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Effects of Phencyclidine on Aggressive Behavior in Mice

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TYLER, C. B. AND K. A. MICZEK. *Effects of phencyclidine on aggressive behavior in mice.* PHARMAC. BIOCHEM. BEHAV. **17**(3) 503–510, 1982.—The effects of phencyclidine on aggressive behavior in mice and the possible mechanism of action for these effects were examined. PCP at a dose of 10.0 mg/kg significantly decreased the number of attacks by resident mice toward intruders. Significant increases in the number of attacks by non-drugged residents toward the intruders who were given high doses of PCP (6.0 and 10.0 mg/kg) were observed. Only the higher doses of PCP (6.0 and 10.0 mg/kg) significantly increased the duration of locomotion. The increase in locomotion was dependent upon the time after administration of the drug. Hyperactivity was present at 30 minutes for both doses and hypoactivity was present at three hours after administration of 3.0 mg/kg. PCP did not significantly alter the frequency of attacks in an unfamiliar test locale. Pretreatment with haloperidol (1 mg/kg) partially blocked the PCP-induced hyperactivity but pretreatment with methysergide (3 mg/kg) did not. Neither haloperidol nor methysergide blocked the suppressive effects of PCP on aggressive behavior. It is concluded that PCP does not increase aggressive behavior in mice but high doses will decrease aggression. PCP-treated intruder animals provoke more aggression by non-drugged animals. PCP-induced hyperactivity appears to be mediated by dopaminergic systems.

Phencyclidine Aggression Aggressive behavior Methysergide Haloperidol Social drug effects Motor activity

PHENCYCLIDINE, 1-(1-phenylcyclohexyl) piperidine (PCP), was first examined in the late 1950's as an anesthetic agent (Trade names Sernyl and Sernylan) in humans. Several clinical and pharmacological effects of PCP in humans and animals have been studied. PCP has stimulant [24], depressant [3], hallucinogenic [1,9] and analgesic [7] properties, but these effects are not universally seen in all species. Some reports suggest that one effect of PCP may be to increase aggressive behavior.

Unprovoked aggression was occasionally seen when phencyclidine was being tested as a possible anesthetic agent for human surgery [7, 8, 9]. Violent acts committed by people after ingesting PCP are cited to such a great extent that PCP use and agression have been closely linked [3,28].

There are only a few studies which examined the effects of phencyclidine on aggression in nonhumans. Rewerski, Kostowski, Piechocki and Rylski [24] examined the effects of PCP on intraspecies aggressive behavior in isolated mice and on mouse killing behavior in rats. A low dose of PCP (1 mg/kg), administered to three isolated mice, completely blocked aggressive behavior after 14 days of isolation. A higher dose (5 mg/kg) significantly increased aggressivity scores and decreased the latency to the first attack in animals isolated for 14 days; but in animals isolated for 28 days, PCP exerted no significant effects. More recently, 1.0 mg/kg PCP, but not 3 mg/kg, was found to increase attack behavior in isolated mice towards group-housed intruder mice [2]. This effect was not seen in mice with previous fighting and drug experience (Burkhalter and Balster, personal communication). Defensive bites and postures in reaction to electric shock pulses were dose-dependently decreased by PCP (0.5–2.0 mg/kg) in rats [5]. An earlier study demonstrated the effects of PCP on aggression indirectly through the examination of communication and group social behavior in rhesus monkeys [23]. Following PCP treatment (0.25 mg/kg) of one animal, there was an overall decrease in social activity for the group. PCP-treated animals frequently approached and touched the other animals. This led to increased aggression toward the treated animals by the dominant animal, resulting in an increase in agonistic behaviors of 13.4%. An increase in aggression by the treated animals was not observed.

The present studies were designed to examine the effects

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of PCP on aggressive behavior in mice at different doses and injection times and to determine its possible mechanism of action. The first study determined the effects of PCP on aggressive behavior when either the attacker or the opponent were given the drug. The second experiment examined the relationship between PCP's behavioral effects and the injection-test interval. In a third experiment, the effects of PCP were studied in mice under conditions which produced low rates of attack. The final study was designed to examine the possible mechanism of action of PCP. Dopamine and serotonin receptor blockers were administered concurrently with PCP, in an attempt to antagonize its effects on aggressive behavior.

EXPERIMENT 1

The following study was conducted to determine the effect of PCP on aggressive behavior in male mice confronting an intruder in their home cages. Either the resident mouse or the intruder was the drug recipient. We attempted to separate the direct effects of PCP on attack behavior from the indirect effects, i.e., changes in attack behavior resulting from interaction with a drugged opponent. The attacking mice lived with female conspecifics. It was established previously that isolated housing is not a necessary prerequisite for aggression in mice [14, 15, 17, 21].

