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DISCRIMINATIVE STIMULUS PROPERTIES OF PHENCYCLIDINE

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Summary—Rats were trained to discriminate intraperitoneal injections of phencyclidine (4.0 mg/kg) from saline in a two-lever drug discrimination task. After reliable discrimination was established and a dose-response curve was obtained, two doses of each of a variety of agents were tested to determine whether they evoked responding on the phencyclidine-appropriate lever. All doses of the indirect dopamine agonist *d*-amphetamine (0.5 and 1.0 mg/kg) and the direct dopamine agonist apomorphine (0.5 and 1.0 mg/kg), the direct serotonin agonists LSD (0.08 and 0.16 mg/kg) and quipazine (1.0 and 2.0 mg/kg), and the anticholinergic drugs atropine (0.5 and 1.0 mg/kg) and ditran (3.0 and 6.0 mg/kg) failed to produce phencyclidine-like discriminative effects, as did diazepam (8.0 and 16.0 mg/kg) and a 7.5 mg/kg dose of ketamine. A 15.0 mg/kg dose of ketamine, a compound structurally and pharmacologically similar to phencyclidine, did produce phencyclidine-like discriminative effects.

The dopamine blocker haloperidol (0.1 and 0.2 mg/kg), the serotonin blocker cyproheptadine (0.5 and 1.0 mg/kg), the cholinesterase inhibitor physostigmine (1.0 and 2.0 mg/kg), and the nicotinic blocking agent mecamylamine (1.0 and 2.0 mg/kg) when given prior to the 4.0 mg/kg dose of phencyclidine failed to affect discrimination significantly. These compounds also failed to produce phencyclidine-like discriminative effects when given alone. Overall, these results parallel previous findings with other procedures in suggesting that the effects of phencyclidine are unique, and may reflect the wide variety of neurochemical actions produced by the drug.

The potent psychotomimetic drug phencyclidine, 1-(1-phencyclohexyl) piperidine (PCP), has emerged as a dangerous agent of abuse among those in the drug community (Garey, Weisberg and Heath, 1977; Balster and Chait, 1976). Although frequently sold as any of a number of other illicit compounds, PCP is also abused by many individuals who have full knowledge of its identity (Garey *et al.*, 1977). Despite its current widespread use, relatively little information concerning the neuropharmacological mechanisms mediating PCP's behavioral effects has been obtained. Existing evidence indicates that the compound affects virtually all known central neurotransmitter systems. Thus, PCP has been characterized as possessing a wide and unique spectrum of central nervous system effects (Domino, 1964; Balster and Chait, 1976).

Originally developed as an anesthetic, PCP was subsequently found to produce a characteristic dissociative state in man (Greifenstein, Yoshitake, DeVault and Gajewski, 1958). This psychotomimetic effect of PCP has generally been ascribed to its anticholinergic activity (Maayani, Weinstein, Cohen and Sokolovsky, 1973; Garey *et al.*, 1977). Recently, however, it has been hypothesized that increased dopaminergic activity similar to that produced by *d*-amphetamine may be responsible for some of the behavioral effects of PCP. Like *d*-amphetamine, PCP has been shown to be a potent competitive inhibitor of dopamine reuptake in the rat striatum (Garey and Heath, 1976). Similarly, results from a number of behavioral tests have implicated an "amphetamine-like" dopaminergic action for PCP: PCP causes ipsilateral rotation in rats with unilateral electrolytic lesions in the substantia nigra (Kanner, Finnegan and Meltzer, 1975), a measure generally taken as evidence of an indirect-acting dopamine agonist (Ungerstedt, 1971). Furthermore, the PCP-induced rotational behavior is reversed by the dopamine antagonists haloperidol and pimozide and by the catecholamine synthesis inhibitor α-methyl-*p*-tyrosine (Kanner *et al.*, 1975; Finnegan, Kanner and Meltzer, 1976). In addition, Balster and Chait (1978) have recently reported that low doses of PCP enhance stereotypic behavior produced by *d*-amphetamine in rats. Finally, PCP affects schedule-controlled behavior in a variety of species in a manner highly similar to *d*-amphetamine (Wenger, 1976; Wenger and Dews, 1976; Murray, 1978; Balster and Chait, 1976).

It has been reported previously that PCP can serve as a discriminative stimulus controlling the choice behavior of rats in a T-maze shock escape task (Overton, 1975; Jarbe, Johansson and Henriksson, 1975). However, the neurochemical mechanisms mediating the discriminative effects of PCP have not been determined clearly. The present study established PCP (4.0 mg/kg) as a discriminative stimulus in a two-lever, positively-reinforced operant task which has proved to be a sensitive and specific technique for investigating the neurochemical processes mediating the behav-

Key words: phencyclidine, cholinergic antagonists, serotonin antagonists, serotonin agonists, dopamine antagonists, dopamine agonists, dissociative anesthetics, stimulus properties of drugs, drugs as discriminative stimuli, mechanisms of action.

ioral effects of various drugs (e.g. White, Kuhn and Appel, 1977; Kuhn, White and Appel, 1978). Then, transfer and antagonism tests were conducted in an attempt to ascertain the involvement of dopaminergic, serotonergic, and cholinergic systems in producing the discriminative stimulus properties characteristic of PCP.

