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The Effects of Atypical Antipsychotics and Phencyclidine (PCP) on Rotorod Performance

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STEINPREIS, R. E., K. A. ANDERS, E. M. BRANDA AND C. K. KRUSCHEL. *The effects of antipsychotics and phencyclidine (PCP) on rotorod performance.* PHARMACOL BIOCHEM BEHAV **63**(3) 387–394, 1999.—A series of six experiments were conducted to determine the effects of haloperidol, clozapine, olanzapine, and phencyclidine (PCP) on rotorod performance. Rodents were trained to walk on a rotorod to avoid a mild shock to a criterion of 20 rpm for 3 min. None of the vehicles of any of these drugs disrupted rotorod performance. Haloperidol disrupted rotorod performance at doses of 0.03, 0.1, and 0.3 mg/kg, and olanzapine disrupted rotorod performance at doses of 3.0 and 10.0 mg/kg. Clozapine produced a much milder disruption across all three doses (3.0, 10.0, and 30.0 mg/kg). PCP produced a consistent and severe disruption of rotorod performance at doses of 4.0 and 6.0 mg/kg, but not at a dose of 2.0 mg/kg. Twenty-four hours postinjection there were no residual PCP effects on rotorod performance. Coadministration of either haloperidol or olanzapine with PCP did not reverse PCP-induced disruption in rotorod performance, while clozapine produced a partial reversal at only one dose. These findings indicate that olanzapine functions similarly to classic antipsychotics with respect to their effects on locomotion and balance. © 1999 Elsevier Science Inc.

Haloperidol Clozapine Olanzapine PCP Locomotion Rotorod

THE development of atypical antipsychotic treatments that do not produce extrapyramidal side effects and treat both the positive and negative symptoms of schizophrenia has been a crucial goal of behavioral pharmacology for the past several decades. In the early 1970s, clozapine was introduced as the first atypical antipsychotic resulting in few, if any, extrapyramidal side effects. However, clozapine produced potentially lethal agranulocytosis in some patients. Very recently, Eli Lilly Laboratories introduced olanzapine, which reportedly has similar clinical outcomes to clozapine, but does not produce agranulocytosis. Olanzapine is a thiobenzodiazepine that is structurally similar to clozapine, and research has demonstrated comparable pharmacological effects to clozapine.

We have spent a great deal of time examining the effects of classic vs. atypical antipsychotic drugs in rodent social interaction models (15,26), in hopes that such a paradigm would more closely model the negative symptoms of schizophrenia (e.g., social withdrawal and flattened affect). We have repeatedly chosen phencyclidine (PCP) as the psychotomimetic to model schizophrenia because it is capable of producing a psychosis that is virtually indistinguishable from an acute psychotic reaction in schizophrenia (12), and it exacerbates existing psychosis in schizophrenics (5,6,13). Along with others, we have argued that the search for atypical antipsychotics should turn away from the locomotor components when examining the properties of a potential compound to treat schizophrenia (27). However, concerns have been raised that the results of these social interaction studies are simply an artifact of locomotor dysfunction (i.e., the rodents might interact if they were physically capable of engaging in social interactions, but the drugs are either producing hypermotility or incoordination). PCP does have some of the properties of a motor stimulant. PCP produces locomotor activity (11), stereotyped behavior and ataxia (23), head bobbing, backward walking, circling, and head swaying (29). Additionally, PCP has been shown to disrupt rotorod performance (22). Also, although it is possible to measure the movement in an open field during social interaction studies using photo beams, the movement of the undrugged

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conspecifics is also detected. Alternately, the number of quadrant crossings can be recorded by a human observer, but this measure produces a figure that may be an artifact of the undrugged conspecifics chasing the injected animal or vice versa. To circumvent this measurement problem, we decided to use the same dose ranges of haloperidol, clozapine, olanzapine, and PCP that we have previously employed in our social interaction studies (26,28) and measure their effects on locomotion and balance using a rotorod. We also wanted to measure the capacity of all three antipsychotics to reverse PCP-induced disruption in rotorod performance. Our initial research studies did not rule out the possibility that at the doses of PCP we were using effected locomotor functioning and balance. We were well aware that 6.0 mg/kg of PCP would produce head weaving and locomotor functioning. Our primary objective for the present study was to utilize the same doses and drug combinations we had used in our social interaction studies.