METHOD

Animals

Thirty-five male and fifteen female albino Swiss Webster CFW mice were obtained from Charles River Laboratories (Wilmington, MA) at 41 days of age. Thirteen of the males were each housed with a female in Plexiglas cages (45×24×20 cm) having a sawdust floor covering. Twenty-two of the males were housed in groups of 11 in cages of the same size. All animals had free access to food (Purina's Rodent Laboratory Chow 5001) and water. They were maintained in a vivarium with controlled temperature (21±1°C), humidity (30–40%), and light cycle (12 hours on, 12 hours off).

Procedure

After pairs of male and female mice had been housed together for at least four weeks, three intruder tests were conducted in order to establish that the male residents would reliably attack a male intruder. Females and pups, if present, were removed from the resident's home cage immediately prior to the test and a partition was placed into the home cage. The mice which were housed in groups served as intruders. The intruder was placed on one side of the partition, and the test commenced when the partition was removed. The latency of the first attack by the resident was recorded. The test was terminated immediately following the first attack or after a five-minute period if no attack occurred. This procedure has been described in detail previously [17,21]. All residents reliably attacked the intruders.

Following these initial tests, three further tests were conducted to determine a baseline rate of attack behavior, and to adapt the mice to the drug injection procedure. The residents received an intraperitoneal (IP) injection of saline 30 minutes prior to testing. These tests were conducted similarly to the initial tests except that the test was continued for a five minute period following the first attack. Tests were terminated if no attack occurred within five minutes after the start of the test.

Drug tests were conducted twice a week. Residents were treated once per week with a different dose of phencyclidine HCl (0.3, 1.0, 3.0, 6.0 or 10.0 mg/kg) until they had received all doses. Order effects were controlled by using a Latin square design to assign treatments. During the second test of the week, the intruders were treated with phencyclidine HCl using the same doses as were used with the resident mice. Residents were paired with a particular intruder only once.

All tests were videotaped and analyzed by two uninformed observers, one focusing on the resident's and the other on the intruder's behavior. Various agonistic and nonagonistic behaviors were measured. A keyboard which was connected to a PDP 11/03 microcomputer (Digital Equipment Co.) was used to record frequency and duration of each event. A key was depressed for the duration of each item of the behavioral catalogue. For the residents, pursuits, rearing, locomotion, self-grooming, allogrooming, anogenital contact, attacks, offensive sideways and tail rattles were recorded. For the intruders, locomotion, rearing, self-grooming, allogrooming, defensive uprights, crouching, submissive supines and escapes were recorded. These items of mouse aggression have been described and illustrated previously [20,21], and are readily identified by experienced observers. Experimental data were collected only after each observer had reached a level of 90% agreement within a series of ten repeatedly conducted reliability tests. Vocalizations emitted by an intruder in reaction to attack bites were recorded via a microphone (Sony, model F-988) located on the test cage lid 15 cm above the floor of the cage. Sounds in the range of 5–15 kHz, i.e., audible squeals, were automatically transcribed from the video tapes onto magnetic diskette of the data storage system.

Drug

Phencyclidine HCl was dissolved in 0.9% saline at concentrations of 0.03, 0.1, 0.3, 0.6 and 1.0 mg/ml and injected IP 30 minutes prior to testing. Saline was used in the vehicle control test. The injection volume was 1 ml/100 grams.

Statistics

A Wilcoxon signed-ranks test for related samples was used to analyze the data. Frequency counts and duration measurements for each item of behavior from each drug dose were compared to the data obtained from the vehicle control test.

RESULTS

Vehicle Tests

In confirmation of our previous experiences with this preparation [14, 15, 17, 21, 22], all resident mice reliably attacked intruders during the vehicle control tests; the intruders never attacked the residents. All items of the behavioral catalogue occurred reliably, and aggressive behavior varied less than 10% during the baseline vehicle control tests.