METHODS

Subjects

Eight experimentally-naive male albino rats, maintained at 85% of free-feeding weights by limiting access to water, served as subjects. They were individually housed with *ad libitum* access to Purina rat chow in a room with controlled temperature (21–23°C), humidity (40–50%), and lighting (12-hr light/dark cycle).

Apparatus

Two sound-attenuated operant conditioning chambers (Lehigh Valley Electronics Model 143-24) were used. Each was equipped with two response levers and a liquid dipper (0.01 ml volume) located between the levers. Constant illumination was supplied by a 7 W white house light; an exhaust fan provided ventilation and masking noise. Electromechanical programming and recording equipment was located in an adjoining room.

Discrimination training

The procedure used has been described in detail elsewhere (Kuhn *et al.*, 1978; White *et al.*, 1977). During initial training, water-deprived rats were injected intraperitoneally (i.p.) with PCP (4.0 mg/kg) or isotonic saline solution 15 min prior to the experimental session. During the session, a single lever was present in the chamber and responses on that lever were reinforced (with presentation of the water-filled dipper) under a fixed-ratio 1 (FR 1) schedule. The lever that was present depended on whether PCP or saline was injected: for four rats, the left lever was designated PCP-appropriate and was present when the drug was given, while the right lever was designated the PCP-appropriate lever for the remaining animals. Saline and PCP injections alternated irregularly across sessions and each subject received an approximately equal number of PCP and saline injections.

Response requirements were gradually increased across sessions until all animals reliably responded under an FR 20 schedule (i.e. the dipper was presented following every twentieth response). After this occurred, the two levers were present simultaneously during all sessions and actual discrimination training was begun. During discrimination training, the animals were reinforced only for responding on the stimulus-appropriate lever; incorrect responses were without programmed consequences. All discrimination training sessions lasted 20 min and were conducted from Monday to Friday; animals were given unlimited access to water in the home cages from Friday evening to Saturday evening (*ca.* 24 hr). Discrimination training continued until percent correct responses prior to delivery of the first reinforcer was 80% or higher for the group during 10 consecutive sessions. This measure was determined by dividing the number of correct (stimulus-appropriate) responses emitted prior to delivery of the first reinforcer by the total number of responses emitted on both levers during this period.

Dose-response testing

Following discrimination training, the effects of substituting 1.0, 2.0, 3.0, 5.0 or 6.0 mg/kg doses of PCP for the 4.0 mg/kg training dose were determined. During this and all subsequent testing, no reinforcers were delivered and the session terminated after 20 responses were made on one or the other of the levers or after 20 min had elapsed, whichever occurred first. Immediately following such extinction sessions, animals were given five minutes of *ad libitum* access to water in home cages. Each rat received each of the above doses on a single occasion; doses were presented in an irregular order. Tests occurred no more than twice a week (generally on Tuesdays and Fridays) and the discrimination training procedure described above was in effect during all non-test sessions. Under all conditions, tests were conducted only when the percentage of correct responses prior to delivery of the first reinforcer was 80% or higher during each of the two preceding discrimination training sessions. Injecting test drugs (and doses) in an irregular temporary sequence and testing no more than twice per week, then only when performance had stabilized following the preceding manipulation, acted as a control for the possibility of test results being influenced by prior manipulations.

Transfer testing with other compounds

Following dose-response testing, generalization testing was conducted as described above with the serotonin agonists *d*-lysergic acid diethylamide (LSD) and quipazine, the dopamine agonists *d*-amphetamine and apomorphine, the anticholinergics ditran and atropine, the benzodiazepine diazepam and ketamine, a compound structurally related to LSD. Two doses of each drug were given (Table 1). The higher dose of each of these compounds was just below a dose found in pilot work and in reported studies from this laboratory and elsewhere to disrupt severely fixed-ratio performance; the lower dose was half the higher one. All drugs were injected intraperitoneally 15 min prior to testing, and each subject received each dose of a given compound on a single occasion. Drugs and doses were administered in an irregular order across subjects.

Antagonism testing

Antagonism testing involved injecting the putative antagonist compound intraperitoneally 1 hr prior to

the experimental session, injecting a 4.0 mg/kg (i.p.) dose of PCP 15 min prior to the session, and measuring performance under conditions where no reinforcers were delivered (above). Mecamylamine, a nicotinic blocker, haloperidol, a dopamine antagonist, physostigmine, a cholinesterase inhibitor and cyproheptadine, a serotonin antagonist as well as a potent antihistaminic, were tested under this procedure. Doses of these compounds were chosen on the basis of previous studies (see Table 2 for doses). These compounds were also injected 1 hr prior to test sessions preceded by saline injections to determine whether they produced PCP-like discriminative effects when given alone.

