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The Effects of Haloperidol and Clozapine on PCP- and Amphetamine-Induced Suppression of Social Behavior in the Rat

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STEINPREIS, R. E., J. D. SOKOLOWSKI, A. PAPANIKOLAOU AND J. D. SALAMONE. *The effects of haloperidol and clozapine on PCP- and amphetamine-induced suppression of social behavior in the rat.* PHARMACOL BIOCHEM BEHAV **47**(3) 579–585, 1994.—Previous work has shown that phencyclidine (PCP) and amphetamine decrease social behavior in rats. The purpose of the present study was to determine the effects of the dopamine antagonists clozapine and haloperidol on PCP- and amphetamine-induced changes in rat social behavior. An intruder paradigm was used, in which rats were injected with drug and placed into a stable home colony of three other rats. Social behaviors were recorded for 30 min. Both amphetamine (4.0 mg/kg) and PCP (4.0 mg/kg) substantially reduced social behavior. Haloperidol and clozapine did not produce a general reversal of the effects of amphetamine or PCP on the total number of social behaviors. Nevertheless, 0.025 mg/kg haloperidol did reverse the effects of PCP and amphetamine on some of the specific social behaviors observed (side threats, mounting, crawling under). Clozapine had no effect on reversing the actions of amphetamine on social behavior, but 2.0 mg/kg clozapine did reverse the effect of PCP on side threats and mounting. These results indicate that DA antagonists do not restore normal social behavior in animals treated with PCP or amphetamine, but can reverse some of the effects of PCP or amphetamine on specific social behaviors.

Haloperidol Clozapine PCP Amphetamine Social behavior

PHENCYCLIDINE (PCP) and amphetamine have been shown to produce psychotic reactions in humans that are strikingly similar to schizophrenia (1,3,24,32). Amphetamine has been particularly successful in mimicking the paranoid subtype of schizophrenia (2,8,18), whereas PCP seems to mimic a broader range of schizophrenic symptoms, including the deficit symptoms such as flattened affect (18,19). Research using animals has demonstrated that PCP and amphetamine have psychomotor stimulant properties, and both drugs have been shown to increase locomotor activity (5,6,13,22,36) and induce stereotyped behavior (22,36). PCP and amphetamine, like several other behavioral stimulants, have been shown to have actions on brain dopamine (DA) systems. Evidence indicates that PCP and amphetamine can stimulate DA release or block DA uptake (10,33,37), which leads to an elevation of extracellular levels of DA (25,35,38).

As well as studying the motor effects of PCP and amphetamine, investigators also have employed tests of social behavior to assess the behavioral effects of these drugs. Several studies have shown that PCP and amphetamine can decrease social interactions in animals (4,14,27–32,34,35). Although PCP and amphetamine can reduce social behavior, it is uncertain if antipsychotic drugs, which typically act by blocking DA receptors, are capable of reversing the effects of PCP and amphetamine on rat social behavior. As noted in a review by Miczek (28), several studies with rodents (4,27) and monkeys (29–31) have failed to show that DA antagonists could reverse the effects of amphetamine on social behavior.

The purpose of the present study was to determine if the DA antagonists clozapine or haloperidol (HP) could reverse the effects of PCP or amphetamine on social behavior. Haloperidol is a DA antagonist that is widely used as an antipsychotic drug, and clozapine is an antipsychotic DA antagonist with a unique clinical profile (7,17). Four separate experiments were conducted (PCP and clozapine, PCP and HP, amphetamine and clozapine, amphetamine and HP). For the

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analysis of social behavior, an intruder paradigm was used, in which rats were injected with drug and placed into a stable home colony of three other rats. Previous studies of resident-intruder interactions have shown that high levels of social behavior can be induced by presentation of intruder animals to established resident social groups (28,29).

METHOD

Subjects

A total of 88 male Sprague-Dawley rats weighing between 350–450 g at the start of the experiment were obtained from Harlan Sprague-Dawley. The 34 intruder rats were housed individually in a colony room with a constant temperature of 72°F and a 12 L : 12 D cycle (lights on at 0700 h). The home colony rats were housed in groups of three in identical 26 × 26 × 14 in. cages with Plexiglas walls and wire mesh ceilings and floors. The home colony rats were placed in these chambers at least 3 weeks before the start of the experiments.

Drugs

Haloperidol was obtained from Sigma Chemical Company and clozapine was donated by Sandoz Pharmaceuticals. Both neuroleptics were dissolved in a warm tartaric acid vehicle (0.3%). Amphetamine was obtained from Sigma and PCP was obtained from the National Institute for Drug Abuse (Washington, DC). PCP and amphetamine were dissolved in 0.9 % saline vehicle.

Observations

To assess the ability of clozapine and HP to reverse the effects of PCP and amphetamine on social behavior, an intruder paradigm was employed. Individually housed rats were injected with drug and placed in a stable home colony of three other rats for a 30-min observation period. Two trained observers (blind to the experimental conditions) recorded behaviors shown by the intruder rats (pinning, boxing, chasing, face offs, side threats, crawling under other rats, and mounting), as well as behaviors shown by the resident social group rats towards the intruders (being pinned, being chased, being mounted). To assess interrater reliability, the observers recorded the same behaviors for one PCP-treated rat and one amphetamine-treated rat for 30 min. Pearson product-moment correlations between observers revealed that there were significant correlations for all behaviors ($r > 0.85$).