PCP Effects on Resident Mice

Phencyclidine (10 mg/kg) significantly decreased attack frequencies when the residents were treated ($p<0.01$). Attack frequencies were not significantly increased by any

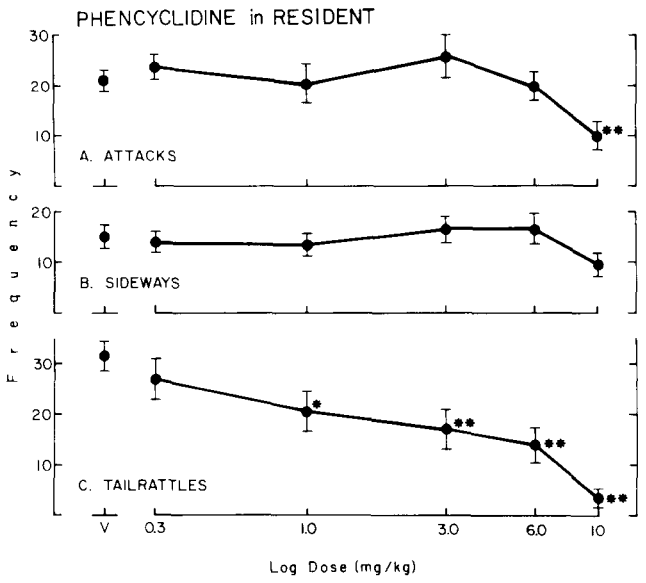

FIG. 1. Dose-response curve for phencyclidine when the resident mice are the drug recipients. Log doses (mg/kg) of phencyclidine are listed along the abscissa with the frequencies of behavior along the ordinate. The behaviors depicted are (A) attacks, (B) offensive sideways and (C) tail rattles. V represents vehicle. Bars represent ±1 SEM with $*p<0.05$ and $**p<0.01$.

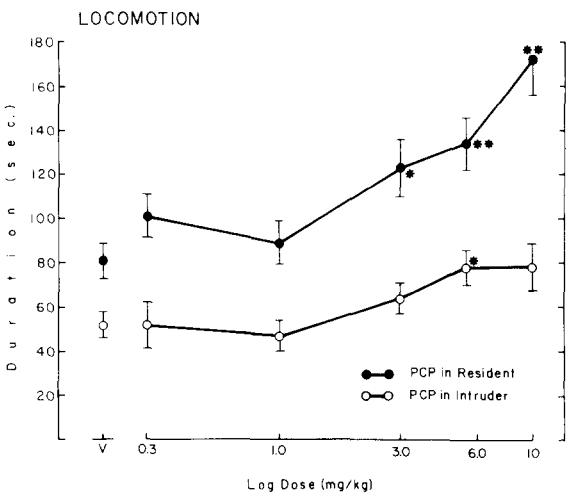

FIG. 2. Dose-response curves for phencyclidine in resident mice (solid circles) and intruders (open circles). Log doses (mg/kg) of phencyclidine are listed along the abscissa with the locomotion duration along the ordinate. V represents vehicle. Bars represent ±1 SEM with $*p<0.05$ and $**p<0.01$.

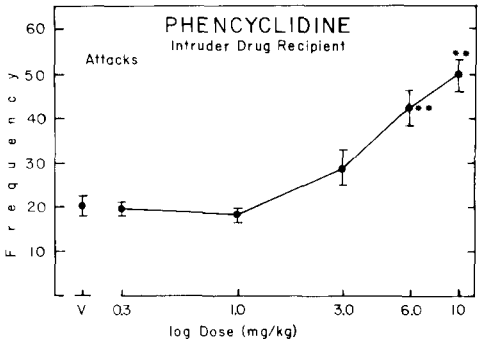

FIG. 3. Dose-response curve for PCP treatment of intruders on attacks by nondrugged residents. Log doses (mg/kg) are given along the abscissa and the frequencies of attacks are listed along the ordinate. V represents vehicle. Bars represent ±1 SEM with $**p<0.01$.

dose. PCP did not affect the number of offensive sideways threats; doses of 3.0, 6.0 and 10.0 mg/kg significantly decreased the number of tail rattles ($p<0.05$, <0.01; Fig. 1). While PCP did not affect locomotor frequencies, doses of 3.0 ($p<0.05$), 6.0 and 10.0 mg/kg ($p<0.01$) significantly increased the duration of locomotion (Fig. 2). Pursuit and self-grooming were significantly decreased after a dose of 10.0 mg/kg ($p<0.05$). Anogenital contact and rearing were not affected by PCP treatment.

Indirect PCP Effects on Resident's Behavior by Drug Treatment of Intruders

When the intruders were treated with PCP (6.0 and 10.0 mg/kg), a significant increase in the frequency of attacks by the non-drugged residents was observed ($p<0.01$; Fig. 3). Similarly, PCP (3.0 to 10.0 mg/kg) in intruders significantly increased the number of offensive sideways threats and pursuits by the non-drugged residents ($p<0.02$, $p<0.01$).

