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A simple procedure for assessing ataxia in rats: Effects of phencyclidine

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Abstract

The present study describes an objective, cost- and time-efficient procedure for characterizing the ataxic effects of psychoactive drugs. Male Sprague–Dawley rats were administered an intraperitoneal injection of either saline or one of three doses (1, 5 or 10 mg/kg) of phencyclidine (PCP) 15 min prior to being placed into an empty standard operant conditioning chamber (all manipulanda were removed). The floor of the test apparatus consisted of parallel rows of metal rods spaced approximately 1.5 cm apart. During a 5-min test, a single observer counted the frequency with which each animal's paws (front or back) slipped between the rows of bars that constituted the cage floor. The data demonstrated that while saline animals exhibited no instability in their ambulation, PCP-treated animals demonstrated a highly reliable dose-dependent increase in the number of "paw slips" in a single trial. Since animals are known to develop tolerance to the ataxic response to PCP, the validity of the test as a measure of drug-induced ataxia was examined in a separate group of animals treated with the middle (5 mg/kg) dose every other day over the course of a 9-day period (i.e., resulting in five injection trials). In this experiment, each subsequent test produced a reliable reduction in the magnitude of the ataxic response, and by the fifth drug challenge, the PCP animals were performing at near-control levels. These results suggest that the "paw slip test" can serve as a simple, reliable, objective and valid measure of drug-induced ataxia. The relevance of the ataxia data for interpreting the locomotor response of animals treated with PCP is also discussed.
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Keywords: Ataxia; Tolerance; PCP; Sensitization; Rats

1. Introduction

The administration of acute phencyclidine (PCP) has been reported to produce two opposing behavioral effects. Some investigators report that the drug acts as a psychomotor stimulant producing reliable increases in locomotor behavior (e.g., Castellani and Adams, 1981a,b; Castellani et al., 1982; Danysz et al., 1994; French, 1988; Greenberg and Segal, 1985; Iwamoto, 1986; Kesner et al., 1981; Sturgeon et al., 1979), while others report behaviors that might be expected to interfere with locomotion, such as stereotypy or ataxic responses (e.g., Meltzer et al., 1981; Sturgeon et al., 1979). Not surprisingly, the directionality of the locomotor response to acute PCP is, in large part, determined by dose with smaller doses (1–5 mg/kg ip in rat) tending to produce predominantly psychomotor stimulant effects (Balster and Chait, 1978; Castellani and Adams, 1981a; Chen et al., 1959; Kesner et al., 1981; Sturgeon et al., 1979; Yang et al., 1991) and moderate to high doses (5–15 mg/kg) producing more severe stereotypic and ataxic responses (Kesner et al., 1981; Sturgeon et al., 1979; Yang et al., 1991). In our own experience, although the predominant behavioral profile of PCP is generally that of a psychomotor stimulant, even at relatively low doses, there is a subset of animals (growing in number as the dose increases) that show considerable sensitivity to the drug's ataxic side effects (Chen et al., 1959; unpublished observations). It is not uncommon, for example, to see an animal that subjectively appears to be highly aroused and hyperactive, but whose limb movements and balance are insufficiently coordinated to result in effective locomotion.

Given the duality of PCP's actions, it seems prudent to include in studies of PCP-induced locomotion an assessment of the drug's ataxic properties. Clearly the presence of ataxia in a subset of animals cannot only dramatically

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increase the variability of scores in the resulting locomotor activity data set, but also act to either mask or suppress the magnitude of the stimulatory behavior. Consider, for example, the fact that repeated exposure to PCP can result in an increased locomotor response that may be accounted for by some form of drug-induced sensitization (e.g., Greenberg and Segal, 1985, 1986; Iwamoto, 1986; Nabeshima et al., 1987; Xu and Domino, 1994). Since animals develop tolerance to the ataxic effects of PCP (e.g., Castellani and Adams, 1981a; Leccese et al., 1986; Smith et al., 1981; Sturgeon et al., 1982), an alternative explanation for the enhanced locomotor actions observed following repeated exposure to PCP is that the reduced ataxia over trials unmasks the drug's acute psychomotor stimulant properties independent of sensitization (Melnick et al., 1997). Such an explanation could not be dismissed without a thorough assessment of PCP's ataxic effects and how they relate to the locomotor response of the drug.