We also deliberately selected the rotorod to index locomotor functioning and balance, rather than an individualized measurement from the open field for three reasons. First, open-field indices vary drastically from one laboratory to another, and the variety of arenas and indices used have been outlined in the literature (30). For example, in our laboratory we use three different-sized open-field observation chambers (i.e., one for the intruder paradigm, another for measuring conditioned place preference, and a third to measure behavioral effects of in vivo dialysis subjects). These open fields have different shapes (e.g., square vs. rectangular), different tactile cues (e.g., wire mesh vs. shavings), different dimensions, and different visual cues. The development of these different open fields was driven by the literature, the hypothesis in question, and the physical limitations of the equipment being used (i.e., the metal tether for dialysis studies). However, the rotorod is a commercially developed apparatus with defined training components, and has a very limited risk of human judgment error. We are not suggesting that open-field studies are obsolete any more than we are suggesting that human observation of motor dysfunction is arcane. Rather, we suggest that the rotorod may have more potential for standardizing measurement across laboratories.

Second, the learning component of the rotorod paradigm may serve to level the playing field in terms of beginning data collection at a point in which all rats are behaving in the same way. For example, some rats may be more prone than others to freezing when initially placed in the open field for social interaction studies. Such individual differences may be a confounding variable, especially when a rat is being placed in this environment for limited periods of time. Although it is helpful to habituate the rat to the open field or even test a drug while the rat is in its home cage, there is no way of predicting what the rat would normally be expected to do during a given period of time. In contrast, the learning component of the rotorod paradigm ensures that all rats are trained to criterion during the brief 7-day training period. Thus, the researcher knows exactly what rats will do when placed on the rotating rod by test day (e.g., rats will attempt to walk on the rod to avoid shock if they are able to). On the rotorod, the rat will either fall or walk. In contrast, in the open field rats may freeze, explore the edges, rear, display drug-induced behavior, engage in social interactions, limit the physical area they occupy (e.g., as with higher or repeated doses of amphetamine), or groom themselves. These are the issues that we struggled to deal with during our initial social interaction studies.

Third, we wanted to underscore the principle that regardless of drug state or even harness/tether state, an animal may explore an open field quite differently when it is alone vs. accompanied by another conspecific. It would be misleading to make a direct comparison from an individual rat's behavior in an open field (i.e., light breaks, quadrant crossings, instances of head weaving, etc.) to our social interaction studies because the conspecifics confound locomotor data. Therefore, we selected the use of an entirely different paradigm (e.g., the rotorod) to index the locomotor and balancing effects of these same drugs and doses.

METHOD

Subjects

A total of 50 male Sprague–Dawley rats (Harlan–Sprague–Dawley, Madison, WI) were used. Each rat weighed between 300–350 g at the beginning of the experiment. All of the rats were housed individually in a colony room with an ambient temperature of 20°C and a 12 L:12 D cycle (lights on at 0700 h). All data was collected during the lights on cycle. Standard lab chow and water were available ad lib.

Drugs

The PCP was obtained from the National Institute On Drug Abuse (Rockville, MD) and was dissolved in a 0.9% saline vehicle. The olanzapine was donated by Eli Lilly Laboratories (West Lafayette, IN) and was dissolved in deionized water. The clozapine was donated by Sandoz (St. Louis, MO) and was dissolved in a 3% tartaric acid vehicle. The haloperidol was purchased from Sigma Chemical Co. (St. Louis, MO), and was also dissolved in a 3% tartaric acid vehicle. All drugs were injected intraperitoneally. Doses of PCP, haloperidol, and clozapine were selected from previous social interaction studies in our laboratory. The dose range for olanzapine was based on pilot data from our laboratory that indicated that these doses were most likely to attenuate PCP-induced social withdrawl.

Apparatus

The rotorod was purchased from Omnitech (Columbus, OH). This apparatus (49 × 48 × 58 cm) consisted of four chambers separated by round, black, opaque flanges (30 cm high). In the center of each chamber was an acrylic rotating rod, which extended 11 cm across the chamber and was 7 cm in diameter. The rod was elevated 40 cm above a shock grid. When the grid was activated and a rat stepped down onto it a mild shock of 1 mA was delivered, producing aversive conditioning. The rod could be set to rotate at variable speeds to facilitate training. The data was collected by electromechanical counters.