Experiments

Four separate experiments were conducted to study the ability of clozapine and HP to reverse the effects of PCP and amphetamine. Each experiment included five treatments (vehicle control, PCP or amphetamine alone, PCP or amphetamine plus low dose of DA antagonist, PCP or amphetamine plus high dose of DA antagonist, DA antagonist alone; see Table 1 for doses and conditions of each experiment). In each experiment rats received two IP injections prior to the tests of social behavior. Saline vehicle, PCP, or amphetamine were injected 5 min before testing, tartaric acid vehicle or clozapine were injected 90 min before testing in Experiments 1 and 3, and tartaric acid vehicle or HP were injected 30 min before testing in Experiments 2 and 4. Separate groups of rats were used for each experiment (n = 8–9 per experiment), and in each experiment all rats were exposed to all five treatments in a randomly varied order, with 1 week between each drug treatment. This experimental design was used so that each rat could serve as its own control, which would be more a more sensitive method for detecting small changes in behavior produced by the drug treatments. Each week, the drug-treated intruder rats were placed into a different resident social group.

TABLE 1

THE DRUG COMBINATIONS AND DOSES IN EACH OF THE EXPERIMENTS

Experiment 1
Veh
4.0 mg/kg PCP
4.0 mg/kg PCP and 1.0 mg/kg clozapine
4.0 mg/kg PCP and 2.0 mg/kg clozapine
2.0 mg/kg clozapine
Experiment 2
Veh
4.0 mg/kg PCP
4.0 mg/kg PCP and 0.025 mg/kg haloperidol
4.0 mg/kg PCP and 0.05 mg/kg haloperidol
0.05 mg/kg haloperidol
Experiment 3
Veh
4.0 mg/kg amphetamine
4.0 mg/kg amphetamine and 1.0 mg/kg clozapine
4.0 mg/kg amphetamine and 2.0 mg/kg clozapine
2.0 mg/kg clozapine
Experiment 4
Veh
4.0 mg/kg amphetamine
4.0 mg/kg amphetamine and 0.025 mg/kg haloperidol
4.0 mg/kg amphetamine and 0.05 mg/kg haloperidol
0.05 mg/kg haloperidol

Selection of Drug Doses

Previous work from our laboratory has shown that 4.0 mg/kg PCP was effective in reducing social behavior, and that doses of 1.0–2.0 mg/kg were ineffective (34,35). Pilot work also showed that 4.0 mg/kg amphetamine produced a suppression of social behavior that was comparable to the effects of PCP, and that lower doses of amphetamine (1.0–2.0 mg/kg) were relatively ineffective. Higher doses of amphetamine and PCP were not used because these doses produced a pronounced stereotypy that made the reductions in social behavior difficult to interpret. Doses of clozapine and HP were selected on the basis of pilot studies, which showed that higher doses of clozapine or HP either had no effect on or only served to exacerbate the suppression of social behavior induced by PCP and amphetamine.

Data Analysis

All behavioral data were log transformed and a separate repeated measures ANOVA was done for each behavior in each of the four conditions. After performing the overall ANOVA for each behavioral measure, planned comparisons were conducted in which the overall error term from the ANOVA was used to make four separate comparisons [see (23), pp. 106–118]. The four comparisons in each experiment were as follows:

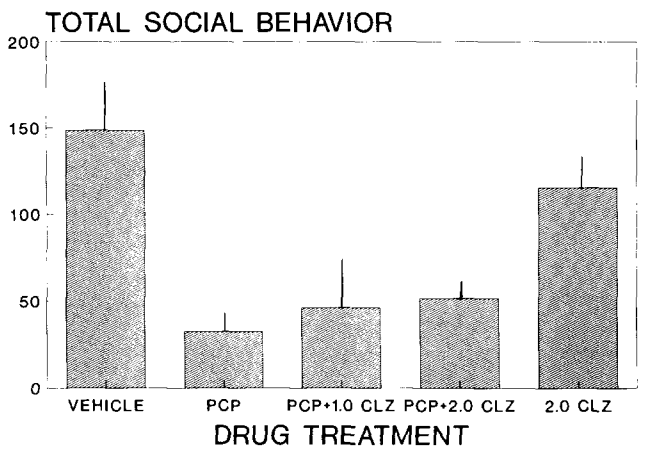

FIG. 1. Mean ± SEM total social behavior score under all five drug treatment conditions in Experiment 1 (CLZ = clozapine).

1. PCP or amphetamine vs. vehicle, to assess the effect of PCP or amphetamine on social behavior,
2. PCP or amphetamine vs. PCP or amphetamine plus low dose of DA antagonist,
3. PCP or amphetamine vs. PCP or amphetamine plus high dose of DA antagonist (comparisons 2 and 3 were used to assess reversal effects), and
4. DA antagonist vs. vehicle, to assess the effect of the DA antagonist alone.