PCP Effects on Intruder Mice

PCP (6.0 and 10.0 mg/kg) significantly increased the number of escapes by the intruders ($p<0.01$), while these same doses decreased the number of defensive uprights (10 mg/kg, $p<0.05$; Fig. 4). While PCP at doses greater than 3.0 mg/kg increased the duration of locomotion, statistical significance was reached only at 6.0 mg/kg ($p<0.05$; Fig. 2). PCP (6.0 and 10.0 mg/kg) significantly decreased self-grooming ($p<0.02$; $p<0.01$) and these higher doses increased the number of submissive supine postures ($p<0.01$). PCP did not affect vocalizations and rearing.

DISCUSSION

PCP did not increase any element of aggressive behavior in mice directly. But when the intruders were treated with the higher doses of PCP (6.0 and 10.0 mg/kg), increases in attacks by the non-drugged residents toward the treated intruders were observed. Increased aggression toward PCP-treated animals has also been observed in rhesus monkeys [23]. The increase in aggression in mice may occur because the locomotor activity of the intruder increases, thereby increasing the frequency of contact between the non-drugged resident and the PCP-treated intruder.

An increase in aggression has been found when mice were given 5 mg/kg of PCP after 14 days of isolation and were then confronted with two other isolated mice, but not when they were treated after 28 days of isolation [24]. Since these results were dependent upon the time of isolation, this might explain why we failed to observe an increase in aggressive behavior since we did not isolate our mice.

Another difference between the present experiments and those by Rewerski *et al.* [24] is the treatment-test interval.

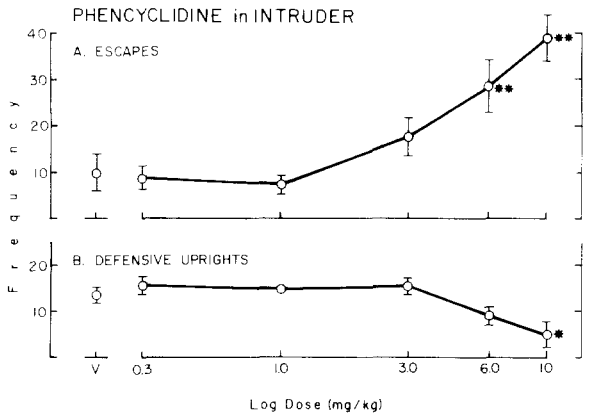

FIG. 4. Dose-response curve for phencyclidine when the intruders are the drug recipients. The behaviors of the intruder depicted are (A) escapes and (B) defensive uprights. Log doses (mg/kg) of phencyclidine are listed along the abscissa with the frequencies of behavior along the ordinate. Bars represent ±1 SEM with $*p<0.05$ and $**p<0.01$.

Rewerski *et al.* [24] used a 45-minute interval, while we used a 30-minute interval. In the earlier study it was found that the PCP-induced hyperactivity in mice had disappeared within 20–25 minutes following injection; however, our animals were still hyperactive at 30–35 minutes post injection. If this hyperactivity is a competing response which interferes with complex behavioral patterns such as attacks and threats, an increase in aggression would not be observed until this effect had subsided.

In humans, the increase in aggression has always been reported to occur hours after ingestion of PCP when the sedative effect has passed. This would correspond to the post-operative recovery period when violent behavior was most likely to be reported [7]. We were observing PCP's effects on aggression at the time of peak activity which may explain why no increase in aggression was observed. This suggested that a time course study might be necessary to examine this effect.

EXPERIMENT 2

While PCP may increase aggression in humans, it may not do so in mice. The fact that PCP has opposite initial effects in the two species, sedation in humans and hyperactivity in mice, may account for different effects on aggression. However, if the effect on aggression is tied to a later phase of PCP's activity, it might produce similar effects in the two species. The following study was conducted in order to examine the relationship between the time after administration of PCP and the occurrence of aggressive behavior.

METHOD

Animals

Animals from the previous experiment were used. They were maintained as described above.

Procedure

The testing procedure was similar to that described in Experiment 1. However, instead of five minute test periods, the test continued for three minutes after the first attack if the subject received PCP and for five minutes if vehicle was injected. Tests were terminated if no attack occurred within three or five minutes after the start of the test depending upon the treatment condition.

Residents (n=8) were treated once per week. On the first test day, the resident received an IP injection of vehicle 30 minutes prior to testing. On the second test day, the residents received an IP injection of PCP (3.0 mg/kg) and were tested at 90 and 180 minutes after injection. On the third test day, the residents received an IP injection of PCP (10.0 mg/kg) and were tested at 30, 90 and 180 minutes after injection. The residents were always paired with the same intruder, which resulted in lower levels of attacks throughout the test sequence.

All drugs were prepared at the appropriate concentrations as described in the first experiment and saline was used as the vehicle.

