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Phencyclidine and Behavior: II. Active Avoidance Learning and Radial Arm Maze Performance[1]

RAYMOND P KESNER, JOHN D HARDY AND JEANNE M NOVAK

Department of Psychology, University of Utah, Salt Lake City, UT 84112

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KESNER, R P J D HARDY AND J M NOVAK *Phencyclidine and behavior II Active avoidance learning and radial arm maze performance* PHARMACOL BIOCHEM BEHAV **18**(3) 351–356, 1983 —Rats with injections of 4 or 8 mg/kg of phencyclidine (PCP) are impaired in the acquisition of active avoidance learning and radial arm maze performance This impairment was not due to a change in detectability of aversive stimuli or the inability to perform the correct response The primary deficit appears to be the inability of PCP injected animals to encode the appropriate attributes (e g , environmental context, response selection, and emotion) associated with each task

Phencyclidine Active avoidance Radial arm maze

SINCE its discovery, phencyclidine 1-(1-phencyclohexyl) piperidine (PCP) has been used as an anesthetic, mainly because of its central nervous system depressant properties However, clinical investigations of its anesthetic properties in humans were discontinued because the drug caused major side effects such as long duration confusional and stuperous states

Recently the drug has appeared on the illicit market and has become known as "angel dust" or "PCP " According to Burns and Lerner [4] one tablet containing 2–6 mg of PCP will result in a "high" which is reached within 15–30 min and will last for 4–6 hr However, a completely normal state is not reached until 24–48 hr later According to Burns and Lerner [4] an overdose of PCP in the range of 1/2 to 1 g leads to severe acute intoxication This state has been either characterized as a confusional and delirious state or as stupor and coma

It is often the case that drugs of abuse have marked effects on cognitive functioning well below the dose necessary for severe acute intoxication These effects may be more subtle and are detectable only with more sophisticated behavioral analyses, including learning and memory tasks

For example, there have been anecdotal reports suggesting that specific episodes experienced while under the influence of PCP are not remembered when the subject recovers from PCP effects [4,8] In the animal literature there have been a number of studies assessing the impact of PCP on well-learned responses For example, Adey and Dunlop [1] showed that 1–3 mg/kg injections of PCP in cats disrupted for many hours performance of a learned approach response in a T maze Lower doses (0 3–1 0 mg/kg) produced a similar but short-acting (seconds) impairment of performance Brown and Bass [3] showed that in monkeys an injection of 0 5 mg/kg PCP resulted in complete disruption of a previously learned avoidance response At lower doses (0 05–0 25 mg/kg) there was a dose-dependent increase in latency to respond Similar results were found in rats, in that 1, 2, 4, or 8 mg/kg PCP injected subcutaneously resulted in a dose-dependent impairment of a previously learned avoidance response [7] However, it is important to note that these injections also blocked escape responding and resulted in gross disorganization Pryor *et al* [16] also found a disruption of a learned conditioned avoidance response with PCP, but not until a dose of 5 mg/kg was given Lower doses (1 25 or 2 5 mg/kg) had no effect

Changes in performance on food-reinforced operant behavior have also been reported following injections of PCP Wenger [17] and Wenger and Dews [18] used a multiple fixed-ratio (FR), fixed interval (FI) schedule of food reinforcement in the mouse and pigeon They report increased response rates at low doses and decreased response rates at high dose levels of PCP during the FI component, but only a dose-related decrease in response rate was observed during the FR component Balster and Chait [2] found that PCP injected in rhesus monkeys produced only decreased response rates in a food reinforced chain FI, FR schedule In rats trained to respond on a variable interval 60 sec schedule of water reinforcement, PCP in doses of 0 25, 0 5, 1 0 mg/kg increased, while doses of 2 and 4 mg/kg decreased response rates [13] Similar results were reported for rats using an FI schedule of reinforcement, namely low doses (1, 2, 4, mg/kg) increased overall response rates, high doses (8 mg/kg) decreased overall response rates [19] Also in squirrel monkeys low doses of PCP produce a small increase in VI responding, while higher doses produce decreases in rates of responding [5] Unfortunately, it is difficult to evaluate all of the above

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mentioned changes in performance, because PCP can produce changes in activity level, motor ataxia, changes in motivational state, and possibly analgesia for painful input All of these changes could alter performance without affecting memory or learning functions