In addition to performing these analyses on each individual behavior, data also were analyzed by calculating a total social behavior score, which was determined for each rat and each condition by adding together all social behaviors initiated by intruder rats (pinning, boxing, chasing, face offs, side threats, crawling under other rats, and mounting). ANOVA and planned comparisons also were used for assessing the effects of the drug treatments on the total social behavior score.

RESULTS

Experiment 1: PCP and Clozapine

The mean ± SEM total social behavior score for each condition is shown in Fig. 1. ANOVA revealed that there was a significant overall treatment effect, $F(4, 32) = 11.6$, $p < 0.01$. Planned comparisons indicated that there was a significant reduction in social behavior produced by PCP relative to vehicle treatment, $F(1, 32) = 11.9$, $p < 0.01$, but no significant differences between PCP alone and PCP plus either dose of clozapine. Clozapine alone did not produce effects that differ from the effects of vehicle. The analyses of individual social behaviors are shown in Table 2. ANOVA revealed a significant overall treatment effect for pinning others, $F(4, 32) = 8.3.$, $p < 0.05$; boxing, $F(4, 32) = 4.6$, $p < 0.05$; chasing others, $F(4, 32) = 12.1$, $p < 0.05$; face offs, $F(4, 32) = 7.2$, $p < 0.05$; side threats, $F(4, 32) = 10.46$, $p < 0.05$; crawl unders, $F(4, 32) = 5.3$, $p < 0.05$; and mounting, $F(4, 32) = 18.8$, $p < 0.05$. Planned comparisons indicated that PCP reduced the frequency of pinning, boxing, chasing, face offs, side threats, crawling under, and mounting relative to the vehicle condition. There was a significant increase in side threats and mounting in the PCP plus 2.0 mg/kg clozapine condition compared to the PCP-alone condition. There were no significant effects of drug treatment on being pinned, being mounted, or being chased.

Experiment 2: PCP and HP

The mean ± SEM total social behavior score for each condition is shown in Fig. 2. ANOVA revealed that there was a significant overall treatment effect ($F(4,28) = 13.04$, $p < 0.01$). Planned comparisons indicated that there was a significant reduction in social behavior produced by PCP relative to vehicle treatment, $F(1, 28) = 33.4$, $p < 0.01$. There were no significant differences between PCP alone and PCP plus either dose of HP, although the comparison between PCP alone and PCP plus 0.025 mg/kg HP did approach statistical significance, $F(1, 28) = 4.0$, $p < 0.1$. The effects of HP alone did not differ from the effects of vehicle. The analyses of individual social behaviors are shown in Table 3. ANOVA revealed a

TABLE 2

EFFECTS OF DRUG TREATMENTS ON SOCIAL BEHAVIOR OBSERVED IN EXPERIMENT 1 (PCP AND CLOZAPINE)

	Vehicle	PCP	PCP + 1.0 Cloz	PCP + 2.0 Cloz	Cloz
Pin	7.2 ± 3.1	0.0 ± 0.0*	2.0 ± 1.9	0.1 ± 0.1	7.1 ± 2.1
Boxing	7.9 ± 2.9	0.1 ± 0.1*	6.4 ± 5.8	1.1 ± 0.7	3.8 ± 1.5
Chase	6.2 ± 1.9	0.1 ± 0.1*	1.0 ± 0.9	0.4 ± 0.2	5.5 ± 1.1
Face off	6.2 ± 1.3	0.4 ± 0.2*	1.3 ± 0.7	1.3 ± 0.7	2.9 ± 0.6
Side threat	61.0 ± 9.9	6.1 ± 1.6*	13.6 ± 6.7	26.0 ± 5.8†	50.4 ± 3.3
Crawl under	23.3 ± 4.4	11.0 ± 3.9*	5.1 ± 2.4	11.1 ± 4.0	16.7 ± 3.6
Mount	36.8 ± 5.3	3.1 ± 1.9*	11.7 ± 10.2	12.8 ± 5.2†	37.8 ± 4.2
Being pinned	4.0 ± 1.7	8.8 ± 3.2	3.6 ± 2.6	4.7 ± 1.9	4.1 ± 1.9
Being chased	12.7 ± 1.9	12.8 ± 3.4	6.2 ± 1.0	12.7 ± 2.4	11.5 ± 2.4
Being mounted	38.5 ± 4.1	41.1 ± 6.4	24.4 ± 2.9	26.1 ± 3.6	30.4 ± 5.6

Values are mean ± SEM.
*$p < 0.05$, different from vehicle.
†$p < 0.05$, different from PCP alone.