Drugs

Phencyclidine HCl, LSD tartrate, quipazine maleate, apomorphine HCl, *d*-amphetamine sulfate, atropine sulfate, ditran, diazepam, haloperidol, physostigmine salicylate and mecamylamine HCl were dissolved in isotonic (0.9%) saline solution. Cyproheptadine HCl was prepared in 15% aqueous propylene glycol. A commercially-available ketamine injection (Bristol Laboratories) diluted with distilled water was used. All drugs were prepared to a 1 ml/kg injection volume, and all doses refer to the total salt.

Data analysis

With the exception of the acquisition data, all data are expressed as percent responding on the PCP-appropriate lever prior to the emission of 20 responses on either of the levers (above). Therefore, the maximum number of total responses for any animal during a test session was always between 20 and 39. Planned-comparison correlated *t*-tests, comparing % PCP-appropriate responses under a particular test condition with average percent PCP-appropriate responses during the last five PCP-training sessions, were used to analyze data. In a transfer test, no significant difference ($P > 0.05$) between performance when PCP was given and performance under the test condition was taken to indicate that the test compound produced PCP-like discriminative effects. In an antagonism test, no significant difference ($P > 0.05$) in performance when PCP was given in the presence and absence of the putative antagonist was taken to indicate the absence of antagonism. Such an analysis can occasionally result in "overinclusiveness," that is, classifying drugs as similar when they may be different in other pharmacological assays, although it is not clear what sort of analysis is more appropriate (Overton, 1974).

RESULTS

The acquisition of the PCP (4.0 mg/kg)–saline discrimination is shown in Figure 1. Mean % correct responses reached 80% within 27 sessions, and stayed at or above this level during all subsequent PCP- and saline-training sessions. Figure 2 shows the dose-response relation obtained when 1.0, 2.0, 2.0, 5.0 and 6.0 mg/kg doses of PCP were substituted for the 4.0 mg/kg training dose. Percent PCP-appropriate responses were similar when 4.0, 5.0 and 6.0 mg/kg doses were given, while % PCP-appropriate responses sequentially decreased at doses of 3.0, 2.0 and 1.0 mg/kg.

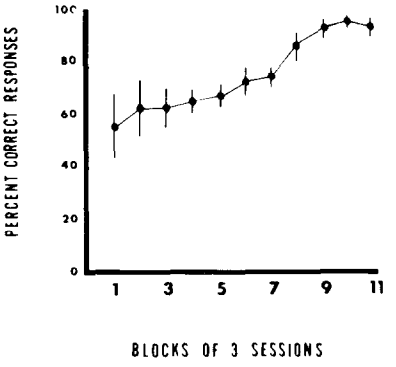

Fig. 1. Acquisition of the PCP-saline discrimination. Each data point represents mean % correct (stimulus-appropriate) responses by eight rats across three consecutive sessions regardless of whether saline or drug injections preceded the sessions. Vertical lines are ±1 S.E.

Transfer testing

Table 1 shows that only the 15.0 mg/kg dose of ketamine produced discriminative effects which were similar to those produced by the training dose of PCP. All other drugs produced effects significantly different from those obtained when (4.0 mg/kg) PCP injections were given, although the 7.5 mg/kg dose of ketamine and both doses (0.5 mg/kg and 1.0 mg/kg) of apomorphine evoked appreciably more PCP-appropriate responses than did saline and the other compounds tested.

Antagonism testing

Table 2 shows that none of the putative antagonists significantly decreased % PCP-appropriate responses

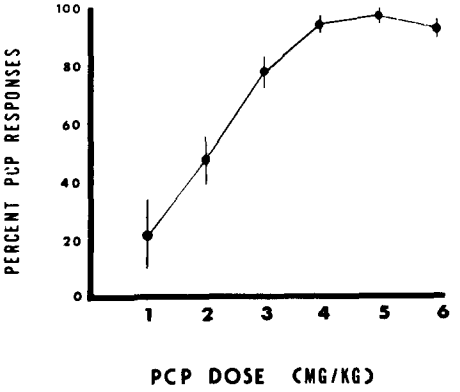

Fig. 2. Dose-response relationship for the PCP discrimination. Each data point represents mean % PCP-appropriate responses by eight rats during a single session. Vertical lines are ±1 S.E.