Even though there have been a large number of studies dealing with the effects of PCP upon performance of a well-learned response, there are relatively few studies that have dealt with the effects of PCP on acquisition, while only one study on the effects of PCP on long-term retention could be found in the literature With respect to acquisition Moerschbaecher and Thompson [11,12] showed that with an increasing dose of PCP injected in monkeys there was an increase in number of errors in the acquisition of a set of response sequences or conditional discriminations Also Domino, Caldwell, and Henke [7] demonstrated that low doses of PCP (600 μg/kg) in rats retard learning of a pole jump avoidance With respect to retention, Glick and Zimmerberg [9] injected PCP in mice 12 min before or immediately after passive avoidance training with a retention test 24 hr later They showed that at 5 mg/kg doses there was a significant impairment in retention, but only when injections were given prior but not after training

Neither of the two above mentioned studies has dealt with the mechanism of action for the impaired acquisition/retention of passive and active avoidance learning Thus, the purpose of the present study was first to demonstrate that PCP affects acquisition of active avoidance learning using dose levels (4 or 8 mg/kg) that in a previous study were shown to have little effect on sensory-motor function [10], and second to subsequently analyze possible mechanisms of action

EXPERIMENT 1

METHOD

Subjects

Forty-five male Long-Evans rats, initially weighing 325–340 g were used as subjects All animals were maintained ad lib throughout the experiment

Apparatus

The apparatus consisted of a rectangular (40×24×54 cm) red, Plexiglas box A black ledge was mounted 10 cm above a brass rod grid floor Scrambled AC shock could be delivered to the grid floor A photocell located above the ledge was used to detect escape or avoidance responses The ledge could be retracted or extended into the box automatically with the use of a motor No handling of the animals was required during learning Relay circuitry was used to program and record events during the experiment

Procedure

The animals were randomly assigned to a 4 mg/kg phencyclidine hydrochloride (Sernylan, Bioceutic Co) (n=13), 8 mg/kg PCP (n=7), or saline (n=25) group Each animal received the appropriate injection IP 30 min prior to onset of acquisition training Each rat was placed in the apparatus and 30 sec later given the first acquisition trial At the commencement of each trial the ledge (CS) was slowly extended Ten seconds later a 1 mA shock (UCS) was delivered and continued until the animal jumped onto the ledge If the animal jumped before the end of the 10 sec CS-UCS interval, an avoidance response was registered and no shock occurred A jump response whether escape or avoidance resulted in a 15 sec intertrial-interval followed by retraction of the ledge until the animal fell off Immediately thereafter the ledge was again extended starting a new trial Each animal was trained until it reached an avoidance learning criterion of 10 consecutive avoidance responses or had been given 100 trials The latter criterion was necessitated by the observation that animals injected with 8 mg/kg of PCP could not learn this task The number of trials to criterion was used as the learning measure

TABLE 1
EFFECTS OF PCP UPON ACQUISITION OF ACTIVE AVOIDANCE

Group	N	Mean number of trials to criterion	Standard Error
Saline	25	39 4	3 6
4 mg/kg PCP	13	56 8	6 2
8 mg/kg PCP	7	95 6	3 2

RESULTS AND DISCUSSION

The mean number of trials to criterion as a function of PCP or saline injections is shown in Table 1 The data clearly indicate that animals under the influence of 8 mg/kg of PCP cannot learn the one-way active avoidance task, while some retardation in acquisition can be seen in the 4 mg/kg group

A one-way analysis of variance resulted in a significant drug effect, $F(2,42)=27\ 3$, $p<0\ 001$ Subsequent Newman-Keuls tests revealed that the 4 mg/kg of PCP group required a significantly higher number of trials to reach criterion than the saline group $p<0\ 05$, but significantly fewer trials than the 8 mg/kg of PCP group $p<0\ 01$ The 8 mg/kg of PCP group required significantly higher number of trials to reach criterion than the saline group $p<0\ 01$

The data are consistent with previous observations by Domino *et al* [7], that PCP impairs the acquisition of active avoidance It is also apparent that animals under the influence of 8 mg/kg PCP cannot learn the task Even though 8 mg/kg PCP does not produce marked changes in responsiveness to olfactory, somato-sensory, and visual stimuli [10] the possibility exists that the inability to learn the active avoidance response is due to a decreased sensitivity to pain Thus, the purpose of the next experiment was to test for the effects of 4 or 8 mg/kg PCP on behavioral sensitivity to painful shocks

EXPERIMENT 2

METHOD

Subjects

Ten male Long-Evans rats (300–450 g) were used Animals were maintained ad lib throughout the experiment