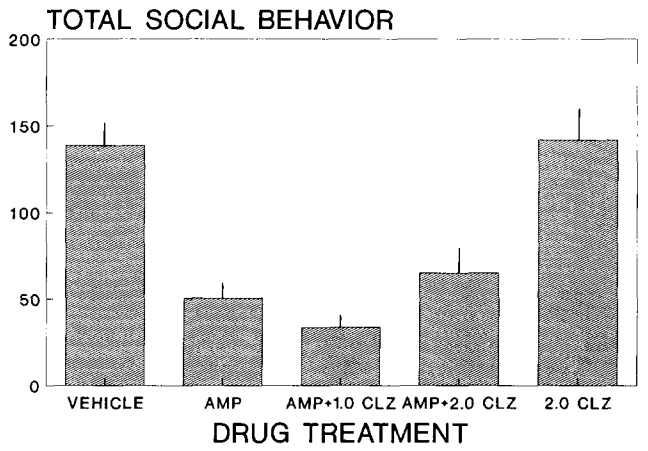

FIG. 2. Mean ± SEM total social behavior score under all five drug treatment conditions in Experiment 2.

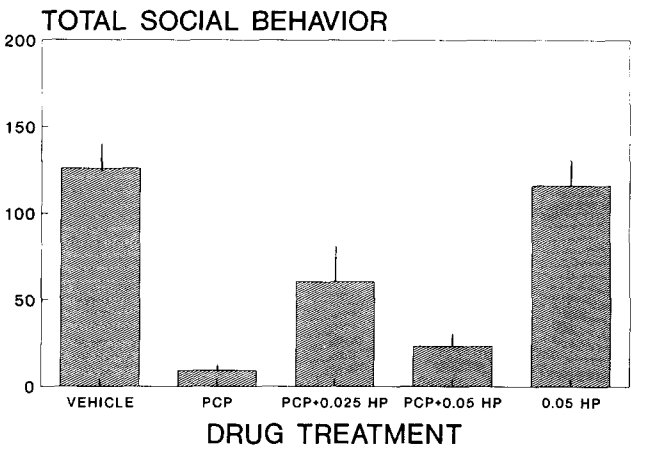

FIG. 3. Mean ± SEM total social behavior score under all five drug treatment conditions in Experiment 3 (AMP = amphetamine, CLZ = clozapine).

significant overall treatment effect for pinning others, $F(4, 28) = 3.5$, $p < 0.05$; boxing, $F(4, 28) = 4.3$, $p < 0.05$; chasing others, $F(4, 28) = 8.8$, $p < 0.05$; face offs, $F(4, 28) = 3.6$, $p < 0.05$; side threats, $F(4, 28) = 7.9$, $p < 0.05$; crawl unders, $F(4, 28) = 7.4$, $p < 0.05$; and mounting, $F(4, 28) = 19.0$, $p < 0.05$. Planned comparisons indicated that PCP reduced the frequency of pinning, boxing, chasing, face offs, side threats, crawling under, and mounting. There was a significant increase in side threats and mounting in the PCP plus 0.025 mg/kg HP condition compared to the PCP-alone condition. There were no significant effects of drug treatment on being pinned, being mounted, or being chased.

Experiment 3: Amphetamine and Clozapine

The mean ± SEM total social behavior score for each condition is shown in Fig. 3. ANOVA revealed that there was a significant overall treatment effect, $F(4, 32) = 14.4$, $p < 0.01$. Planned comparisons indicated that there was a significant reduction in social behavior produced by amphetamine relative to vehicle treatment, $F(1, 32) = 18.8$, $p < 0.01$, but no significant differences between amphetamine alone and amphetamine plus either dose of clozapine. Clozapine alone did not differ from the effects of vehicle. The analyses of individual social behaviors are shown in Table 4. ANOVA revealed a significant overall treatment effect for pinning others, $F(4, 32) = 10.7$, $p < 0.01$; boxing, $F(4, 32) = 5.3$, $p < 0.01$; chasing others, $F(4, 32) = 7.3$, $p < 0.05$; face offs, $F(4, 32) = 12.5$, $p < 0.05$; side threats, $F(4, 32) = 5.5$, $p < 0.05$; crawl unders, $F(4, 32) = 4.6$, $p < 0.05$; and mounting, $F(4, 32) = 20.3$, $p < 0.01$. Planned comparisons indicated that amphetamine reduced the frequency of pinning, boxing, chasing, face offs, side threats, crawling under, and mounting. There were no significant increases in any social behavior in either of the amphetamine plus clozapine conditions compared to the amphetamine-alone condition. There were no significant effects of drug treatment on being pinned, being mounted, or being chased.

Experiment 4: Amphetamine and HP

The mean ± SEM total social behavior score for each condition is shown in Fig. 4. ANOVA revealed that there was a

TABLE 3

EFFECTS OF DRUG TREATMENTS ON SOCIAL BEHAVIOR OBSERVED IN EXPERIMENT 2 (PCP AND HALOPERIDOL)

