

Phencyclidine and Behavior: I. Sensory-Motor Function, Activity Level, Taste Aversion and Water Intake¹

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KESNER, R. P., J. D. HARDY AND L. D. CALDER. *Phencyclidine and behavior: I. Sensory-motor function, activity level, taste aversion and water intake*. PHARMAC. BIOCHEM. BEHAV. 15(1) 7-13, 1981.—Phencyclidine (PCP) injections in rats at doses of 4 mg/kg increased activity level, which might have been a function of impaired habituation. At doses of 8 mg/kg PCP produced a marked reduction in activity level. At doses of 12 mg/kg and above there were profound disruptive effects in detection of odors, visual square and touch measures, and performance of placing reflexes requiring visuo-motor coordination, righting, grasping reflexes, and equilibrium. Decreases in water intake occurred only at higher dose levels of PCP (16 and 24 mg/kg). On a qualitative basis the changes observed in rats are similar to changes described for humans.

Phencyclidine Behavior Sensory-motor function Activity Taste aversion Water intake

SINCE its discovery, phencyclidine 1-(1-phenylcyclohexyl) 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 stuporous states.

Recently the drug has appeared on the illicit market and has become known as "angel dust" or "PCP". According to Burns and Lerner [2] 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 hours. However, a completely normal state is not reached until 24-48 hr later. According to Burns and Lerner [2] 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.

For example, Morgenstern, Beech, and Davies [8] tested 18 human subjects given 7.5 mg of PCP orally and measured sensory thresholds based on perimetry, audiometry, visual acuity, taste thresholds, touch thresholds, two-point discrimination, and position sense. Over the first 2 hours of testing they found sensory impairment in all sensory modalities. Some modalities were affected more than others, in

particular two-point discrimination and touch thresholds were markedly altered. It appears that general sensory effects precede the drug's psychological effects. Morgenstern *et al.* [8] suggested that the psychological symptoms produced by PCP might be a function of partial sensory deprivation. Cohen *et al.* [4], Domino and Luby [6], and Rosenbaum *et al.* [11] have reported that PCP (0.1 mg/kg in 150 cc of 5% glucose) given intravenously to normal human volunteers resulted in a constellation of symptoms including hyperactive reflexes, diminution in position sense, pain, touch, staggering gait, gross distortions of subjective body image, anxiety, feelings of isolation, and timelessness.

Since experimentation with human subjects is limited to ethical concerns, the development of an animal model for PCP effects upon general functioning including sensory, perceptual, motor, motivational, emotional, social, learning, and memory aspects, would be of importance.

Based on PCP effects upon sensory responsiveness [8,11] and motor coordination in humans [12], it appeared to be of primary importance to determine the effects of various dose levels of PCP upon sensory and motor function in the rat. Thus far, using the rat very little systematic research concerning the effects of various doses of PCP upon sensory and motor function has been conducted. Domino [5] reported that in a pole-jump avoidance task escape latencies to foot-shock were markedly increased in rats under the influence of PCP. It appeared that these animals were disorganized and blind. They would jump haphazardly and miss the pole accounting for enhanced escape latencies. Pryor, Husain, Lar-

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sen, McKenzie, Car, and Braude [10] described similar PCP effects in that rats appear to run literally into any barrier present. These two studies suggest that PCP might alter visual and perhaps proprioceptive and painful inputs. With respect to PCP effects on motor coordination, Chen, Ensor, Russell and Bohner [3] and Pryor *et al.* [10] noted ataxia and impairment on a rotarod test at low doses (2–10 mg/kg) and tremors with a cataleptoid state at extremely high doses (50 mg/kg). Also, Murray and Horita [9] reported that PCP produces a dose dependent increase in head swaying, circling, and backward walking. Thus, in general, it appears that PCP impairs sensory and motor functions, but more specific and systematic study is necessary.

EXPERIMENT 1

METHOD

Subjects

Twelve male Long-Evans rats, initially weighing 325–450 g, were used as subjects. All animals were maintained ad lib throughout the experiment.

Procedure

All animals were injected IP with 4, 8, 12, 16, or 24 mg/kg of PCP (Sernylan, Bioceutic Co.) or saline. Each animal received each drug dose or saline with the order of drug injections counter-balanced among animals. Injections were given once a day.

