by pretreatment with putative receptor antagonists. This allows for suggestive evidence on the mechanism of drug action. In these stimulus antagonists studies, the stimulus produced by the drug used in training will theoretically only be blocked by those antagonists that somehow interfere with the drug's mechanism of action (Glennon, 1985). The implication in the present study is that if pretreatment with the serotonin depleting agent *p*-CPA is observed to decrease the discrimin-

Table 1. Mean quantal and quantitative measurements with vehicle or drug at 3, 5 and 9 days after multiple treatments of saline or 100 mg/kg *para*-chlorophenylalanine (*p*-CPA)

		After 3 × saline				After 3 × *p*-CPA			
Drug (N)	Day	Vehicle		Drug		Vehicle		Drug	
AMPH (9)	3	0.0	4.3[a]	100.0	86.5	11.1	17.1	88.9	81.5
	5	0.0	9.1	88.9	85.9	0.0	2.2	100.0	86.5
	9	0.0	6.3	100.0	86.5	0.0	9.1	100.0	89.1
CATH (9)	3	0.0	6.3	100.0	97.8	22.2	29.7	100.0	94.7
	5	0.0	8.2	100.0	86.5	0.0	15.9	100.0	95.7
	9	22.2	24.7	100.0	92.8	0.0	22.4	100.0	91.2
YOH (6)	3	0.0	4.8	100.0	96.6	16.7	20.3	100.0	93.8
	5	0.0	5.0	100.0	95.2	0.0	14.3	100.0	85.7
	9	16.7	19.1	100.0	93.8	0.0	21.1	83.3	83.8
MDMA (6)	3	0.0	4.8	100.0	100.0	16.7	19.4	50.0	42.9[b]**
	5	0.0	3.2	100.0	100.0	16.7	20.6	33.3	35.5[b]*
	9	0.0	18.9	100.0	100.0	16.7	23.9	83.3	63.3
MDE (6, 5)	3	0.0	13.8	83.3	81.0	0.0	5.2	40.0	40.4[b]**
	5	16.7	32.3	83.3	81.8	20.0	21.8	100.0	86.7
	9	0.0	14.9	100.0	92.9	0.0	27.5	80.0	82.9
FEN (10)	3	10.0	20.8	100.0	87.7	0.0	12.3	80.0	69.2
	5	0.0	12.3	100.0	88.5	0.0	16.0	50.0	53.9[b]*
	9	20.0	37.2	100.0	83.9	20.0	36.7	50.0	52.4[b]*
	12	ND		ND		20.0	32.0	100.0	78.1

[a]Quantal: quantitative measurements. See text for explanation.
[b]Significant difference from quantitative measurement for drug on same post-treatment day after 3 × saline; paired *t*-test; $*P < 0.05$, $**P < 0.01$.
ND: Not determined.

ation of a drug, the mechanism of that drug's action most probably involves pre-synaptic (indirect) serotonergic mechanisms. If the decreased serotonin synthesis has no effect, the implication is that the mechanism of action is either not serotonergic in nature or that it may involve a post-synaptic (direct) serotonergic mechanism. Furthermore, *p*-CPA, as a reversible serotonin depletor allows the investigation of the time-course of depletion and repletion of 5-HT as it may alter discriminative performance. This allows for evidence on drug effects upon serotonin's presynaptic action (i.e. release), whereas many studies have been reported employing selective 5-HT subtype antagonists to indicate post-synaptic events (e.g. Arnt, 1989; Cameron and Appel, 1973).

The results of the present experiments (Table 1) indicate that well-trained rats will continue to discriminate between a drug and its vehicle even though they had not received reinforcement for six test trials over 9 days. Thus, the possibility of extinction of learned behavior by non-reinforcement does not seem to interfere with the animals' continued ability to discriminate after multiple saline administrations. This observation precludes the necessity for continued training during the post-*p*-CPA treatment period which, if conducted, may have biased the results in that rats might have been trained to new interoceptive cues during this time with recognition based on decreased 5-HT concentrations in the brain. A recent report has shown that discontinued training during a 12-day period, likewise, does not affect task performance in rats trained to discriminate distilled water from 0.75 mg/kg amphetamine in a similar two-lever drug discrimination task (Caul *et al.*, 1989).