	Vehicle	PCP	PCP + 0.025 HP	PCP + 0.05 HP	HP
Pin	3.9 ± 1.7	0.0 ± 0.0*	0.8 ± 0.7	0.1 ± 0.1	3.1 ± 0.6
Boxing	3.5 ± 1.3	0.1 ± 0.1*	0.4 ± 0.3	0.0 ± 0.0	5.0 ± 1.7
Chase	7.9 ± 2.1	0.2 ± 0.2*	2.0 ± 1.3	0.2 ± 0.2	5.8 ± 2.1
Face off	5.0 ± 3.9	0.5 ± 0.3*	1.0 ± 0.4	0.3 ± 0.1	0.6 ± 0.1
Side threat	30.1 ± 11.5	1.4 ± 0.9*	23.5 ± 11.7†	3.8 ± 1.8	29.6 ± 10.4
Crawl under	36.2 ± 4.7	5.1 ± 1.7*	16.8 ± 7.3	8.2 ± 3.1	28.6 ± 6.0
Mount	37.1 ± 5.4	1.1 ± 0.3*	15.4 ± 9.2†	5.7 ± 3.3	35.6 ± 6.7
Being pinned	6.1 ± 3.0	0.9 ± 0.7	1.0 ± 0.9	3.6 ± 1.9	5.4 ± 1.9
Being chased	13.4 ± 3.0	5.4 ± 1.9*	6.2 ± 1.9	4.9 ± 1.7	13.6 ± 3.2
Being mounted	36.0 ± 7.8	23.8 ± 2.6	13.0 ± 2.4	14.4 ± 3.4	31.9 ± 4.4

Values are mean ± SEM.
*$p < 0.05$, different from vehicle.
†$p < 0.05$, different from PCP alone.

TABLE 4

EFFECTS OF DRUG TREATMENTS ON SOCIAL BEHAVIOR OBSERVED IN EXPERIMENT 3 (AMPHETAMINE AND CLOZAPINE)

	Vehicle	Amph	Amph + 1.0 Cloz	Amph + 2.0 Cloz	Cloz
Pin	8.0 ± 2.0	0.1 ± 0.1*	2.1 ± 2.0	0.4 ± 0.2	4.7 ± 0.8
Boxing	6.8 ± 2.9	0.6 ± 0.5*	0.4 ± 0.3	2.4 ± 0.9	5.0 ± 1.3
Chase	5.1 ± 1.3	1.7 ± 0.8*	0.0 ± 0.0	1.1 ± 0.7	4.8 ± 1.1
Face off	5.3 ± 2.1	0.5 ± 0.3*	0.6 ± 0.2	1.4 ± 0.5	6.1 ± 0.9
Side threat	49.6 ± 7.1	17.1 ± 3.5*	13.1 ± 3.7	27.0 ± 7.5	48.7 ± 5.4
Crawl under	26.6 ± 4.1	17.6 ± 4.0*	9.3 ± 1.9	14.6 ± 3.6	21.2 ± 3.3
Mount	47.0 ± 5.3	11.6 ± 5.1*	2.8 ± 0.5	16.2 ± 5.3	34.1 ± 2.4
Being pinned	5.1 ± 2.2	0.7 ± 0.4	2.1 ± 0.9	4.5 ± 2.7	6.7 ± 3.3
Being chased	16.8 ± 2.4	10.2 ± 1.5	15.3 ± 2.4	13.2 ± 2.4	12.4 ± 2.4
Being mounted	40.6 ± 5.9	34.2 ± 4.9	32.2 ± 5.3	28.4 ± 4.6	39.7 ± 6.3

Values are mean ± SEM.
*$p < 0.05$, different from vehicle.

significant overall treatment effect, $F(4, 28) = 14.5$, $p < 0.01$. Planned comparisons indicated that there was a significant reduction in social behavior produced by amphetamine relative to vehicle treatment, $F(1, 28) = 37.5$, $p < 0.01$. Although there were no significant differences between amphetamine alone and amphetamine plus either dose of HP, the comparison between amphetamine alone and amphetamine plus 0.025 mg/kg HP did approach statistical significance, $F(1, 28) = 4.1$, $p < 0.1$. The effects of HP alone did not differ from the effects of vehicle. The analyses of individual social behaviors are shown in Table 5. ANOVA revealed a significant overall treatment effect for pinning others, $F(4, 28) = 3.3$, $p < 0.05$; boxing, $F(4, 28) = 3.05$, $p < 0.05$; chasing others, $F(4, 28) = 10.3$, $p < 0.05$; face offs, $F(4, 28) = 5.8$, $p < 0.05$; side threats, $F(4, 28) = 11.4$, $p < 0.01$; crawl unders, $F(4, 28) = 7.2$, $p < 0.05$; and mounting, $F(4, 28) = 10.9$, $p < 0.05$. Planned comparisons indicated that amphetamine reduced the frequency of pinning, chasing, side threats, crawling under, and mounting. There was a significant increase in side threats and crawl unders in the amphetamine plus 0.025 HP condition compared to the amphetamine-alone condition. There were no significant effects of drug treatment on being pinned, being mounted, or being chased.