The experimenter was naive as to the drug dose administered as well as the type of drug administered (i.e., PCP or saline).

Neurological tests. All tests were administered on each of the six days. Thirty minutes after injection all animals were first placed in a small wooden box with a Plexiglas front (24×24×13 inches) and observed for a 5 min period. The animals were then given specific neurological tests. For the first four tests animals were placed on a table.

(A) Sensory Tests

1. *Olfaction orienting test.* Since normal rats will tend to orient to novel stimuli, two pungent (to humans) scents were used in this test (ammonia and Mennen Skin Bracer) to determine the effects of PCP on the olfactory orienting response. A cotton swab was moistened with either scent. Then the swab was brought from behind the animal's head toward the nose. The swab was not allowed to enter the animal's visual field, nor was it allowed to touch the animal. The rating scale of response was 0 if no orienting response occurred and 1 if the animal oriented by sniffing at the swab. There were four tests (2 with each odor) brought from the right and the left sides. The average of the four tests was used as an index of olfactory detection.

2. *Visual stimulus orienting test.* A 2×2 inch corrugated cardboard square was held by a pair of hemostats. This square was brought from behind the animal's head into its peripheral field of vision. The rating scale for response was the same as above. There were two tests, one from the right and the other from the left. The average of the two tests was used as an index of visual detection.

3. *Somatosensory orienting tests.* Using a Von Frey hair of 2 g pressure, the rat's shoulders, mid-section, and hindquarters were touched on both right and left sides. The animal's orienting response was recorded using the following

scale: 0 for no response, 1 for an orienting response. The average of the six responses was used as an index for somatosensory detection.

4. *Whisker touch orienting test.* A cotton swab was brought from behind the animal's head out of the animal's visual field and put in contact with the vibrissae successively on their right and left sides. The response recorded was based on the same scale as tests 1 and 2. The average of the two responses was used as an index of whisker touch detection.

(B) Sensory-Motor Tests

1. *Placing reflex test.* For this test the animal was suspended by the tail. While suspended the animal was brought close to the edge of a table. When within reach of the table a normal animal will respond by reaching for the table. If the only stimulus necessary for forelimb extension was the sight of the table it was rated as a 1, if it required first touch of the vibrissae the score was 3/4, if it required the touch of the snout the score was 1/2, if it required the maintenance of the snout touching the table the score was 1/4, and if no response was elicited a 0 was given.

2. *Tilted platform test.* Each animal was placed on the center of a 30×30 cm square of carpet-covered plywood. The plywood was tilted down to 30° so that the rat's head was at the low end. If the animal responded normally it would turn around so its head faced up the slope. This response was given a 1. If the animal remained in the original position a 0 was given.

(C) Motor Tests

1. *Grasping reflex.* The rat was suspended by the nape of the neck then the palms of both front feet were touched by a single piece of stiff piano wire. Grasping is accomplished by flexion of fingers around the wire. The rating scale used was 0 for no response, 1 for grasping the wire.

2. *Righting reflex (roll over).* In this test the animal was placed on its back, if the animal righted itself the score given was a 1, if the animal failed to right itself the score given was a 0.

3. *Righting reflex (free fall).* In this test the animal was held upside down 40 cm above a foam pad, then the animal was dropped. If the animal landed on its feet a score of 1 was given, if anything else a 0. All tests were completed within 3 minutes.

RESULTS AND DISCUSSION

General Observations

During the 5 min observation period, saline injected animals first engaged in exploratory behavior, such as sniffing, righting, and rearing at the walls of the box. As these behaviors decreased the animals spent more time grooming and washing. With a dose of 4 mg/kg PCP the animals did not differ from saline injected animals, but they appeared more active in their exploratory behavior. With a dose of 8 mg/kg PCP, the animals were much less active than either 4 mg/kg PCP or saline injected groups. Two animals exhibited stereotypic motor movements (head swaying from side to side). Also one animal exhibited unsteady gait and a loss of balance. With a dose of 12 mg/kg PCP, the number of animals exhibiting stereotypic head swaying, unsteady gait and loss of balance increased to 83%. One animal walked in circles repetitively. With a dose of 16 mg/kg PCP stereotypic