Table 1. Mean % responding on the PCP-appropriate lever after injection of various compounds

Drug*	Dose (mg/kg)	% ±S.E.M.
PCP	4.0	90 ± 3
Saline	—	8 ± 2
LSD	0.08	11 ± 5†
LSD	0.16	14 ± 5†
Quipazine	1.0	13 ± 7†
Quipazine	2.0	14 ± 6†
Apomorphine	0.5	25 ± 7†
Apomorphine	1.0	32 ± 14†
d-Amphetamine	0.5	7 ± 5†
d-Amphetamine	1.0	7 ± 3†
Atropine	0.5	11 ± 3†
Atropine	1.0	5 ± 2†
Ditran	3.0	7 ± 2†
Ditran	6.0	11 ± 5†
Diazepam	8.0	12 ± 10†
Diazepam	16.0	13 ± 6†
Ketamine	7.5	46 ± 15†
Ketamine	15.0	83 ± 4‡

* All drugs were injected intraperitoneally 15 min before the session.
† Significantly different from PCP.
‡ Not significantly different from PCP.

when given prior to (4.0 mg/kg) PCP injections, or significantly increased % PCP-appropriate responses when given prior to saline injections. Thus none of these compounds antagonized the discriminative effects of PCP or produced discriminative effects like those produced by the training dose of PCP.

DISCUSSION

The finding that PCP (4.0 mg/kg) was able to exert control over lever choice in rats performing a water-reinforced bar-press discrimination confirms and extends the results of earlier studies which established PCP as a discriminative stimulus in electrified T-maze (Overton, 1975; Jarbe *et al.*, 1975). The dose-response relation for the PCP discrimination was orderly; PCP-appropriate responding decreased progressively as the dose of PCP was decreased with respect to the training dose. Similar dose-response relationships have been obtained for various compounds (e.g. Overton, 1974).

Recent reports have suggested that the behavioral effects of PCP may be mediated by the compound's ability to act as a dopamine agonist (e.g. Finnegan *et al.*, 1975; Balster and Chait, 1978; Wenger, 1976; Kanner *et al.*, 1975), to block cholinergic activity (e.g. Kanner *et al.*, 1975; Finnegan *et al.*, 1976), or to inhibit the uptake of serotonin (Smith, Meltzer, Dekirmenjiar and Davis, 1975) while increasing whole-brain 5-hydroxytryptamine levels (Tonge and Leonard, 1969, 1971). However, in the present study, the discriminative stimulus properties of phencyclidine did not seem to reflect a simple serotonergic, dopaminergic, or anticholinergic action: direct and indirect dopamine agonists (apomorphine and *d*-amphetamine), anticholinergics (ditran and atropine) and direct serotonin agonists (quipazine and LSD) failed to produce PCP-like discriminative effects, while a dopamine antagonist (haloperidol), a nicotinic cholinergic antagonist (mecamylamine), a cholinesterase inhibitor (physostigmine) and a serotonin antagonist (cyproheptadine) neither blocked nor mimicked the discriminative properties of PCP.

As in earlier studies (Overton, 1975; Jarbe *et al.*, 1975), the only drug that produced a PCP-like discriminative cue was the structurally-related compound ketamine. Jarbe and coworkers (Jarbe *et al.*, 1975) also observed a transfer with cyclohexamine, which is similar in structure to both PCP and ketamine.

Table 2. Mean % responding on the PCP-appropriate lever after injection of putative antagonists with saline and PCP

Putative antagonist*	Dose (mg/kg)	PCP or saline	% ±S.E.M.
Mecamylamine	1.0	PCP	77 ± 8‡
Mecamylamine	1.0	Saline	7 ± 3†
Mecamylamine	2.0	PCP	79 ± 6‡
Mecamylamine	2.0	Saline	91 ± 4†
Haloperidol	0.1	PCP	96 ± 3‡
Haloperidol	0.1	Saline	7 ± 2†
Haloperidol	0.2	PCP	84 ± 6‡
Haloperidol	0.2	Saline	9 ± 3†
Cyproheptadine	0.5	PCP	83 ± 8‡
Cyproheptadine	0.5	Saline	14 ± 4†
Cyproheptadine	1.0	PCP	84 ± 4‡
Cyproheptadine	1.0	Saline	12 ± 2†
Physostigmine	1.0	PCP	84 ± 5‡
Physostigmine	1.0	Saline	11 ± 3†
Physostigmine	2.0	PCP	82 ± 6‡
Physostigmine	2.0	Saline	9 ± 2†

* All drugs were injected intraperitoneally 1 hr before the session.
† Significantly different from PCP (Table 1).
‡ Not significantly different from PCP (Table 1).

The mechanism of action of ketamine and cyclohexamine, unfortunately, are as complex and ill-defined as those of PCP. At present, it is clear that the mechanism by which PCP produces its internal cueing effect remains to be elucidated, although it apparently is not via an isolated agonistic or antagonistic interaction with dopaminergic, serotonergic or cholinergic neuronal systems.

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