Apparatus

The testing apparatus consisted of a clear Plexiglas box 30×21×20 cm and a grid floor composed of 1/8 in metal rods spaced 1 cm apart through which electric shock could be delivered

TABLE 2
EFFECTS OF PCP UPON MEAN SHOCK THRESHOLD

	Flinch (mA)		Vocalization (mA)		Avoidance (mA)		3× Jump and Squeal (mA)	
	Mean	Standard Error	Mean	Standard Error	Mean	Standard Error	Mean	Standard Error
Saline	1 2	(0 16)	3 2	(0 24)	3 2	(0 43)	4 3	(0 35)
4 mg/kg PCP	1 7	(0 22)	3 5	(0 28)	3 7	(0 29)	4 5	(0 34)
8 mg/kg PCP	1 6	(0 12)	3 7	(0 30)	3 9	(0 37)	4 9	(0 31)

Testing Procedure

All animals were injected IP with 4 or 8 mg/kg PCP or saline 30 min prior to testing Each animal received each drug dose or saline with the order of the drug injection counterbalanced among animals Injections were given once a day with 2 days between injections

The experimenter was naive as to the drug dose administered as well as the type of drug administered (i e , PCP or saline) Thirty minutes after injection each animal was given a shock threshold test to determine its sensitivity to shock Each animal was introduced and adapted for 1 min to the small box After the adaptation period, footshocks (starting with 0 5 mA intensity) were delivered in ascending order of shock intensity until jump and squeal responses were observed on three consecutive footshocks or until 8 0 mA intensity was reached Shocks were delivered by a scrambled AC shock generator using a train duration of 0 5 sec Successive shocks were increased by 0 5 mA steps The intershock interval was approximately 4 sec, but shocks were delivered only when the animal was making contact with the grid floor with all four paws The shock intensities required to initiate a flinch, a vocalization, an avoidance response, and reach the criterion of three consecutive jump and squeal responses were used as dependent measures A flinch was defined as a response to shock characterized by crouching or a rapid change in posture or limb movement without body position movement in relation to the grid floor A vocalization was characterized by one or more audible vocalizations An avoidance was characterized by rapid body movement across the grid, crossing more than half the floor width A jump and squeal was characterized by the combination of jumping and one or more detectable vocalizations A response was rated as a jump when all four of the animal's paws were off the grid at one time

RESULTS AND DISCUSSION

The mean shock threshold for flinch, vocalization, avoidance, and 3× jump and squeal under the influence of 4, 8 mg/kg PCP or saline are shown in Table 2 There appear to be no differences on any of the measures One-way ANOVAs on each measure revealed that there were no significant differences among the three groups Since PCP had no effect on detection of shock, a change in responsivity to aversive stimuli cannot account for the poor active avoidance acquisition of PCP injected animals

EXPERIMENT 3

However, it is possible that animals can learn the task but under the influence of 8 mg/kg PCP cannot perform the appropriate escape or avoidance response (jumping on a platform) In order to test this possibility, animals were initially trained to criterion on the active avoidance task and then tested for retention of the avoidance response If the animals cannot perform the avoidance response under the influence of PCP, then the animals should show no retention and should take on the average 95 trials (see Experiment 1) to reacquire the avoidance response If the animals relearn or retain the avoidance response in significantly fewer than 95 trials, then it could be argued that PCP has an effect on learning

METHOD

Subjects

Twenty-four male Long-Evans rats (300–450 g) were used Animals were maintained ad lib throughout the experiment

Apparatus

The apparatus was the same as described in Experiment 1

Procedure

The animals were randomly assigned either to a 4 mg/kg (n=9), 8 mg/kg (n=8) PCP, or saline (n=7) group On Day 1 the procedure was identical to that described in Experiment 1, except that no drugs were injected on this day On Day 2 (24 hrs later) animals received appropriate injections (IP) 30 min prior to the retention test which consisted of training trials until the animal reached an avoidance criterion of 10 consecutive avoidance responses or had been given 100 trials

RESULTS AND DISCUSSION

The mean number of trials to criterion on the retention test (Day 2) as a function of PCP or saline injections is shown in Table 3 The data indicate that animals under the influence of 8 mg/kg PCP take somewhat more trials to relearn the active avoidance response in contrast to the 4 mg/kg PCP and saline groups It should be noted, however, that the animals under the influence of 8 mg/kg PCP can perform and retain the active avoidance response in fewer trials than