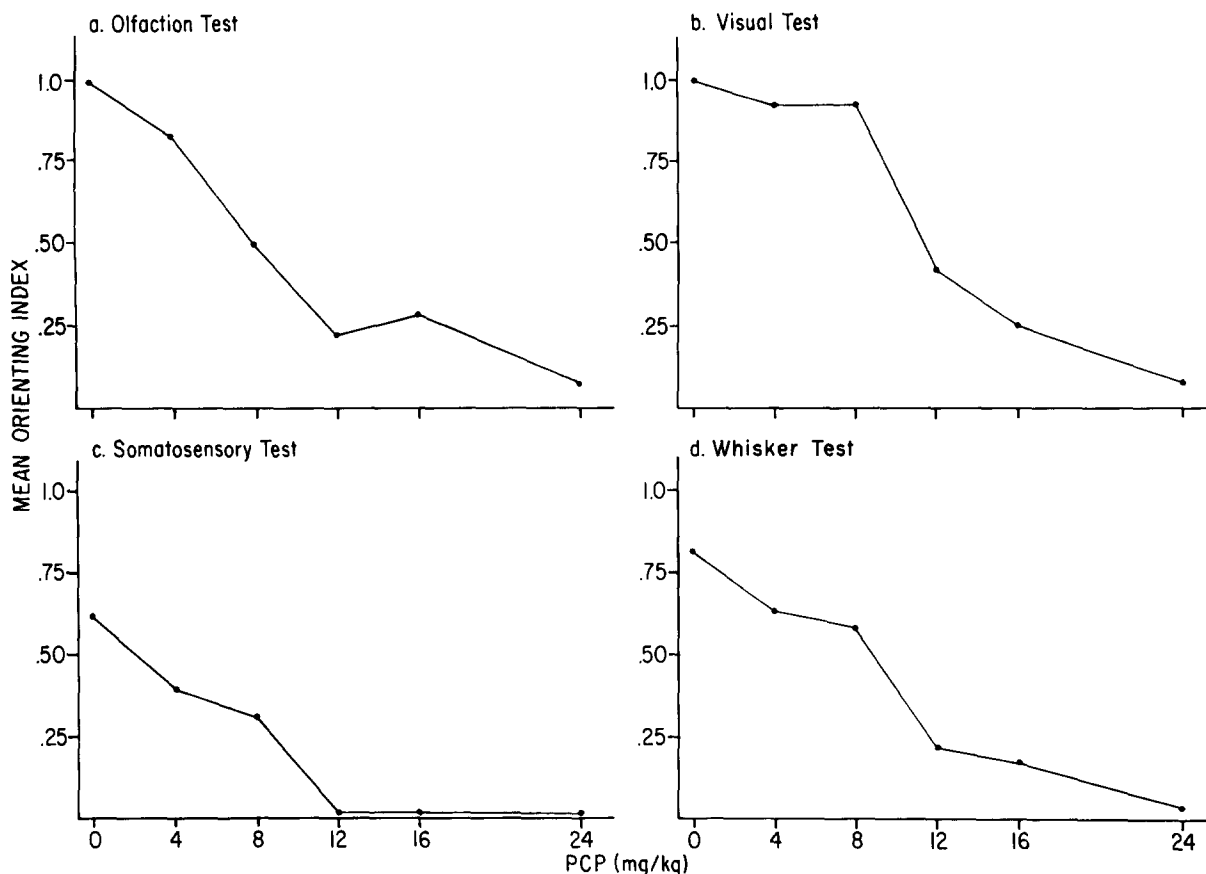


FIG. 1. The effects of various doses of PCP (4, 8, 12, 16, and 24 mg/kg) and saline (0) upon mean orienting index for (a) detection of odors (olfaction test), (b) detection of a visual stimulus (visual test), (c) detection of touch (somatosensory test), and (d) detection of whisker touch (whisker test).

head swaying, unsteady gait, and a loss of balance occurred in all animals. Two animals were unable to stand. With a dose of 24 mg/kg PCP, again head swaying occurred in all animals. Grooming, chewing, and licking were most prevalent and half of the animals could not walk or stand.