The inability of *p*-CPA pretreatment to affect the animals' discriminative performance after the psychostimulants amphetamine and cathinone is not surprising as previous research has indicated that the discriminative stimulus properties of both amphetamine (Schechter and Cooke, 1975) and cathinone (Schechter, 1986a) are mediated by dopaminergic mechanisms. From the results of the present study it would, therefore, be fair to suggest that 5-HT is not critically, if at all, involved in the discriminative stimulus properties of these drugs. This extends previous reports that indicated that *p*-CPA pretreatment has no effect upon the stimulus cues produced by phencyclidine (Järbe *et al.*, 1975), fentanyl (Colpaert *et al.*, 1977) or nicotine (Schechter and Rosecrans, 1972).

The exact mechanism of action of yohimbine is more problematic. In addition to α_2-adrenoreceptor effects (Goldberg and Robertson, 1983), yohimbine appears to act upon dopamine (Sanghvi and Gerson, 1974), benzodiazepine (Lal *et al.*, 1983), as well as 5-HT (Pettibone *et al.*, 1985) systems. More germane to the present work, yohimbine has been reported to produce similar discriminative effects (i.e. to generalize) in rats trained to the serotonergically mediated drugs LSD (Colpaert, 1984) and tetrahydro-β-carboline (Schechter, 1986b). More recently, in rats trained to the specific 5-HT_{1A} ligand 8-OH-DPAT in a two-lever drug discrimination procedure, yohimbine was shown to produce 8-OH-DPAT-appropriate responding (Winter, 1988). The present results (Table 1) indicate that there was no significant effect of 5-HT depletion upon yohimbine drug discrimination. Previous research (Winter, 1978) indicated that pretreatment with the serotonergic antagonist BC-105 was, likewise, unable to antagonize yohimbine discrimination.

In contrast to these negative findings, *p*-CPA pretreatment significantly decreased the animals' ability to discriminate stimulus properties produced by the "designer" drugs MDMA and MDE, as well as the anorectic agent fenfluramine. Previous work in this laboratory has indicated that both MDMA (Schechter, 1989a) and MDE (Boja and Schechter,

1987) discrimination are mediated by serotonergic mechanisms. Likewise, fenfluramine has been shown (McElroy and Feldman, 1984; White and Appel, 1981) to produce its discriminative stimulus effects via 5-HT mechanisms. In one of these previous studies (White and Appel, 1981), a pretreatment *p*-CPA regimen similar to the one used in the present study decreased the discriminative performance after 1.0 mg/kg fenfluramine from 97 to 45%. Unfortunately, the time-course of this effect was not followed and only one (unspecified) time post *p*-CPA was investigated.

The observation that discriminative performance with MDMA was significantly decreased on days 3 and 5, whereas MDE discrimination was affected only on day 3 post-*p*-CPA and that fenfluramine discrimination declined on days 5 and 9, is difficult to explain. *p*-CPA has been reported, in biochemical studies, to reduce total brain 5-HT to about 10% of normal levels for several days, with a slow return to pre-administration levels over a period of about 10 days (Koe and Weissman, 1966; Tenen, 1967). The longer duration of *p*-CPA-induced serotonergic depletion effects upon fenfluramine may be a result of the critical necessity for serotonin systems to be intact for fenfluramine discriminative performance. In contrast, MDMA and MDE may have a duality of mechanisms which involve both serotonin and dopamine. This duality of effect of the "designer" drugs has been reported in biochemical (Stone *et al.*, 1986) and behavioral studies (Schechter, 1989a). In any case, it does appear that the *p*-CPA depletion of serotonin can significantly affect those drugs which require an intact central serotonergic system to fully express their discriminative stimulus properties.

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