Procedure

The rats were trained to run on the rotorod using an eight phase schedule. This was a modification of a procedure used by other researchers (1,2). Training took place over the course of 7 days. To complete phase 1 of the training schedule each of the rats had to perch on the stationary rod for 120 s. The rats were given five trials to complete each of the eight phases. The shock grid was reset after each trial. If the task was completed before the fifth trial, the rat continued on to the next phase. During the second phase, the rats were trained to walk on the rotorod at 3 rpm for 180 s. In phase 3, the speed was increased to 10 rpm for 30 s. In phase 4, the rats main-

tained the 10 rpm speed, but the time increment was increased to 120 s. In phase 5, they were maintained at 15 rpm for 60 s. In phase 6, the rats maintained the 15 rpm speed, but the time increment was increased to 120 s. During the last 2 days of the training schedule, a constant speed of 20 rpm for 60 and 120 s was maintained. This training schedule is summarized in Table 1. Four of the 50 rats were unable to master the eight phases of training and were eliminated from the rest of the study. Therefore, the data analysis was conducted on 46 rats.

Testing began once the eight phases of rotorod training were completed. Every test was run at phase 4 conditions (i.e., 120 s at 10 rpm). The purpose of day 1 was to determine if any of the control procedures could disrupt rotorod performance. Therefore, the rats were randomly divided into five groups, receiving either haloperidol vehicle, clozapine vehicle, olanzapine vehicle, PCP vehicle, or no injection. The rats were then tested on the rotorod 1 h postinjection, and were given five opportunities to complete a 120-s run on the rotorod at 10 rpm. Testing was completed for day 1 if the rats remained on the rotorod for 120 s before all five trials were completed.

The purpose of day 2 of testing was to compare the effects of the control groups to the dose response curve for PCP. Accordingly, the rats were divided into two groups. Group 1 consisted of haloperidol vehicle, clozapine vehicle, olanzapine vehicle, PCP vehicle, and a no injection group. Group 2 consisted of a PCP vehicle, and either 2.0, 4.0, or 6.0 mg/kg doses of PCP. Each rat was once again given five trials to complete a 120-s run on the rotorod. As before, if the rat completed the 120-s run before the five trials were completed, it was finished for the day. The purpose of day 3 of testing was to determine if there were any residual effects of PCP 24 h postinjection. Therefore, all 46 rats were tested 24 h postinjection.

The purpose of day 4 of testing was to determine the effects of the antipsychotic drugs on rotorod performance. Rats were assigned to an antipsychotic group based on their having previously received the vehicle for that group. Therefore, rats who had previously received haloperidol vehicle received either 0.03, 0.1, or 0.3 mg/kg of haloperidol. Rats who had previously received clozapine vehicle received either 3.0, 10.0, or 30.0 mg/kg of clozapine. And finally, rats who had previously received olanzapine vehicle received either 1.0, 3.0, or 10.0 mg/kg of olanzapine. All the rats were tested at phase 4 on the rotorod 1 h postinjection. On day 5, all of the 46 rats were tested for any residual effects of the drugs administered on day 4.

The purpose of day 6 of testing was to determine which, if any, of the antipsychotics could reverse PCP-induced disruption of rotorod performance. On day 6 each rat received the same dose of antipsychotic it had received on day 4. One hour later each rat received an injection of 6.0 mg/kg PCP. Five minutes after the rats received PCP, they were run on phase 4 of the rotorod.

TABLE 1
TRAINING AND TESTING SCHEDULE

Phase of Training	Revolutions Per Minute	Seconds on Rotorod
1	0	120
2	3	180
3	10	30
4	10	120
5	15	60
6	15	120
7	20	60
8	20	120

Test day 1: Following training, rats were divided into five groups: haloperidol vehicle, clozapine vehicle, olanzapine vehicle, PCP vehicle, or no injection. One hour postinjection they were placed on the rotorod and given five opportunities to perform at the phase 4 level of training.

Test day 2: Rats were placed into either the vehicle group (i.e., receiving the same vehicles as they had on test day 1) or in the PCP dose–response curve group (i.e., receiving either PCP vehicle or 2.0, 4.0, or 6.0 mg/kg of PCP. They were placed on the rotorod and given five opportunities to perform at the phase 4 level of training.

Test day 3: All rats were placed on the rotorod 24 h postinjection and given five opportunities to perform at the phase 4 level of training.