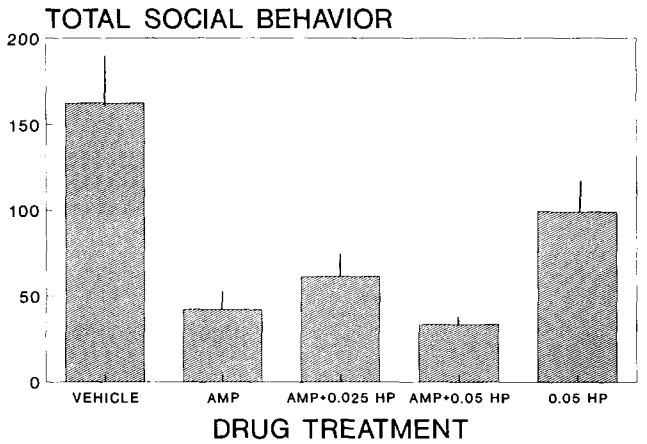

FIG. 4. Mean ± SEM total social behavior score under all five drug treatment conditions in Experiment 4 (AMP = amphetamine).

DISCUSSION

Amphetamine and PCP produced substantial reductions in a variety of social behaviors shown by intruder rats, including pinning, boxing, chasing, face offs, side threats, crawling under other rats, and mounting. These findings are consistent with previous results showing that amphetamine (4,14) and PCP (34,35) can reduce social behavior in rats. In general, PCP and amphetamine did not affect the behaviors directed towards the intruders by rats in the resident social group, which is consistent with previous studies on the effects of PCP in a similar behavioral paradigm (35). Coadministration of amphetamine and PCP with either clozapine or HP did not restore normal social behavior. As measured by the total social behavior score, there were no cases in which clozapine or HP significantly reversed the effects of amphetamine or PCP.

Despite the fact that clozapine and HP did not restore the overall pattern of normal social behavior in rats treated with PCP or amphetamine, there were some instances in which clozapine and HP did reverse the effects of PCP or amphetamine on specific social behaviors. The 2.0 mg/kg dose of clozapine significantly reversed the effect of PCP on side threats and mounting behavior. HP injected at a dose of 0.025 mg/kg significantly reversed the effects of PCP on side threats and mounting, and also reversed the effects of amphetamine on side threats and crawl unders. It is important to emphasize that there were some consistent patterns shown by these results. The same dose of DA antagonist was successful in each of the cases in which a successful reversal was reported (2.0 mg/kg for clozapine, 0.025 mg/kg for HP; see Tables 2–5).

The effects of PCP on mounting were reversed by both clozapine and HP. The suppressive effects of PCP and amphetamine on side threats were particularly susceptible to reversal with DA antagonists, with the only exception being the inability of clozapine to reverse the effect of amphetamine. The three behaviors for which some reversal effects were shown (i.e., side threats, mounting, and crawling under) were also the three behaviors that were most frequently initiated by intruder rats.

Overall, the present studies offer a mixed pattern of results.

TABLE 5

EFFECTS OF DRUG TREATMENTS ON SOCIAL BEHAVIOR OBSERVED IN EXPERIMENT 4 (AMPHETAMINE AND HP)

	Vehicle	Amph	Amph + 0.025 HP	Amph + 0.05 HP	HP
Pin	4.6 ± 3.5	0.1 ± 0.1*	0.4 ± 0.3	0.0 ± 0.0	3.1 ± 1.0
Boxing	1.4 ± 0.9	0.9 ± 0.5	0.6 ± 0.5	0.2 ± 0.1	3.6 ± 1.1
Chase	4.8 ± 1.2	0.2 ± 0.2*	0.9 ± 0.6	0.1 ± 0.1	4.3 ± 1.8
Face off	2.1 ± 0.8	0.8 ± 0.7	0.0 ± 0.0	0.0 ± 0.0	3.4 ± 0.7
Side threat	32.9 ± 10.6	4.5 ± 1.9*	18.2 ± 7.9†	6.8 ± 2.2	23.9 ± 7.9
Crawl under	35.0 ± 5.5	12.2 ± 1.9*	23.7 ± 5.2†	16.0 ± 4.8	26.0 ± 4.7
Mount	52.3 ± 8.7	14.1 ± 9.8*	17.5 ± 5.4	8.2 ± 3.0	30.8 ± 6.9
Being pinned	3.1 ± 1.7	2.9 ± 0.9	0.0 ± 0.0	0.5 ± 4.6	4.7 ± 2.8
Being chased	9.8 ± 2.6	11.5 ± 3.8	8.1 ± 1.1	11.9 ± 2.8	8.0 ± 1.2
Being mounted	27.1 ± 5.7	28.5 ± 5.8	25.0 ± 3.1	29.0 ± 4.7	33.1 ± 8.6

Values are mean ± SEM.
*$p < 0.05$, different from vehicle.
†$p < 0.05$, different from amphetamine alone.