Neurological Tests

The effects of PCP on sensory detection are shown in Fig. 1. In Fig. 1, the mean orienting index for each sensory test represents the mean of the groups performance on each sensory test's detection index (see METHOD) as a function of saline (0) or various doses of PCP (4, 8, 12, 16, 24 mg/kg). The results indicate that 12, 16, 24 mg/kg of PCP produces a marked disruption in responsiveness to odors, visual, and somatosensory stimuli. No critical changes appear to occur with 4 or 8 mg/kg of PCP. A one-way repeated measures analysis of variance resulted in significant F values ($p < 0.01$) for each sensory test. Newman-Keuls tests revealed that on the olfactory test the 12, 16, and 24 mg/kg of PCP resulted in an orienting index that was reliably lower compared to saline and 4 mg/kg ($p < 0.01$). On the visual square test and the whisker touch test the 12, 16, and 24 mg/kg doses of PCP resulted in an orienting index that was reliably lower compared to saline, 4, or 8 mg/kg doses of PCP ($p < 0.01$). On the somatosensory test the 12, 16, and 24 mg/kg doses of PCP resulted in an orienting index that was reliably lower compared to saline ($p < 0.01$).

The effects of PCP on sensory-motor tests and motor tests are shown in Figs. 2 and 3. The results indicate that 12, 16, and 24 mg/kg of PCP produces a marked disruption in the occurrence of placing, grasping, and righting reflexes and a loss of adequate performance on the tilted platform test. No critical changes appear to occur with 4 or 8 mg/kg doses of PCP. On each test a one-way repeated measures analysis of variance resulted in significant F values ($p < 0.01$). Newman-Keuls tests revealed that for placing, grasping, and righting (roll over and free fall) reflexes 16 and 24 mg/kg of PCP inhibits performance compared to saline, 4, and 8 mg/kg of PCP ($p < 0.01$). Twelve mg/kg of PCP affects placing and grasping reflexes, but not the righting reflexes and performance on the tilted platform.

In summary, the data indicate that impairments in normal sensory-motor and motor functions occurred at doses of 12, 16, and 24 mg/kg of PCP. Some non-significant changes occurred at 8 mg/kg, but no impairments were seen at 4 mg/kg of PCP. Based on counterbalancing the order of drug presentations across subjects and the observed consistency in pattern of drug effect on sensory-motor functioning, it is not likely that tolerance effects of PCP could have contributed to the results. Similar to [9] stereotypic behaviors (head swaying and circling) were observed, but whereas Murray and Horita observed these behaviors at 4 mg/kg, in the present study the behaviors were not seen until 8 or 12 mg/kg of PCP were used. Strain differences (Long-Evans vs Sprague-