All tests were videotaped as previously described, but only the resident's behavior was measured.

Statistics

Data were analyzed as described in the previous experiment. The data for each time period following PCP were compared to the data obtained during the first three minutes of the test following saline. The data for PCP (3.0 mg/kg) at 30 minutes after injection represent information gathered three weeks earlier from these animals with the same intruders; only data from the first three minutes of the earlier tests were used.

RESULTS

Administration of 3.0 mg/kg of PCP did not significantly affect the frequency of either attacks or offensive sideways at any time after injection. The duration of locomotion was significantly increased at 30 minutes after injection ($p<0.05$) but the frequency was unaffected. While no significant effects were observed at 90 minutes after injection, there were significant decreases from saline levels for locomotor frequency and duration measurements at 180 minutes after injection ($p<0.05$; Fig. 5). PCP also significantly decreased the number of tail rattles at this time ($p<0.05$).

Administration of 10.0 mg/kg of PCP significantly decreased the frequency of both attacks and tail rattles at 30 minutes after injection ($p<0.05$). While a slight recovery was observed for attacks, the number of tail rattles remained significantly depressed at both 90 and 180 minutes after injection ($p<0.05$). The frequencies of offensive sideways threats and locomotion were not significantly affected. Locomotor duration was significantly increased only at 30 minutes after injection ($p<0.05$; see Fig. 5).

DISCUSSION

These results offer further support for the conclusion that PCP does not increase aggression in mice. The test that was conducted at three hours after injection should have corresponded to the time when an increase in aggressive behavior is reported in humans following PCP anesthesia.

This experiment suggests that the lack of an increase in aggression may not be attributed to the hyperactivity which was present in earlier tests because no increase in aggression occurred even after the hyperactivity had subsided. However, the hyperactivity may have induced the decrease in

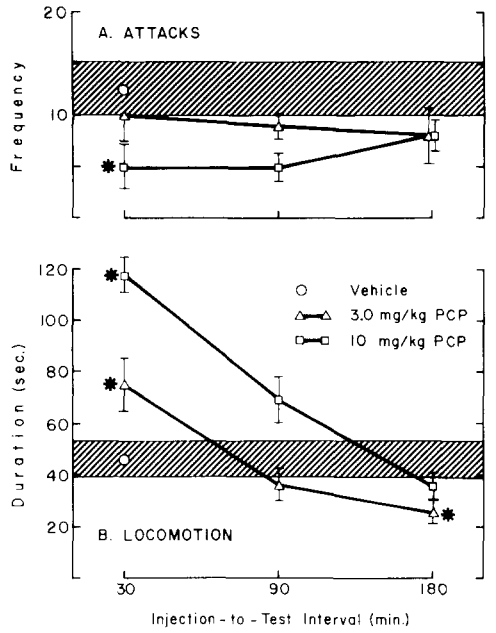

FIG. 5. Effects of phencyclidine on resident mice at various post-injection times. The injection-to-test interval (minutes) is listed along the abscissa. The frequency of behavior for graph A and the duration of behavior for graph B are given along the ordinate. The behaviors depicted are (A) attacks and (B) locomotion. The open circle represents the vehicle control level with the shaded area the ±1 SEM. The triangles represent the 3 mg/kg dose and the squares represent the 10 mg/kg dose of PCP. Bars represent ±1 SEM with *$p<0.05$.

attacks following a high PCP dose (10 mg/kg) since attack levels show a recovery as the hyperactivity subsides. This recovery may result from the drug's effect on motor behavior wearing off.

EXPERIMENT 3

It is possible that an increase in attacks following phencyclidine was not observed because the animals were already performing at a high rate of attack. It has been previously established that attack levels of resident mice are suppressed when they are tested in a neutral cage rather than in their home cage [21,22]. The following study was conducted to determine whether phencyclidine would increase aggression under conditions which generate low attack frequencies.

METHOD

Animals

Twenty male and twenty female albino Swiss-Webster HLA-mice were obtained from Hilltop Laboratories (Scottsdale, PA) at 49 days of age. Each male was housed with a female as described earlier. Twenty male Swiss-Webster mice obtained from our colony were housed in groups of ten per cage. The animals were maintained as in the previous experiments.

Procedure

The testing procedure was similar to that described in the first experiment, except that tests were conducted in both the resident's home cage and in cages identical in size to the home cages, but unfamiliar to both opponents, i.e., neutral.