Test day 4: Rats were assigned to one of these nine drug/dose groups: haloperidol at 0.03, 0.1, or 0.3 mg/kg; clozapine at 3.0, 10.0, or 30.0 mg/kg; or olanzapine at 1.0, 3.0, or 10.0 mg/kg. One hour postinjection they were placed on the rotorod and given five opportunities to perform at the phase 4 level of training.

Test day 5: All rats were placed on the rotorod 24 h postinjection and given five opportunities to perform at the phase 4 level of training.

Test day 6: Rats were administered the same drug/dose they received on test day 4. One hour later they were injected within 6.0 mg/kg PCP and 5 mis after that second injection, the rats were given five opportunities to perform at the phase 4 level of training.

RESULTS

All behavioral data was log transformed, and a separate between-groups ANOVA was performed for each of the experiments.

Experiment 1: The Effects of Vehicle Injections on Rotorod Performance

The purpose of the first experiment was to determine if an injection of the vehicles of the target compounds would produce a disruption in rotorod performance. Most of the rats received a single intraperitoneal injection of either 3% tartaric acid, deionized water, or 0.9% saline solution (e.g., the vehicles of haloperidol, clozapine, olanzapine, and PCP, respectively). The remaining group of rats were not injected at all, but were taken out of their home cages and handled for about 1 min. The rats in all groups were drug naive for this first experiment. One hour later, the rats who had received antipsychotic vehicle or no injection were tested on the rotorod. The rats in the group that received the PCP vehicle were tested on the rotorod 5 min after injection. As revealed in the remaining experiments, the regimen used in this first experiment was set up to mirror the time course of administration and maximal behavioral effects seen in the later experiments (Fig. 1).

The index used was the number of trials it took for the rats to successfully stay on the rotorod for 120 s at 10 rpm. The results were analyzed using a between-groups ANOVA, and there were no significant differences between the vehicle treatment group and the group of rats that received no injection, $F(4, 19) = 0.84$, $p > 0.5$. None of the rats in the first experiment had difficulty performing on the rotorod.

Experiment 2: The Dose–Response Curve For PCP-Induced Disruption of Rotorod Performance

The purpose of the second experiment was to determine the dose range of PCP-induced disruption of rotorod performance. The doses were selected based on our studies of PCP

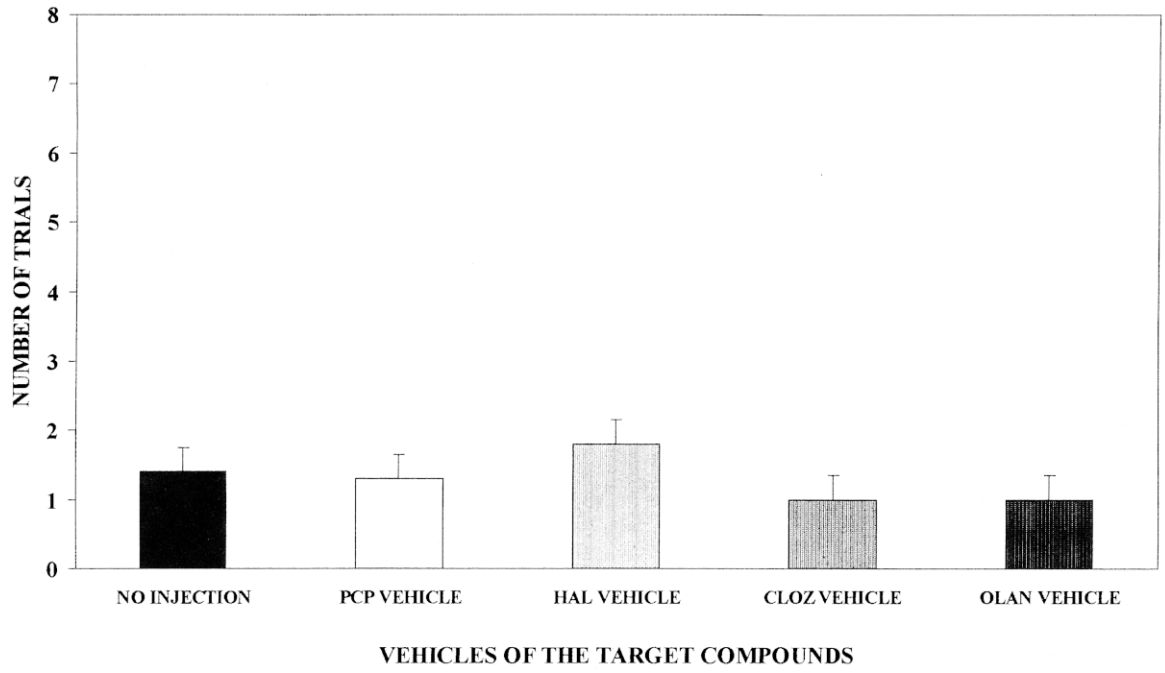

FIG. 1. Mean (±SEM) number of trials subjects took to successfully remain on the rotorod for 120 s at 10 rmp 5 min postinjection.