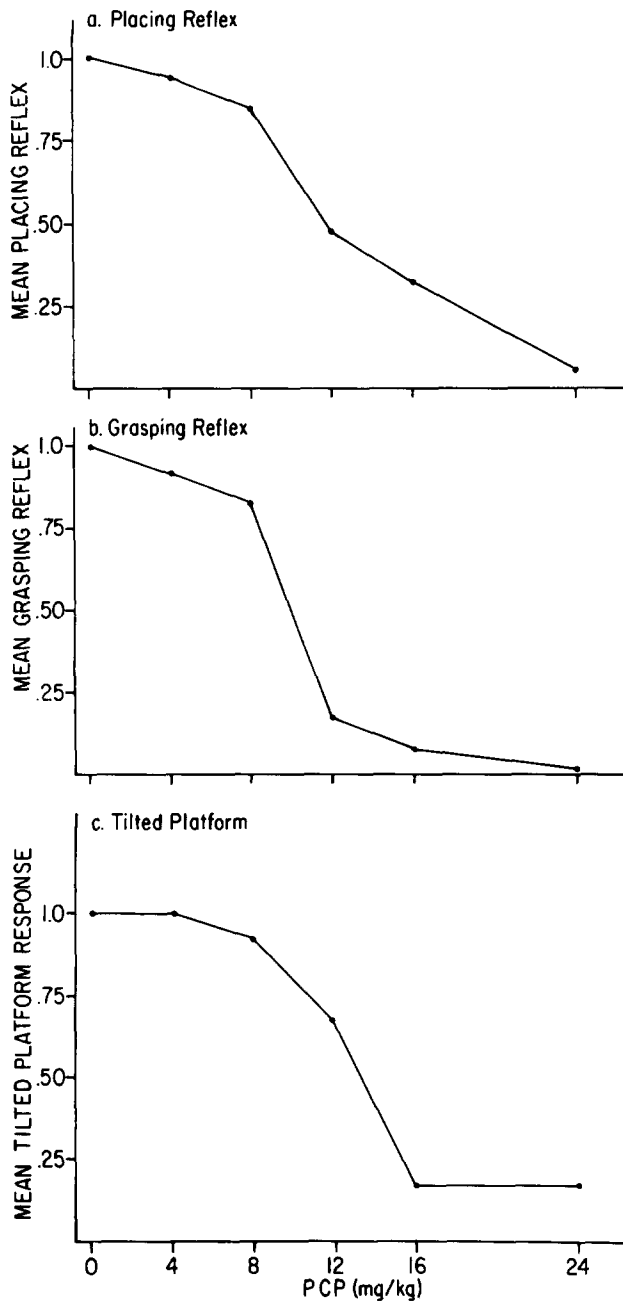


FIG. 2. The effects of various doses of PCP and saline upon (a) mean placing reflex, (b) mean grasping reflex, and (c) mean tilted platform response.

Dawley) could perhaps account for this differential sensitivity to PCP.

EXPERIMENT 2

Since in humans PCP produces sedative and emotional effects (e.g., negativism, hostility, and irritability), leading to impoverished social interactions [2, 6, 12], it is of importance to determine the effects of various dose levels of PCP upon activity level and emotionality. Only a few investigators have studied the effects of PCP on activity level and emo-

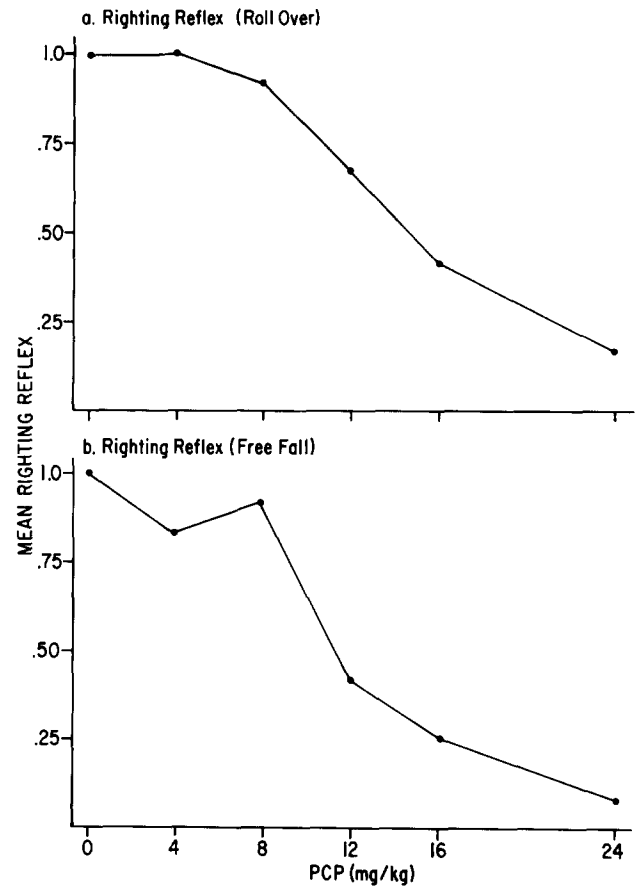


FIG. 3. The effects of various doses of PCP and saline upon (a) mean righting reflex (Roll Over) and (b) mean righting reflex (Free Fall).

tionality in animals. Chen *et al.* [3] showed that (on the basis of 3 rats per dose) 2, 4, and 8 mg/kg PCP results in a marked increase in activity level as measured by a jiggle cage. With higher doses (50 mg/kg), however, they report that PCP produces a cataleptic state. Pryor *et al.* [10] also described an increase in spontaneous locomotor activity, but only with a 5 mg/kg PCP dose; lower doses 1.25, 2.5 mg/kg PCP produced no significant change in activity level. In an open field, however, these same authors found that 2.5 mg/kg PCP markedly enhanced locomotor activity without changes in time spent grooming. With respect to possible measures of emotionality in the open field like frequency of urination and defecation, Pryor *et al.* [10] observed increases in urination without changes in defecation. Thus, in general, PCP appears to produce increases in activity with low doses and decreases with high doses.

The purpose of this experiment was to investigate more thoroughly the possible dual dose-dependent effects of PCP upon activity level.