On the one hand, there was not a general restoration of normal social behavior produced by the DA antagonists. This finding is consistent with previous research showing that HP did not restore normal social interactions that were altered by administration of amphetamine in monkeys (29–31). Previous work with rats also has shown that HP did not reverse the amphetamine-induced suppression of social play behavior in juveniles (4). Nevertheless, some of the effects of PCP and amphetamine on individual social behaviors in the present study were reversed by coaministration of DA antagonists. The doses of HP used in the present study (0.025–0.05 mg/kg) were lower than those used in most studies. For the four cases in which HP did produce reversal effects on individual behavioral measures, these effects were only seen at the lower dose of HP, and in each case the higher dose of HP was ineffective. In addition, it may be that some specific behaviors (e.g., side threats, mounting, or crawling under) are relatively more useful than other behaviors for detecting the ability of DA antagonists to reverse the effects of PCP or amphetamine. It is possible that reliance on composite scores that include all social behaviors, or the use of one particular social behavior such as a pin (4), makes it difficult to detect specific changes observed only in a few of the social behaviors. Thus, there may be some advantages to analyzing social behavior data in terms of each individual behavior type.

It is important to consider why it is difficult to produce a general reversal of the effects of amphetamine and PCP on social behavior with coadministration of DA antagonists. Possibly, neurotransmitters other than DA mediate the effects of amphetamine and PCP on social behavior. Amphetamine has actions on other catecholamines as well as DA, and PCP has a wide variety of pharmacological actions, including effects as a noncompetitive NMDA antagonist (20,21). Another reason for the general lack of reversal of the effects of amphetamine and PCP on social behavior may be that these effects are due to actions on subtypes of DA receptors that are not adequately antagonized by low doses of clozapine and HP. Acute administration of DA antagonists was employed in the present study, and it is possible that chronic administration, which is typically used for antipsychotic treatments in humans, would have been more effective. It also is possible that normal social behavior depends upon a delicately balanced level of DA transmission. Evidence indicates that social behavior can be disrupted either by overstimulating or blocking dopaminergic transmission (28). Thus, it appears that there is a moderate level of dopaminergic transmission that is necessary for the performance of normal social behavior. Clozapine and HP may have only reversed a small subset of social behaviors in amphetamine- or PCP-treated rats because combinations of agonists and antagonists do not precisely restore the exact balance of dopaminergic transmission upon which the execution of social behavior depends. In this respect, social behavior effects may be quite different from some of the motor effects of stimulant drugs, which are relatively easy to reverse with DA antagonists (27,28).

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REFERENCES

1. Angrist, B.; Gershon, S. The phenomenology of experimentally induced amphetamine psychosis—preliminary observations. Biol. Psychiatry 2:95–107; 1970.
2. Angrist, B.; Lee, H. K.; Gershon, S. The antagonism of amphetamine-induced symptomology by a neuroleptic. Am. J. Psychiatry 131:817–819; 1974.
3. Ban, T. A.; Lohrenz, J. J.; Lehmann, H. E. Observations on the action of Sernyl—A new psychotic drug. Can. Psychiatr. Assn. J. 6:150–157; 1961.
4. Beatty, W. M.; Costelo, K. B.; Berry, S. L. Suppression of play fighting by amphetamine: Effects of catecholamine antagonists, agonists and synthesis inhibitors. Pharmacol. Biochem. Behav. 20:747–755; 1984.
5. Carlson, A. Amphetamine and brain catecholamines. In: Costa,