TABLE 3

EFFECTS OF PCP UPON RETENTION OF ACTIVE AVOIDANCE

Group	N	Mean number of trials to criterion	Standard Error
Saline	7	14 6	1 5
4 mg/kg PCP	9	14 2	2 4
8 mg/kg PCP	8	28 1	10 6

animals that were required to learn the active avoidance response under the influence of 8 mg/kg PCP (see Experiment 1)

A one-way analysis of variance revealed that there were no significant drug effects, $F(2,21)=1\ 77$, $p<0\ 25$ Thus it can be concluded that animals that have learned the active avoidance response can perform the response under the influence of 8 mg/kg PCP, ruling out that the initial learning deficit seen in Experiment 1 is due to the animals' inability to perform a jumping response under the influence of PCP

EXPERIMENT 4

The possibility exists that animals under the influence of PCP have an encoding deficit, that is they do not perceive and register the reinforcement contingencies and/or are unable to select the appropriate avoidance response (jumping onto the platform) However, it is also possible that information is encoded properly, but that consolidation of information is impaired Thus, the purpose of the next experiment is to differentiate between the above mentioned possibilities by injecting PCP before or after ten training trials and a subsequent retention test 24 hr later Support for a more direct effect of PCP on the encoding process would come from the observation that pre-training injections had deleterious effect upon retention, while post-training injections had no effect Support for a more direct effect of PCP on the consolidation process would come from the observation that post-training injections produced an impairment of retention, while pre-training injections had no effect

METHOD

Subjects

Fifty male Long-Evans rats (300–450 g) were used Animals were maintained ad lib throughout the experiment

Apparatus

The apparatus was the same as described in Experiment 1

Procedure

The animals were randomly assigned either to a 4 mg/kg (n=8), 8 mg/kg (n=8) PCP or saline (n=8) pre-training group or a 4 mg/kg (n=7), 8 mg/kg (n=7), 12 mg/kg (n=4) PCP, or saline (n=8) post-training group The procedure was identical to that described in Experiment 1 with the only difference that animals in the pre-training groups received 10 trials under the influence of 4 or 8 mg/kg PCP or saline injected 30 min prior to training, while the animals in the post-training groups received the appropriate injection immediately after ten training trials Twenty-four hours later they were tested for retention and trained to criterion

TABLE 4

EFFECTS OF PRE- AND POST-TRAINING PCP INJECTIONS ON RETENTION OF ACTIVE AVOIDANCE

Injections	Groups	N	Mean number of Trials to Criterion	Standard Error
	Saline	8	14 8	3 0
Before	4 mg/kg PCP	8	16 5	2 1
	8 mg/kg PCP	8	30 4	5 8
	Saline	8	15 2	2 9
	4 mg/kg PCP	7	19 1	3 0
After	8 mg/kg PCP	7	25 6	6 4
	12 mg/kg PCP	4	17 8	2 7

RESULTS AND DISCUSSION

The effects of different doses of PCP injected before or after training upon mean number of trials to criterion are shown in Table 4 The data indicate that animals initially trained under the influence of 8 mg/kg of PCP have impaired retention 24 hr later as indicated by the larger number of trials required to reach criterion compared to saline or 4 mg/kg PCP injected animals A similar but much smaller retention deficit can be seen in animals that received 8 mg/kg of PCP after training A one-way analysis of variance revealed that there was a significant treatment effect $F(6,43)=2\ 98$ $p<0\ 05$ Further Duncan-Range tests revealed that the group that received 8 mg/kg PCP after training had significantly poorer retention than the saline and 4 mg/kg PCP injected groups ($p<0\ 05$) However there were no significant differences between the two groups of animals that received 8 mg/kg PCP before or after training

The present experiment suggests that there is a dose-dependent disruption of retention primarily when PCP is injected before training This suggests that the primary effect of PCP might be on the initial encoding process However there might also be a small effect on the consolidation process Given that PCP has a major effect upon the encoding of critical information, it is still necessary to determine the exact nature of this encoding deficit

EXPERIMENT 5

It is possible that animals under the influence of PCP cannot encode the environmental context, especially spatial aspects, emotional consequences of painful shocks or selection of appropriate motor response In order to accentuate the importance of spatial aspects of the environment and minimize painful experiences we selected to study the effects of PCP on radial arm maze performance It has been suggested that performance on this task requires appropriate encoding of extra-maze (spatial) cues [14]