With some notable exceptions (e.g., Meltzer et al., 1981; Sturgeon et al., 1979), the vast majority of PCP locomotor studies do not include a behavioral assay for drug-induced ataxia. Undoubtedly, a large part of the reason for this is the labor intensive nature of such assays and/or the fact that an "inability to behave" is often difficult to objectively quantify. For example, some investigators have examined PCP effects in a rota-rod test where animals are required to walk on top of a rotating wheel. Falling off the apparatus provides an easy, objective and highly quantifiable assessment of PCP's disruptive effects of motoric behavior (Carter, 1994; Chaudieu et al., 1989; Pinchasi et al., 1978). However, the rota-rod requires initial training of the animals (to produce a consistent baseline against which drug effects are tested), and might be expected to produce "falls" even in nonataxic animals whose locomotor behavior is stimulated by the drug (as might be expected with PCP). Along similar lines, others have used a balance task in mice where subjects are required to remain atop a horizontal bar for a criterion duration (e.g., 30 s). PCP interferes with an animal's ability to perform in this task (e.g., Flint and Ho, 1980; Nabeshima et al., 1982; Noda et al., 1996). Although the task is quite simple, like the rota-rod, it can require prior conditioning to ensure that the animals are first able to consistently perform for the "criterion" duration before the drug is applied. Additionally, large numbers of animals are needed since the ataxia measure is generally defined by the percentage of drug-treated animals that fall off of the bar.

A simpler, but labor-intensive approach is to have observers blind to the treatment condition of the animal, describe the subjects' unconditioned spontaneous behavior using an "ataxia rating scale". This method has been widely used for the study of PCP where it has revealed reliable dose-dependent effects of the drug (e.g., Castellani and Adams, 1981a,b; Castellani et al., 1982; Contreras et al., 1986; Greenberg and Segal, 1985, 1986; Hiramatsu et al., 1989; Popoli et al., 1990; Smith et al., 1981; Steinpreis and Salamone, 1993; Sturgeon et al., 1979, 1981; Szekely et al., 1994; Tanii et al., 1994; Tsutsumi et al., 1995). Unfortunately, there is no generally accepted standard in the way that different investigators employ rating scales to assess drug-induced ataxia. Thus, the number and meaning of the points on the scales differ from investigator to investigator as does the number and duration of observation periods. In addition, the subjective nature of observational techniques requires a minimum of two observers whose ratings are then checked against each other to assess interobserver reliability. Together, these factors undoubtedly serve to dissuade investigators from studying ataxia for lack of a fast and easy method of assessment during studies of PCP-induced locomotion.

The present study describes a simple, objective, cost- and time-efficient method for measuring the ataxic response of animals administered PCP (or other behavior-impairing compounds). Informal observations of our PCP-treated animals in locomotor activity tests revealed a problem in the subjects' ability to effectively ambulate across a floor consisting of parallel rows of metal rods. Drug-treated animals often had their paws slip between the rods of the floor—a problem that almost never occurred in nondrugged animals. The present experiment was devised to determine whether such "paw slips" could, in fact, serve as a simple but valid measure of PCP-induced ataxia. A single untrained observer counted the number of times an animal's paws slip between the parallel rows of metal rods that make up the floor of a standard operant test chamber in animals treated with varying doses of PCP (0–10 mg/kg). In a separate experiment, as a means of assessing the face validity of this measure, the effects of repeated PCP administration over a 9-day test protocol were examined to determine whether the putative ataxic response demonstrated signs of tolerance as have been reported with the use of observational behavioral rating scales (e.g., Castellani et al., 1981a; Melnick et al., 1997; Smith et al., 1981; Sturgeon et al., 1982; but see Greenberg and Segal., 1986).