disruption of social interaction in both the intruder paradigm (7,22) and the tether paradigm (14). Drug naive rats received a single intraperitoneal injection of either 2.0, 4.0, or 6.0 mg/kg of PCP, or PCP vehicle (0.9% saline solution). Five minutes after injection, the rats were tested on the rotorod.

The results of Experiment 2 are presented in Fig. 2. A between-groups ANOVA revealed a significant effect for drug treatment, $F(3, 19) = 4.35$, $p < 0.01$. Bonferroni-corrected t-tests indicated significant impairment in rotorod performance in the group of rats receiving the 6.0 mg/kg dose of PCP, compared to the control group ($p < 0.05$).

Experiment 3: The Residual Effects of PCP on Rotorod Performance

The purpose of the third experiment was to determine if there was any residual disruption in rotorod performance 24 h after PCP injection. The rats used in Experiment 2 were not injected, but were placed on the rotorod and their performances were recorded. The results of Experiment 3 are presented in Fig. 3. A between-groups ANOVA indicated no significant differences between the rats who had previously received PCP vs. the rats who had previously received PCP vehicle, $F(3, 19) = 0.78$, $p > 0.05$.

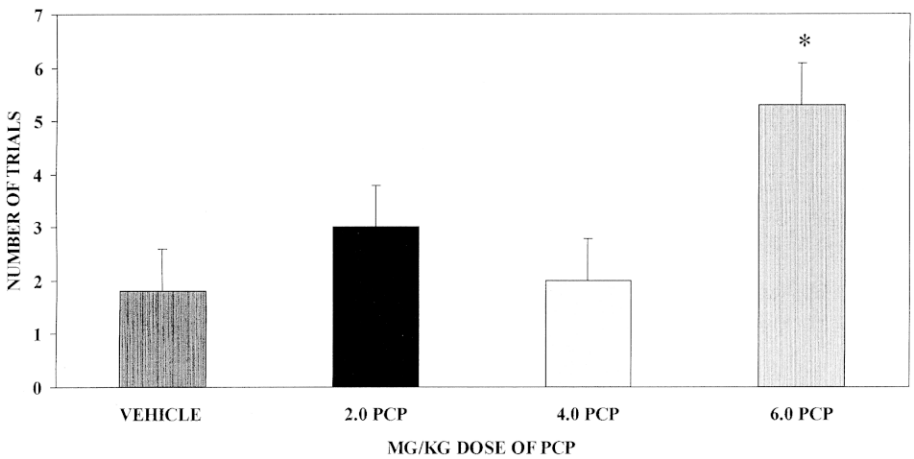

FIG. 2. Mean (±SEM) number of trials subjects took to remain on the rotorod for 120 s at 10 rpm 5 min postinjection. The asterisk indicates a significant difference from the vehicle group.