METHOD

Subjects

Five male Long-Evans rats (weight 325–400 g) served as

subjects Animals were maintained at 80% of their ad lib body weight, but allowed continuous access to water

Apparatus

The apparatus consisted of an eight arm maze similar to that described by Olton and Samuelson [14] The central platform was 27 cm in diameter Eight arms radiated from the center platform at equidistant points Each arm was 10 cm wide and 86 cm long The entire apparatus was constructed of wood painted white and was elevated 47 cm above the floor The testing room was well lighted with fluorescent lights and with many pictures on the surrounding walls

Procedure

Animals were trained using the standard eight arm procedure with all arms reinforced [14] Reinforcement consisted of small pieces of Froot Loops cereal Each trial (one per day) continued until the rat has visited and eaten the food on all 8 arms Reentry into an arm previously visited was scored as an error Entries into arms were recorded by a single observer Each trial lasted about 5 min After reaching criterion of errorless performance which was usually reached within 20 trials, each animal received increasing doses of PCP (2, 3, 4, 5, 6, 7, 8, 9 mg/kg) with two days of saline injections between each dose of PCP This procedure was used because in a previous study [10], no behavioral tolerance effects were observed with repeated PCP injections Animals were always tested 30 min after injection When an animal reached a dose which resulted in errors on the radial arm maze, the animal would be tested four times at the same dose level with two saline injections in between each test When an animal made errors on at least three of four tests, no additional PCP injections were administered

RESULTS AND DISCUSSION

The average dose of PCP that resulted in errors in at least 3 of 4 trials was 6 6 mg/kg with a range from 5–9 mg/kg The mean total number of errors for the 4 trials was 15 4 with a range from 11–22 errors Animals injected with saline or doses of PCP less than 5 mg/kg produced very few errors It is of interest that the dose level that resulted in a failure to perform correctly on the radial arm maze is similar to the dose levels used to disrupt acquisition and retention of active avoidance learning To the extent that encoding of spatial aspects of the environment is critical for errorless performance on the radial arm maze, the results suggest that PCP might indeed play a critical role in this encoding process

GENERAL DISCUSSION

The data indicate that there is a dose-dependent disruption of active avoidance learning with PCP (Experiment 1) This result is consistent with the observations of Domino *et al* [7], who also demonstrated that PCP resulted in an acquisition deficit of a somewhat different type of active avoidance task It should be noted that Domino *et al* [7] were able to obtain this deficit with significantly lower doses of PCP Further analysis revealed that this acquisition impairment is not due to possible PCP induced changes in response sensitivity to shock, since there is no change in shock threshold in animals with PCP injections (Experiment 2) Also animals under the influence of PCP can perform the appropriate avoidance response if the drug was injected after animals had previously learned the response, ruling out the possibility that the acquisition deficit is due to the inability to jump onto the platform (Experiment 3) Possible changes in activity level also cannot account for the active avoidance deficit because (a) even though both 4 and 8 mg/kg PCP resulted in active avoidance impairments 4 mg/kg PCP injected animals show increases in activity level, while 8 mg/kg PCP injected animals show decreases [10], and (b) 8 mg/kg PCP injections before training in a passive avoidance learning situation produces a retention deficit 24 hrs later (unpublished observations) If a decrease in activity were responsible for the active avoidance deficit, then one would have expected facilitation of retention of passive avoidance learning

The findings that animals with 8 mg/kg PCP injections before training failed to show retention 24 hrs later, whereas animals that received PCP injections after training displayed relatively normal retention is consistent with the results of Glick and Zimmerberg [9] and suggest that the primary impact of PCP is on the encoding phase (i e , inadequate coding of appropriate attributes) However, we must be cautious in stating that PCP affects only the encoding of critical information, because (a) any effect on the encoding process could easily have secondary effects on consolidation or retrieval and (b) a certain level of long-term consolidation might be taking place during the training phase

The exact nature of the encoding deficit still needs to be determined The observation that animals cannot perform in a radial arm maze (Experiment 5), cannot learn and retain an active avoidance response (Experiments 1 and 4), and cannot retain a passive avoidance response (unpublished observations) and cannot learn conditional discriminations [11,12] implies a difficulty in encoding of a variety of attributes, but especially the environmental context It is important to note that with low doses of PCP in humans there is also an impairment in encoding of spatial components of the environmental context [15] More work needs to be done to characterize the exact nature of the encoding deficit

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