E.; Garattini, S., eds. Amphetamine and related compounds. New York: Raven Press; 1970.
6. Castellani, S.; Adams, P. M. Acute and chronic phencyclidine effects on locomotor activity, stereotypy, and ataxia in rats. Eur. J. Pharmacol. 73:143–154; 1981.
7. Chouinard, G.; Annable, L. Clozapine in the treatment of newly schizophrenic patients: A pilot study. J. Clin. Pharmacol. 16: 289; 1976.
8. Connell, P. H. Amphetamine psychosis. London: Chapman and Hill; 1958.
9. Costa, E.; Groppetti, A.; Naimzada, M. K. Effects of amphetamine on the turnover rate of brain catecholamines and motor activity. Br. J. Pharmacol. 44:742–751; 1972.
10. Coyle, J. T.; Snyder, S. H. Catecholamine uptake by synaptosomes in homogenates of rat brain: Stereospecificity in different areas. J. Pharmacol. Exp. Ther. 170:221–231; 1969.
11. Davis, M. Cocaine: Excitatory effects on sensorimotor reactivity measured with acoustic startle. Psychopharmacology (Berlin) 86: 31–36; 1985.
12. Ellison, G. D.; Eison, M. S. Continuous amphetamine intoxication: An animal model of acute psychotic episode. Psychol. Med. 13:751–761; 1983.
13. Freed, W. J.; Weinberger, D. R.; Bing, L. A.; Wyatt, R. J. Neuropharmacological studies of phencyclidine (PCP)-induced behavioral stimulation in mice. Psychopharmacology (Berlin) 71: 291–297; 1980.
14. Gambill, J. D.; Kornetsky, C. Effects of chronic *d*-amphetamine on social behavior of the rat: Implications for an animal model of paranoid schizophrenia. Psychopharmacology (Berlin) 50:215–223; 1976.
15. Giannini, A. J.; Loiselle, R. J.; Price, W. A.; Giannini, M. C. Chlorpromazine vs. meperidine in the treatment of phencyclidine psychosis. J Clin. Psychiatry 46:52–54; 1985.
16. Groves, P. M.; Rebec, G. V. Biochemistry and behavior: Some central actions of amphetamines and antipsychotic drugs. Palo Alto, CA: Annual Reviews; 1976. (Annu. Rev. Psychol., vol. 27.)
17. Honigfield, G.; Patin, J.; Singer, J. Clozapine: Antipsychotic activity in treatment-resistant schizophrenics. Adv. Ther. 1:77; 1984.
18. Janowski, D. S.; Risch, C. Amphetamine psychosis and psychotic symptoms. Psychopharmacology (Berlin) 65:73–77; 1979.
19. Javitt, D. C. Negative schizophrenic symptomology and the PCP (phencyclidine) model of schizophrenic. Hillside J. Clin. Psychiatry 9:12–35; 1987.
20. Jones, S. M.; Snell, L. D.; Johnson, K. M. Inhibition by phencyclidine of excitatory amino acid-stimulated release of neurotransmitter in the nucleus accumbens. Neuropharmacology 26:173–179; 1987.
21. Jones, S. M.; Snell, L. D.; Johnson, K. M. Phencyclidine selectively inhibits N-methyl-D-aspartate-induced hippocampal [3H] norepinephrine release. J. Pharmacol. Exp. Ther. 240:492–497; 1987.
22. Kelly, P. H.; Seviour, P. W.; Iversen, S. D. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and the corpus striatum. Brain Res. 94:507–522; 1975.
23. Keppel, G. Design and analysis: A researchers handbook. Englewood Cliffs, NJ: Prentice Hall; 1982.
24. Luisada, P. V. The phencyclidine psychosis: Phenomenology and treatment. Natl. Inst. Drug Abuse Res. Monogr. Ser. 21:241–253; 1978.
25. McCullough, L. D.; Salamone, J. D. Increases in extracellular dopamine and locomotor activity after direct infusion of phencyclidine into the nucleus accumbens. Brain Res. 577:1–9; 1992.
26. Meltzer, H. Y.; Sturgeon, R. D.; Simonovic, M.; Fessler, R. G. Phencyclidine as an indirect dopamine agonist. In: Domino, E.F., ed, PCP (phencyclidine): Historical and current perspectives. Ann Arbor: MI: NPP Books; 1979:207–242.
27. Miczek, K. A. Differential antagonism of d-amphetamine effects on motor activity and agonistic behavior in mice. Soc. Neurosci. Abstr. 7:343; 1981.
28. Miczek, K. A. The psychopharmacology of aggression. In: Iversen, L. L.; Iversen, S. D.; Snyder, S. H., eds. Handbook of psychopharmacology. New York: Plenum Press; 1987:183–328.
29. Miczek, K. A.; Yoshimura, H. Disruption of primate social behavior by d-amphetamine and cocaine: Differential antagonism by antipsychotics. Psychopharmacology (Berlin) 76:163–171; 1982.
30. Schiorring, E. Changes in individual and social behavior induced by amphetamine and related compounds in monkeys and man. In: Ellinwood, E. H.; Kilbey, M., eds, Cocaine and other stimulants. New York: Plenum Press; 1977:481–522.
31. Scraggs, P. R.; Ridley, R. M. The effects of dopamine and noradrenaline blockade on amphetamine-induced behavior in the marmoset. Psychopharmacology (Berlin) 62:41–45; 1979.
32. Segal, D. S.; Janowsky, D. S. Psychostimulant-induced behavioral effects: Possible models of schizophrenia. In: Lipton, M. A.; DiMascio, A.; Killam, K. F., eds. Psychopharmacology: A generation of progress. New York: Raven Press; 1978:1113–1123.
33. Smith, R. C.; Meltzer, H. Y.; Arora, R. C.; Davis, J. M. Effects of phencyclidine on ^{3}H-catecholamines and ^{3}H-serotonin uptake in synaptosomal preparations from rat brain. Biochem. Pharmacol. 26:1435–1439; 1977.
34. Steinpreis, R. E.; Longyhore, C.; Salamone, J. D. Behavioral characterization of PCP-induced changes in rat social behavior: A possible model of schizophrenic symptoms. Soc. Neurosci Abstr. 16:582; 1990.
35. Steinpreis, R. E.; Salamone, J. D. The role of nucleus accumbens dopamine in the neurochemical and behavioral effects of phencyclidine: A microdialysis and behavioral study. Brain Res. 612: 263–270; 1993.
36. Sturgeon, R. D.; Fessler, R. G.; Meltzer, H. Y. Behavioral rating scales for assessing phencyclidine-induced locomotor activity, stereotyped behavior and ataxia in rats. Eur. J. Pharmacol. 59:169–179; 1979.
37. Vickroy, T. W.; Johnson, K. M. Similar dopamine-releasing effects of phencyclidine and nonamphetamine stimulants in striatal slices. J. Pharmacol. Exp. Ther. 223:669–674; 1982.
38. Zetterstrom, T.; Sharp, T.; Marsden, C. A.; Ungerstedt, U. In vivo measurements of dopamine and its metabolites by intracerebral dialysis: Changes after d-amphetamine. J. Neurochem. 41: 1769–1773; 1983.