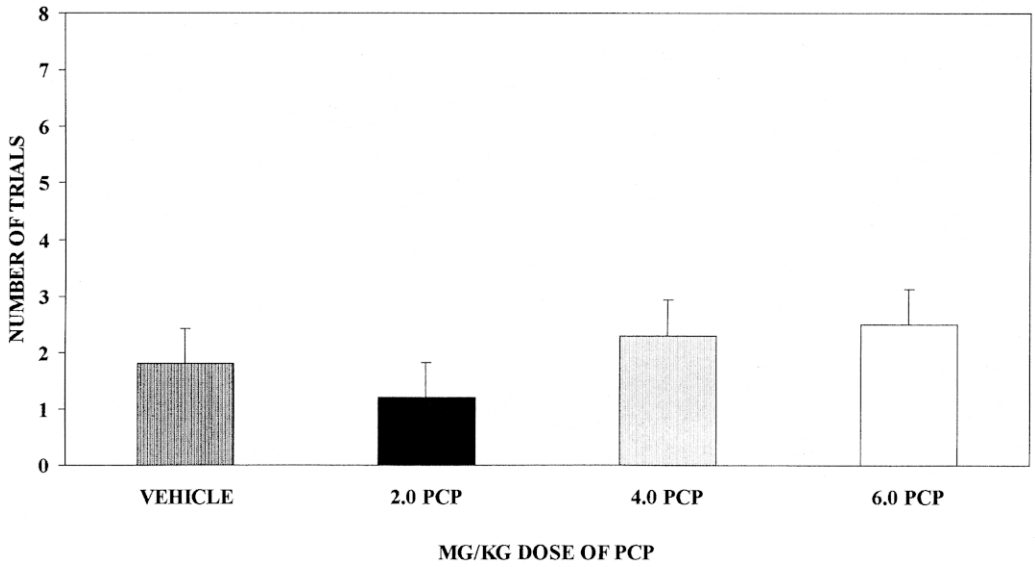

FIG. 3. Mean (±SEM) number of trials subjects took to remain on the rotorod for 120 s at 10 rpm 24 h post-injection.

Experiment 4: The Effects of Classic and Atypical Antipsychotics on Rotorod Performance

The purpose of the fourth experiment was to determine the dose range of antipsychotic-induced disruption of rotorod performance. Each rat that had previously been given the vehicle of each of these compounds was now given one of the following doses: 0.03, 0.1, or 0.3 mg/kg of haloperidol; 3.0, 10.0, or 30.0 mg/kg of clozapine; or 1.0, 3.0, or 10.0 mg/kg of olanzapine. These doses were selected based on pilot data and on previous work with these compounds (26). One hour after injection, all rats were tested on the rotorod.

The results of Experiment 4 are presented in Fig. 4. The antipsychotics produced such a severe disruption in rotorod performance, that we had to scale down our index of performance. Instead of using the number of trials it took for the rats to successfully stay on the rotorod for 120 s at 10 rpm, we used the sum of the total number of seconds the rats were able to stay on the rotorod across all five trials. A between-groups ANOVA revealed a significant effect for drug treatment, $F(8, 37) = 8.08$, $p < 0.001$. As can be seen in Fig. 4, haloperidol produced the biggest disruption in rotorod performance, and even at the lowest dose, the rats were able only to stay on the

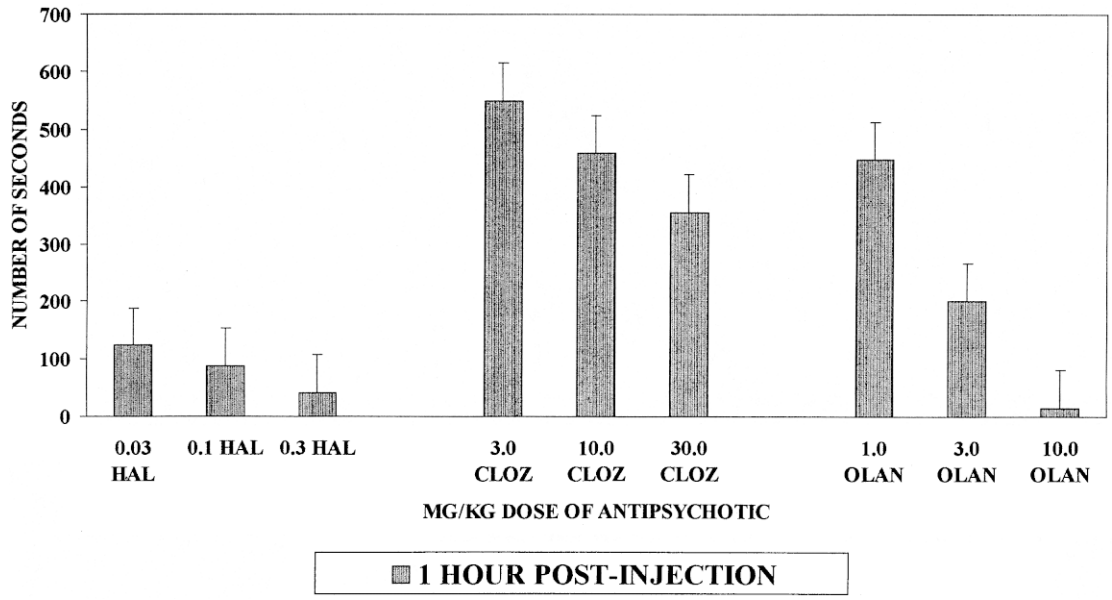

FIG. 4. Mean (±SEM) number of seconds the rats could stay on the rotorod, summed across all five trials.

rotorod a few seconds during each trial. Olanzapine produced a similar disruption at the highest dose, but the lowest dose of olanzapine was similar to clozapine. All of the doses of clozapine were only marginally disruptive. However, they produced more disruption than would be seen in vehicle animals.