2. Method

2.1. Animals

Fifty-six male Sprague–Dawley albino rats (300–325 g at the start of the study) were purchased from Charles River Laboratories (Wilmington, MA) and served as subjects. Animals were individually housed in wire-hanging cages located within a temperature-controlled (23 °C) animal vivarium maintained under a 12:12-h light/dark schedule (lights on at 07:00 hours). Rat Chow (Purina) and water were freely available throughout the experiment.

2.2. Drug preparation

PCP hydrochloride was dissolved in a vehicle solution of 0.9% physiological saline and injected intraperitoneally (ip) 15 min prior to testing in a volume of 1.0 ml/kg.

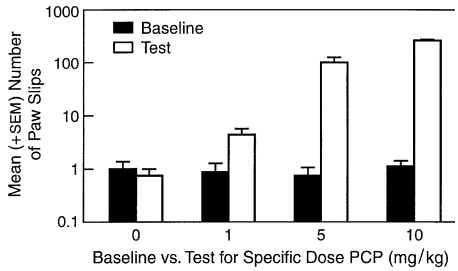

Fig. 1. Effects of PCP on a paw slip measure of ataxia. The figure depicts the mean (+S.E.M.) number of "paw slips" for different groups of rats (n=8/group) on an untreated baseline (left bars in each pair) and on a single 5-min test trial conducted 24 h later. Each group was treated with a single dose of PCP (0.0, 1.0, 5.0 or 10.0 mg/kg ip) 15 min prior to testing. PCP clearly produced a dose-dependent increase in this behavioral measure of drug-induced ataxia.

Each subject was injected with either 0, 1, 5 or 10 mg/kg (see Procedure).

2.3. Apparatus

Two standard operant conditioning chambers (Med Associates, St. Albans, VT) served as test apparatus. There were no levers or manipulanda in the chambers whose floors consisted of parallel rows of metal rods spaced 1.5 cm apart. An IBM-PC running Med Associates software controlled the timing of the test sessions by illuminating the chamber house lights upon initiation of each trial.

2.4. Procedure

Animals were handled during each of six consecutive days prior to the start of the experiment. Subjects were then randomly assigned to one of the two test chambers and all behavioral testing was conducted in the same chamber for each rat. Subjects were then acclimated to their test chamber during daily 5-min sessions conducted over a 3-day period.

2.4.1. "Paw slips" as a dependent measure

Ataxia was operationally identified by the occurrence of "paw slips" between the floor rods. A paw slip occurred when any one of a subject's four paws slipped below the plane of the floor thereby exposing the animal's ankle joint to an observer. The paw slip response is either present or absent and hence does not require a subjective "decision" on the part of the observer—merely the maintenance of a frequency count. Hence, we did not employ multiple observers although the person was kept blind to the animal's past performance and group assignment.

2.4.2. Dose–response analysis of PCP-induced ataxia

In an initial experiment, eight animals were randomly assigned to one of four groups each corresponding to a different dose of PCP (0, 1, 5 or 10 mg/kg). Following the 3-day acclimation period, a single 5-min baseline trial was conducted where paw slips were counted for each animal with no prior treatment. Twenty-four hours later, each animal was administered one of the four doses of PCP and, 15 min later, again placed into the apparatus for a final 5-min behavior test.

2.4.3. Effects of repeated PCP exposure on the ataxic response

Twenty four new (naive) animals were used to examine whether the ataxic response observed in the dose–response study (described above) would undergo tolerance with repeated drug exposure. Twelve rats were assigned to a drug group (the middle 5.0 mg/kg dose of PCP was selected) and the remaining 12 to a saline control group (0.0 mg/kg PCP). Three days of habituation were immediately followed by nine consecutive days of testing where the number of paw slips made by each animal was recorded during single 5-min sessions. On the five odd-numbered trials (Days 1, 3, 5, 7 and 9), subjects were pretreated with either PCP or saline 15 min prior to testing. On the four even-numbered trials (Days 2, 4, 6 and 8), no intraperitoneal pretreatments were administered.