Subjects

Thirty naive male Long-Evans rats, initially weighing 325–450 g, were used as subjects. All animals were maintained ad lib throughout the experiment.

Apparatus

The open field for evaluating level of activity and emo-

TABLE 1
MEAN FREQUENCY OF NON-LOCOMOTOR BEHAVIORS AS A
FUNCTION OF DRUG INJECTIONS

Group	Mean frequency of defecations and urinations	Mean frequency of righting, washing, grooming and scratching responses
Saline	3.2	39.1
4 mg/kg PCP	2.6	18.4
8 mg/kg PCP	3.2	10.4

tionality consisted of a large wooden square box (120×120 cm) with 29 cm high walls. The floor of the box was painted white and was divided by black lines into 64 square sections each measuring 15×15 cm.

Behavioral Procedure

Thirty minutes after a saline (n=10), 4 mg/kg PCP (n=10) or 8 mg/kg PCP (n=10) injection each animal was placed in the center of the open field for a 10 min period. The number of squares entered and the number of different activities (grooming, scratching, righting, washing, defecating, urinating) that were emitted during each minute were recorded. A "square entry" in the open field consisted of having all four feet within one square.

Calculations

For each animal the urination and defecation frequencies were combined into a single score. This score was used as an index of emotionality. For each animal the righting, washing, scratching, and grooming frequencies were also combined into a single score. This score was used as an index of activity other than locomotion.

RESULTS

The effects of 4 or 8 mg/kg PCP and saline injections on the mean urination and defecation score and the righting, washing, grooming, and scratching score are shown in Table 1. No differences were found in terms of average frequency of urination and defecation. However, marked differences occurred for righting, washing, grooming, and scratching. An analysis of variance revealed a significant difference among the groups, $F(1,27)=18.33$, $p<0.001$. Additional Newman-Keuls tests indicated that compared to saline both 4 and 8 mg/kg PCP resulted in a significant ($p<0.01$) reduction in frequency of righting, washing, grooming, and scratching responses.

The mean number of squares traveled per minute across a 10 min period are shown in Fig. 4 for saline, 4, and 8 mg/kg PCP injected animals. The data indicate that 4 mg/kg PCP injections result in an activity level that is not different from saline injected animals, at least for the first 5 min, but that saline injected animals habituate (decrease their exploration) while 4 mg/kg PCP injected animals maintain the same level of activity for the next 5 minutes. The 8 mg/kg PCP injected animals show a decrease in activity level, but they slowly increase in activity across time. A two-way analysis of variance revealed a significant drug by minutes interaction, $F(18,243)=2.23$, $p<0.01$. Further tests using Newman-Keuls

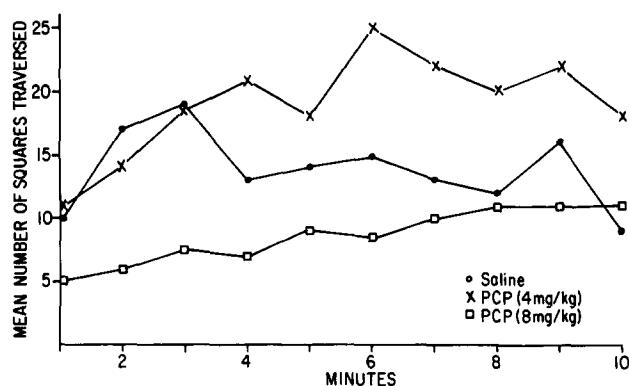


FIG. 4. Effects of saline, 4, 8 mg/kg PCP upon mean number of squares traversed across a 10 min period.

revealed that for minutes 2 and 3 both saline and 4 mg/kg PCP groups showed greater number of squares traversed as compared to the 8 mg/kg PCP group ($p<0.05$). For minutes 4 and 5 only the 4 mg/kg PCP group displayed increased activity compared to the 8 mg/kg PCP group ($p<0.05$). For minutes 6, 7, 8, and 9 the 4 mg/kg PCP group displayed greater activity level compared to the saline and 8 mg/kg PCP groups ($p<0.05$). No significant differences emerged on the first or the last minutes of the open field test.