Experiment 5: The Residual Effects of Antipsychotics on Rotorod Performance

The purpose of the fifth experiment was to determine if there were residual disruptions in rotorod performance 24-h after the rats received injections of antipsychotics. The rats used in Experiment 4 were placed (uninjected) on the rotorod and performance was recorded. Figure 4 presents the results. A between-groups ANOVA revealed a significant residual effect 24-h postdrug treatment, $F(8, 37) = 3.57$, $p < 0.005$.

Experiment 6: The Reversibility of PCP-Induced Disruption of Rotorod Performance With Classic and Atypical Antipsychotics

The purpose of the sixth, and final, experiment was to determine if the disruption of rotorod performance produced by PCP could be partially or completely reversed by either haloperidol, clozapine, or olanzapine. Following a 48-h drug washout period, the rats who had previously received only one dose of antipsychotic were given the identical dose of antipsychotic they had received in Experiment 4. Fifty-five minutes later, they were injected with the 6.0-mg/kg dose of PCP and were tested on the rotorod 5 min later.

The results of Experiment 6 are presented in Fig. 5. We used the mean number of trials the rats were able to stay on the rotorod for 120 s at 10 rpm. A between-groups ANOVA revealed no significant reversal effects for any dose of haloperidol or olanzapine, $F(8, 37) = 0.838$, $p < 0.5$. Clozapine appeared to produce a partial reversal at its middle dose.

DISCUSSION

In this study, six separate experiments were conducted to determine the effects of anitpsychotics and PCP on locomotion and balance as indexed by the rotorod. We were also interested in determining if these drugs produced residual effects if the animals were tested 24 h postinjection. None of the vehicles of any of these drugs disrupted rotorod performance. Haloperidol disrupted rotorod performance at doses of 0.03, 0.1, and 0.3 mg/kg. Olanzapine disrupted rotorod performance at doses of 3.0 and 10.0 mg/kg, but not at 1.0 mg/kg. Clozapine produced a much milder disruption across all three doses (i.e., 3.0, 10.0, and 30.0 mg/kg). The middle dose of clozapine was found to be more effective than the higher doses at reversing PCP-induced disruption in rotorod performance. The reasons for this narrow range of effectiveness are unclear, but it may be that at the higher dose of clozapine rats begin to show haloperidol-like motor problems, as we have previously demonstrated (24). PCP produced a consistent and severe disruption of rotorod performance at doses of 4.0 and 6.0 mg/kg, but not at a dose of 2.0 mg/kg. This finding is consistent with the literature on PCP-induced motility in rats (4,21,25,28). Twenty-four hours postinjection there were no residual PCP effects on rotorod performance.

Coadministration of either haloperidol or olanzapine with PCP did not reverse PCP-induced disruption in rotorod performance, while clozapine produced a partial reversal at only one dose. These findings indicate that olanzapine functions similarly to classic antipsychotics with respect to their effects on balance and locomotion, as indexed by rotorod performance. This is consistent with the results of human and animal studies on the differential effects of clozapine and halo-