3. Results

3.1. Dose–response analysis

Animals treated with varying doses of PCP exhibited highly reliable dose-dependent increases in the number of paw slips during testing (see Fig. 1). A two-factor analysis of variance (Group×Trial) revealed the following statistically significant effects: (1) a main effect for Trial [$F(1,28)=143.8$, $P<.001$] indicating that when averaged across all groups, drug trials produced higher ataxic scores than nondrug baseline trials; (2) a main effect of Dose

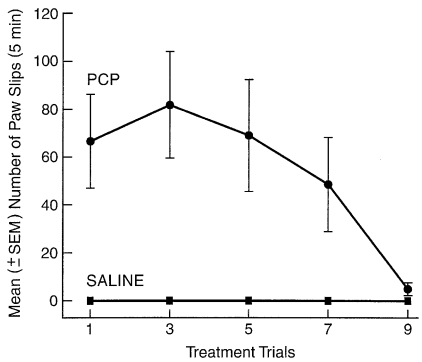

Fig. 2. Effects of repeated exposure to PCP on the paw slip measure of drug-induced ataxia. Subjects were administered either saline (n=12) or 5.0 mg/kg PCP (n=12) intraperitoneally 15 min prior to each 5-min ataxia test. Mean (±S.E.M.) number of paw slips are shown for treatment trials on Days 1, 3, 5, 7 and 9. Rats injected with PCP reliably decreased paw slips from the first to the last trial while saline-treated rats rarely if ever made paw slips. These data demonstrate that the ataxia induced by PCP diminished with repeated trials.

(Group) reflective of the dose-dependent increases in paw slips clearly depicted in Fig. 1 [$F(3,28)=64.1$, $P<.001$]; and (3) a reliable Trial×Dose interaction confirming that the change in behavioral response from baseline to test performance differed across groups [$F(3,28)=64.6$, $P<.001$] (e.g., the groups behaved comparably on baseline but showed differences in their test-day drugged behavior).

3.2. Repeated PCP testing

Fig. 2 illustrates the mean (±S.E.M.) number of "slips" made by the PCP-treated (5 mg/kg) and saline-treated animals on the five treatment trials of the 9-day experiment. As was observed in the dose–response study, PCP-treated animals made many more "paw slips" (Trial 1) than did subjects tested following saline injections. However, as one can clearly see from the figure, the number of paw slip counts in the drug group declined over the course of repeated testing and was virtually indistinguishable from saline treated controls by the final treatment day (Trial 9). In this experiment, saline animals exhibited virtually no ataxia and paw slips were rare for either group during the intervening nontreatment trials (data not shown). The observation of behavioral tolerance was confirmed by a two-factor (Group×Trial) analysis of variance computed on the data depicted in Fig. 2. Once again, the ANOVA revealed statistically reliable main effects for Group (saline versus PCP) [$F(1,22)=21.61$, $P<.001$], Trial (when averaged across groups, paw slips decreased with repeated testing) [$F(4,88)=3.10$, $P<.02$] and a Trial×Group interaction (the changes in paw slip behavior observed in the PCP group over trials was different from those observed in the saline group) [$F(4,88)=3.07$, $P<.03$]. Since the saline-treated animals made no paw slips, these results are all clearly attributable to the behavior of the PCP-treated group. Bonferroni-corrected t tests were employed to make post hoc comparisons of the PCP- and saline-treated groups on each treatment trial. These tests identified statistically significant group differences on Trials 1 [$t(11)=3.33$, $P<.04$] and 3 [$t(11)=3.65$, $P<.02$). Thus, by Trial 5, the PCP and saline groups were no longer reliably different from one another.

The data from the intervening nontreatment days are not depicted in the figure since there were very few observations of paw slips during these trials. However, when such behavior did occur, it was restricted to the PCP group, suggesting that there may be some residual effects of PCP 24 h posttreatment. A two-factor Group×Trial ANOVA computed on the data from the four nontreatment trials surprisingly revealed a small but reliable effect of Group [$F(1,22)=5.25$, $P<.04$] but no effects of Trial [$F(3,66)=0.98$, n.s.] nor a Group×Trial interaction [$F(3,66)=1.35$, n.s.]. The "Group" effect is attributable to the small number of paw slips that occasionally occurred in the PCP group. Although this behavior was observed, on average, less than 0.5 times per 5-min session, the comparison to a saline control group that exhibited no slips on any trial and, hence, had a mean and variance of zero, was sufficient to render a statistically significant effect.