Residents were tested twice per week. In the first week, the residents received an IP injection of saline vehicle 30 minutes prior to testing in the resident's home cage. During subsequent weeks, tests in the resident's home cage and tests in a neutral cage alternated. Residents received an IP injection of vehicle 30 minutes prior to all home cage tests. Thirty minutes before all neutral cage tests, residents received an IP injection of either vehicle (first and last tests in the series) or phencyclidine HCl (1.0, 3.0, 10.0 mg/kg). Drug treatments were randomly assigned across the second through fourth tests. Residents were paired with a particular intruder only once.

All drugs were prepared as described in the first experiment. Saline was used in vehicle tests. The data were analyzed as described in experiment one.

RESULTS

Only the data from subjects who attacked during the last neutral cage test were included in the analysis. Out of twenty resident mice, seven mice attacked during the first and second saline vehicle tests.

In the home cage, attack, sideways threats and tail rattle did not significantly differ across the test sessions during five consecutive weeks. In the neutral cage, there was a shift in the baseline level of attacks from the first to the second saline vehicle test. The attack frequency in the last test was lower than in the first test; the average between the two tests was computed and the drug tests were compared to this average. Phencyclidine did not significantly affect attack frequency. Phencyclidine also did not significantly affect attack frequency or sideways threats when compared to the last neutral cage test. All doses of phencyclidine significantly decreased tail rattles ($p<0.05$), while sideways threats were not significantly affected when compared to the average score (Table 1). While the average vehicle attack level in the neutral cage was lower than attack frequencies in the home cage, this difference was not significant. During the fifth week of experimentation when the last neutral cage test was conducted, attack levels had become significantly lower than the home cage levels.

The frequency of locomotion did vary across the sequence of home cage tests. Once again there was a shift in the baseline level of the frequency of locomotion in the neutral cage. In comparison to the average of the vehicle tests, phencyclidine (10.0 mg/kg) significantly decreased the frequency of locomotion ($p<0.05$). Both 3.0 and 10.0 mg/kg of phencyclidine increased the duration of locomotor activity (see Table 1).

DISCUSSION

Even when tested under conditions which suppress attack and threat behaviors, phencyclidine did not increase aggressive behavior in mice. While there was a shifting baseline in the attack levels of the neutral cage tests, the residents reliably attacked in the home cage. The drug effects may have been confounded by the decrease in attack behavior during the course of the neutral cage tests. Attacks following phencyclidine treatment were not significantly different from the low levels of attack obtained during the last neutral cage test. Therefore, no dramatic change in aggressive behavior fol-

TABLE 1

EFFECTS OF SALINE VEHICLE ON HOME CAGE TESTS AND PHENCYCLIDINE IN NEUTRAL CAGE TEST ON AGGRESSIVE BEHAVIORS AND LOCOMOTOR ACTIVITY

	Home Cage Vehicle					Neutral Cage Phencyclidine (mg/kg)			
						0*	1.0	3.0	10.0
Behavior Attack (Frequency)	20.9 ± 3.10	19.4 ± 3.15	22.7 ± 2.81	17.4 ± 4.56	15.3 ± 3.29	12.6 ± 1.43	10.7 ± 3.46	12.4 ± 4.09	9.3 ± 6.49
Locomotion (Frequency)	57.3 ± 6.22	59.4 ± 6.25	69.6 ± 5.69	45.0 ± 6.16	50.4 ± 5.63	66.6 ± 5.03	56.1 ± 9.76	71.1 ± 4.76	50.6* ± 6.29
Locomotion (Duration)	67.7 ± 7.97	72.1 ± 8.37	73.0 ± 10.05	46.0* ± 6.58	63.3 ± 8.03	88.2 ± 8.07	80.7 ± 13.70	145.9* ± 13.93	111.1 ± 15.10
Sideways (Frequency)	23.4 ± 3.44	24.1 ± 5.65	22.1 ± 2.85	16.9 ± 5.02	14.0 ± 2.94	12.0 ± 1.47	7.9 ± 2.23	10.0 ± 2.89	12.9 ± 8.44
Tail Rattles (Frequency)	43.6 ± 5.45	40.3 ± 9.57	41.1 ± 5.02	31.9 ± 7.85	35.3 ± 7.54	27.5 ± 3.73	16.4* ± 5.29	14.1* ± 3.83	7.0* ± 6.02

*This represents the average between the two vehicle tests.
†$p<0.05$; N = 7.

lowing phencyclidine treatment occurs even when attack levels are suppressed.

EXPERIMENT 4

This study was conducted to examine the possible mechanism of action of PCP. Dopamine receptor antagonists block PCP-induced rotational behavior in rats [6,10] and PCP-induced stereotypies in monkeys [26], and have been used to treat PCP-induced psychosis in humans [1,27]. Stereotypic behaviors are believed to be mediated through brain dopamine systems [11], and the increase in locomotion following PCP seems to be related to stereotyped circling behavior. A dopamine antagonist should block this effect. It has been demonstrated that 1 mg/kg of either haloperidol or pimozide blocks PCP-induced rotational behavior [6].