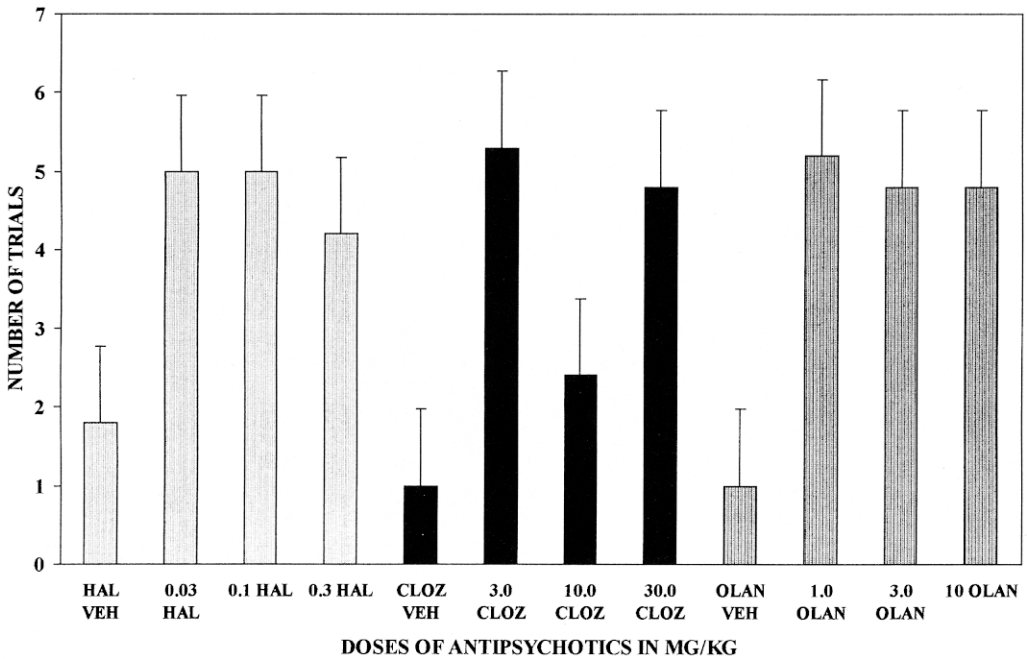

FIG. 5. Mean (±SEM) number of trials subjects took to successfully remain on the rotorod for 120 s at 10 rpm after coadministration with 6.0 mg/kg of PCP.

peridol on motor functioning (3,16). For example, clozapine does not produce catalepsy in rats (20), which was formerly considered a defining index of the classic antipsychotic profile. Although rotorod performance was not used in this series of experiments as a measure of catalepsy, any drug that impacts catalepsy (e.g., haloperidol) will very likely impair rotorod performance. Research has shown that PCP-induced behavioral stimulation in mice can be blocked by clozapine, but not haloperidol (10). The ability of antipsychotics to reverse PCP-induced behavior has been used as evidence of antipsychotic efficacy (25). In general, atypical antipsychotics have been superior in suppressing the behavioral deficits associated with acute PCP administration. Despite the fact that olanzapine has been touted as an atypical antipsychotic, its effects on rotorod performance in this dose range is more similar to the classic antipsychotic haloperidol than to the atypical antipsychotic clozapine. In fact, the highest doses of olanzapine (3.0 and 10.0 mg/kg) resulted in a disruption of rotorod performance, while the lowest dose (1.0 mg/kg) resembled the effects of clozapine. We should note that clozapine resulted in a marginal, yet distinct, disruption of rotorod performance compared to control rats. One explanation for these results is that the combination of neurotransmitters that PCP disrupts (14,17) is not adequately balanced by the antipsychotics tested to restore rotorod performance. Alternatively, the present findings may reflect difficulty in temporally addressing the effects of PCP. We utilized acute administration of antipsychotics, and it is possible that chronic administration, which is typically used for antipsychotic treatment in humans, may be a more accurate reflection of reversal effects. Consequently, normal motility likely depends on a delicate balance of the neurotransmitters involved in locomotion and balance, in much the same way that social behavior can be disrupted either by overstimulating or blocking dopaminergic transmission (8,9,18,19). The dose combinations and administration regimen used in the present study may have missed that delicate balance.

We previously studied the effects of these same compounds on rodent social interactions in the intruder paradigm. We found that PCP produced social withdrawal when an injected rat was placed as an unfamiliar intruder into a stable home colony of three other rats (26). We subsequently determined that the withdrawal was initiated by the injected animal, rather than the surrounding injected conspecifics (15). This was determined by the use of a tether paradigm in which we demonstrated that their social behavior was below saline levels only in the condition in which the injected rat's movement was unrestricted. Social behavior was not attenuated in the condition where the injected rat's movement was restricted to one-half of the observation chamber by a tether and harness. Thus, the injected rat could not escape from interaction with the undrugged conspecifics.

In conclusion, our findings in the present study paralleled the effects we found in our social interaction studies in the free-moving intruder paradigm (26). The rotorod provides us with accurate data that is easily replicable from laboratory to laboratory. Although the rotorod does not replace the usefulness of open-field and social interaction studies, it can be a useful augmentation to improve our understanding of the effects of compounds on locomotion and balance as they impact on social behavior.

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