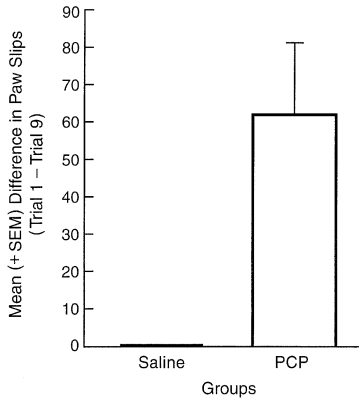

Fig. 3. The mean (±S.E.M.) difference in paw slips from Trial 1 to Trial 9 are depicted for the saline-and PCP-treated animals. The saline group exhibited virtually no change in paw slips from Trial 1 to Trial 9 because their behavior was stable and error-free throughout the study. However, the PCP group made an average of 61.8 fewer paw slips on Trial 9 compared to Trial 1. These data suggest that the animals develop a behavioral tolerance to PCP's ataxic effects with repeated drug exposure.

Tolerance to the disruptive effects of PCP can be assessed by comparing the performance of the two groups across trials as the experiment progressed. Fig. 3 illustrates the change in behavior observed for each group from the first to the last treatment day by plotting the mean "difference scores" for paw slips on Trial 1 less Trial 9. To assess whether each group's behavior had reliably changed from Trial 1 to Trial 9, a single-sample t test was conducted for each mean to determine if the mean changes depicted in the figure were reliably different from zero. As expected from inspection of the data, and suggested by the reliable Group×Trial interaction obtained in the overall ANOVA (see above), the change in performance from Trial 1 to Trial 9 was statistically reliable for the PCP-treated animals [$t(11)=3.21$, $P<.01$] but not for the saline group [$t(11)=1.0$, n.s.]. These results reflect the fact that PCP-treated animals exhibited 61.8 (±19.2) fewer paw slips on Trial 9 than they did on Trial 1 despite being administered the same 5.0 mg/kg dose of drug prior to each trial.

4. Discussion

Ataxia is characterized by the loss of control of bodily movements (Carter, 1994; Meltzer et al., 1981; Sturgeon et al., 1979) and is observed following the administration of a wide variety of psychoactive drugs (Arvola et al., 1958; Carter, 1994; Siegel and Larson, 1996; Soderpalm et al., 1989). Attempts to accurately assess the degree of ataxia produced by a treatment have essentially come in two forms: objective and subjective. Objective tests of ataxia consist of assessments of motor coordination and balance that examine a drug's effects on the animal's ability to

maintain performance such as walking on a rota-rod or remaining atop a balance beam (e.g., Flint and Ho, 1980; Pinchasi et al., 1978). These measures typically require some prior training to ensure that animals are performing at some consistent baseline level prior to the administration of the test compound. The subjective tests involve observations and ratings of the animals' ataxic behavior (e.g., Castellani and Adams, 1981a,b; Castellani et al., 1982; Contreras et al., 1986; Greenberg and Segal, 1985, 1986; Hiramatsu et al., 1989; Popoli et al., 1990; Smith et al., 1981; Steinpreis and Salamone, 1993; Sturgeon et al., 1979, 1981; Szekely et al., 1994; Tanii et al., 1994; Tsutsumi et al., 1995). Although no prior conditioning and testing are required (as in the objective tests), the rating scales require at least two observers who must themselves undergo prior training. In addition, the subjective nature of the ratings requires that the observers be ''blind'' to the treatment conditions and agree about the degree of ataxia that they are concurrently observing.