PCP also blocks the reuptake of serotonin [29]. PCP has been shown to both increase and decrease serotonin levels [30, 31, 32]. PCP has been postulated to have direct action on serotonin receptors [30]. Therefore, to examine if any of PCP's effects may be mediated by actions on serotonergic systems, a serotonin receptor antagonist, methysergide, was given in combination with PCP.

In previous experiments we determined the effective dose range for haloperidol and methysergide in resident-intruder tests [17]. On the basis of those results, we selected 1 mg/kg of haloperidol and 3 mg/kg of methysergide. The effect of PCP on aggressive behavior was examined after pretreatment with either haloperidol or methysergide.

METHOD

Animals

Twenty-seven Swiss-Webster mice from Charles River Labs. were used; they were maintained as described in the first experiment.

Procedure

For the antagonism study, the test procedure was similar to that described in the first experiment. The resident mice (n=7) were tested twice per week. During the first week, residents received IP injections of vehicle prior to testing. In following weeks, residents received one vehicle and one drug session per week. Either haloperidol (1.0 mg/kg), methysergide (3.0 mg/kg) or saline were given with PCP (10.0 mg/kg) prior to the session.

All tests were videotaped and analyzed as described in the second experiment.

Drugs

Phencyclidine hydrochloride was dissolved in 0.9% saline at a concentration of 1.0 mg/ml and injected 30 minutes prior to testing. Haloperidol was dissolved in a 0.1% lactic acid at a concentration of 0.10 mg/ml and injected one hour prior to testing. Methysergide was dissolved in warm 0.9% saline at a concentration of 0.3 mg/ml and injected 30 minutes prior to testing. The injection volume was 1 ml/100 grams.

RESULTS

Effects of Haloperidol plus PCP on Resident Mice

PCP (10 mg/kg) significantly increased the total duration of locomotor behavior ($p<0.05$) and significantly decreased the frequencies of attacks, sideways threats and tail rattles ($p<0.01$; $p<0.05$; $p<0.02$). Pretreatment with haloperidol (1

mg/kg) did not affect locomotor frequency but the increase in total duration of locomotor behavior usually observed following PCP was decreased and did not significantly differ from saline control levels. Following haloperidol pretreatment, the frequencies of attacks, tail rattles and sideways threats were still significantly decreased from saline levels ($p<0.01$; $p<0.02$; $p<0.02$; see Fig. 6).

Effects of Methysergide plus PCP on Resident Mice

Pretreatment with methysergide (3.0 mg/kg) did not affect locomotor frequency and did not significantly affect the increase in total duration of locomotor behavior following PCP. Methysergide did not antagonize the effects of PCP on aggression; the frequency of attacks, tail rattles and sideways threats were still significantly decreased from saline control levels ($p<0.01$; $p<0.01$; $p<0.02$; see Fig. 6).

DISCUSSION

Pretreatment with haloperidol did decrease PCP-induced hyperactivity when compared to saline levels; yet, this decrease was not significant when compared to PCP-treated subjects. It is possible that a slightly higher dose might have blocked PCP-induced hyperactivity more effectively. Pretreatment with methysergide did not effectively block PCP-induced hyperactivity.

GENERAL DISCUSSION

The present studies demonstrate that PCP does not directly increase aggressive behavior in mice. The only direct effect by PCP on aggressive behavior was a decrease in attacks following 10.0 mg/kg.

An increase in aggression by the non-drugged resident toward the PCP-treated intruder was observed. Indirect drug effects have been observed in a social colony of rhesus monkeys following PCP treatment [23] and in rats following the administration of mescaline using a shock-induced aggression paradigm [25]. Increases in aggression by the dominant animal toward the treated subordinate animal have been reported following THC [18], alcohol [19], amphetamine [13,16] and chlordiazepoxide [13]. By contrast the number of biting attacks decrease toward an animal treated with increasing, anesthetic doses of chlorpromazine and pentobarbital [4]. Indirect drug effects may occur because of an impairment of important components of the defensive behavior by the subordinate animal [18,19], but this impairment does not necessarily increase aggression by the dominant animal.

Increases in aggressive behavior in non-treated mice have been observed following treatment of the intruder mice with LSD [12], methamphetamine [21], methylphenidate [21] and d-amphetamine [14], while cocaine and L-dopa failed to change the non-drugged resident's behavior [14,21]. This may explain why Rewerski *et al.* [24] found an increase in aggressiveness following treatment with PCP since the animals were tested in groups of three with all of the animals receiving the drug.

Environmental factors determine the rates of selected behaviors, including aggression. A comparison of aggressive behavior in mice when tested in a neutral cage versus their home cage demonstrates this phenomenon. Attack and threat behaviors are lower when the animals are tested in the neutral cage [21,22]. These factors may also alter the effect a drug has upon these behaviors.

Alcohol (300 mg/kg) and chlordiazepoxide (5 mg/kg) increase attack and threat behavior in resident mice when tested in a neutral cage [22]. However, these same doses had no effect when the animals were tested in the resident's home cage. This suggests the drug's differential effect may be related to the baseline levels of the behavior and the environmental conditions under which it occurs. Phencyclidine (10 mg/kg) significantly ($p<0.05$) decreased the frequency of locomotion and failed to significantly increase the duration of locomotor activity in the neutral cage. In our prior experiments, this dose reliably produced hyperactivity in all animals when tested in their home cage. The failure of PCP to affect attacks in the neutral cage parallels similar results with amphetamine and cocaine [21].

The PCP-induced hyperactivity may have interfered with a specific effect on aggressive behaviors by disrupting this complex sequence of behaviors. However, the present experiments do not support this interpretation since there was

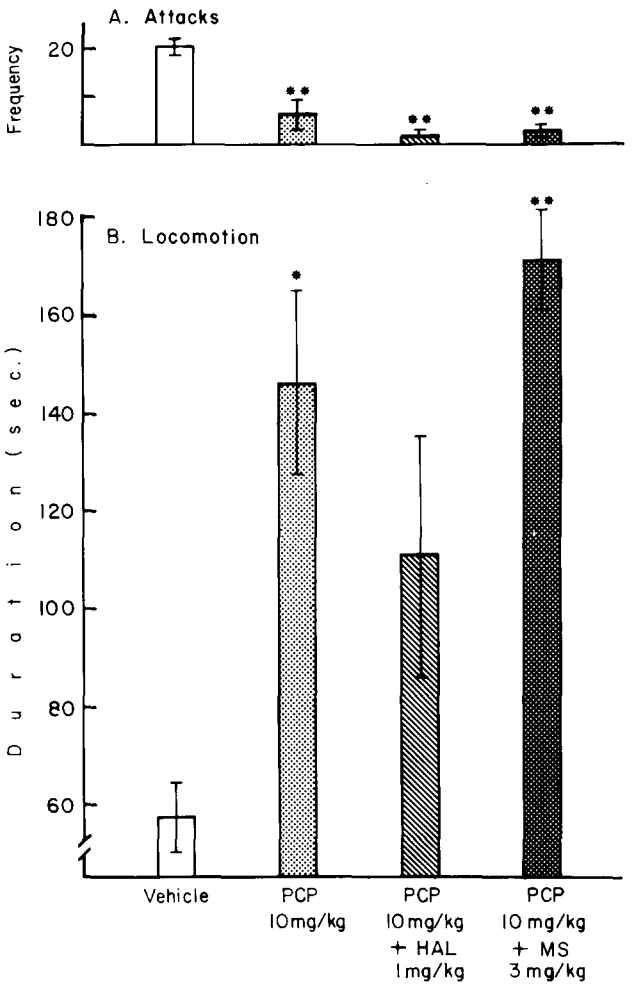

FIG. 6. Effects of combined administration of PCP and haloperidol or methysergide. Drugs and doses are listed along the abscissa with the open bar representing saline, the dotted bar being PCP (10.0 mg/kg), the striped bar being PCP (10.0 mg/kg) plus haloperidol (1 mg/kg) and the cross-hatched bar being PCP (10.0 mg/kg) plus methysergide (3.0 mg/kg). The frequency of behavior for graph A and the duration of behavior for graph B are listed along the ordinate. The behaviors depicted are (A) attacks and (B) locomotion. Bars represent ±1 SEM with $*p<0.05$ and $**p<0.01$.

no increase in aggression at times when the hyperactivity had subsided or when it had been partially blocked by haloperidol.

The partial block of the PCP-induced hyperactivity by haloperidol suggests that this effect may be mediated by dopaminergic systems. In contrast, methysergide did not block this effect, suggesting that serotonergic systems do not appear to be important to PCP-induced hyperactivity. Since haloperidol (1 mg/kg), given by itself, decreased the frequency of attacks, sideways and tail rattles, as well as locomotor behavior, this may account for its inability to reverse PCP's (10 mg/kg) decrease of these behaviors.

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