The current study describes an objective simple, cost- and time-efficient procedure for assessing drug-induced ataxia. Ataxic animals have difficulty maintaining their balance, the current test makes use of this fact by counting the frequency with which the paws of drugged animals slip through the flooring rods of a standard behavioral testing chamber. The test lasts for only 5 min and can be administered by a single observer. In addition, no prior training is required on the part of either the animals or the observer. Although we have not yet done so, the procedure can also be easily automated by use of a video camera or infrared photocell technology.

The administration of PCP has been reported to produce both locomotor activation (Castellani and Adams, 1981a,b; Castellani et al., 1982; Danysz et al., 1994; French, 1988; Greenberg and Segal, 1985; Iwamoto, 1986; Kesner et al., 1981; Sturgeon et al., 1979) and ataxia (Carter, 1994; Castellani and Adams, 1981a,b; Castellani et al., 1982; Kesner et al., 1981; Sturgeon et al., 1979) in laboratory animals. At moderate doses (such as the one employed in the current study), subsets of animals often show one or the other of these two behavioral responses. Clearly, the presence of an ataxic reaction can severely limit or mask the locomotor response to the drug. The current study was therefore devised to examine the putative ataxic effects of PCP using the paw slip assessment procedures described herein. While saline-treated animals make very few paw slips, PCP-treated animals were observed to exhibit significant numbers of this behavior. Furthermore, the paw slip behavior was found to increase reliably with dose of PCP (see Fig. 1). Additionally, others have reported that animals develop tolerance to the ataxic effects of PCP upon repeated drug administration (Castellani and Adams, 1981a; Flint and Ho, 1980; French, 1988; Leccese et al., 1986; Nabeshima et al., 1982; Noda et al., 1996; Smith et al., 1981; Sturgeon et al., 1982). The current procedures were also sensitive to such effects as revealed by the progressive reduction in the frequency of ''paw slips'' over the course of repeated drug testing (Fig. 2). By the end of the study (i.e., by the fifth injection), the PCP-treated animals were virtually as stable on their feet as the saline control animals. Indeed, as can be seen in Fig. 3, PCP-treated animals made on average over 60 fewer ''slips'' on the final drug trial than they did on the initial PCP trial. Thus, the present data are consistent with the observation of tolerance to PCP's disruptive behavioral effects although they do not address the nature of the underlying mechanism for the ''tolerance'' observed in this study. It is possible that receptor changes, metabolic changes or even conditioned effects could individually or cumulatively account for the reduced impact of PCP with repeated exposure. Nevertheless, it is clear that the nonspecific behavioral impairment produced by PCP is dramatically and reliably reduced with repeated drug exposure.

The demonstration of behavioral tolerance to PCP's ataxic effects might have relevance for the understanding of how and why behavioral ''sensitization'' develops to the drug's locomotor-activating properties. Several investigators have reported that repeated systemic administration of PCP can result in a progressively increasing locomotor stimulatory effect (Greenberg and Segal, 1985, 1986; Iwamoto, 1986; Nabeshima et al., 1987; Xu and Domino, 1994). This result is generally accounted for by a form of drug-induced sensitization that presumably reflects a change in the neuronal substrate(s) where PCP is acting (Greenberg and Segal, 1986; Iwamoto, 1986; Nabeshima et al., 1987). For example, apomorphine and methamphetamine, dopamine agonists, reliably increased locomotion in rats chronically administered PCP as compared to saline pretreatment (Nabeshima et al., 1987), indicating a supersensitivity of the dopaminergic system. Changes in the sigma receptor have also been suggested since PCP-sensitized rats increased locomotor responses to *N*-allynormetazocine (NANM), a sigma receptor agonist (Greenberg and Segal, 1986; Iwamoto, 1986). The current data suggest that a note of caution be inserted into this discussion. If ataxic reactions to PCP are, in fact, present during initial tests of the drug's locomotor-activating effects (whether in all animals at some weak level or even in a subset of animals), then any increase in subsequent mean group activity levels might be accounted for in part by the development of tolerance to these ataxic reactions. Clearly, one would expect such a process to unmask other behavioral actions of the drug, such as the locomotor behavior.

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