DISCUSSION

Based on the urination and defecation score of emotionality no significant changes occurred with PCP doses of 4 and 8 mg/kg. The reduction in frequency of righting, washing, grooming, and scratching responses as a result of PCP injections was partially a function of alterations in motor coordination, especially in the 8 mg/kg PCP injection group and could clearly be seen in difficulty in negotiating a righting response. With respect to overall activity level, it is clear that 4 mg/kg PCP results in an increase in activity level and 8 mg/kg PCP results in a decrease supporting previous observations of Chen *et al.* [3] and Pryor *et al.* [10]. However, a closer scrutiny of the data reveals that the increase in activity seen with 4 mg/kg PCP might be a function of a lack of habituation to the open field. There were no differences between saline and 4 mg/kg PCP during the first five minutes, but for the next 5 minutes the 4 mg/kg PCP maintained a high level of exploration, whereas, the saline treated animals reduced their activity level. There was clearly a reduction in activity level with 8 mg/kg PCP, but note that there was also a lack of habituation. It cannot be ascertained from the reports of Chen *et al.* [3] and Pryor *et al.* [10] whether reduced habituation to the testing apparatus was responsible for the PCP-induced increases in overall activity level. Thus, there appears to be a strong possibility that PCP has only direct depressant effects on activity, which would be consistent with observations of PCP in humans. PCP-induced increases in activity level would be a secondary consequence of impaired habituation.

EXPERIMENT 3

Since in humans PCP can produce abdominal cramps, nausea, and vomiting [1,2], it was deemed to be of importance to determine whether PCP produces illness in rats,

TABLE 2

MEAN GRAPE JUICE CONSUMPTION (PERCENTAGE OF WATER BASELINE) AS A FUNCTION OF DRUG INJECTION

Group	Test 1	Test 2
Saline	36%	67%
8 mg/kg PCP	33%	49%
24 mg/kg PCP	37%	60%
15 mg/kg Apomorphine	47%	24%

even though Sioris and Krenzelock [14] and Shulgin and MacLean [13] have suggested that illness effects are due to byproduct contaminants rather than from PCP itself.

Subjects

Thirty-six naive Long-Evans animals initially weighing 325–450 g were used as subjects. They were maintained on a 23³/₄ hr water deprivation schedule.

Procedure

One week later all animals were divided into four groups and given a 15 min drinking period of grape juice (Test 1) (Bel-Air frozen concentrate, diluted 3/1 in water) followed immediately by an IP injection of 8 mg/kg PCP (n=8), 24 mg/kg PCP (n=12), saline (n=8), or 15 mg/kg apomorphine (n=8). The next day all subjects were given 15 min of water. On the third day the grape juice was again offered instead of water and consumption for the 15 min was measured (Test 2). Decreases in consumption of grape juice on Test 2 relative to Test 1, expressed as a percentage of initial consumption of water, was used as an index of degree of taste aversion.

RESULTS

The results are shown in Table 2 and indicate that 8 and 24 mg/kg doses of PCP result in an increase in grape juice consumption on Test 2 relative to Test 1, indicating a total absence of taste aversion. In contrast apomorphine produces a decrease in grape juice consumption on Test 2 relative to Test 1, indicating the development of taste aversion. A two-way analysis of variance revealed that there were significant changes in grape juice consumption comparing Test 1 and 2, $F(1,32)=9.78$, $p<0.01$, and there was a significant interaction between tests and drug treatment, $F(3,32)=10.36$, $p<0.01$. The interaction resulted from increased consumption on Test 2 for saline, 8, and 24 mg/kg PCP injections and decreased consumption on Test 2 for apomorphine injections.

DISCUSSION

It was found that doses of 24 mg/kg of PCP, which produce clear sedative effects (animals looked sick), do not produce taste aversion. The results are consistent with the suggestion of Sioris and Krenzelock [14] and Shulgin and MacLean [13] that abdominal cramps, nausea, and vomiting in humans are more likely due to byproduct contaminants found in street samples rather than from PCP itself.

TABLE 3

MEAN WATER CONSUMPTION (cc) AS A FUNCTION OF DRUG INJECTION

Group	First 15 min	First hour
Saline	17.0	25.0
4 mg/kg	18.5	32.0
8 mg/kg	17.5	30.0
12 mg/kg	13.5	23.5
16 mg/kg	7.0	15.5
24 mg/kg	0.0	0.0

These data are also in agreement with the lack of taste aversion observed with monkeys [15], but do not agree with the induced taste aversion reported for low doses (10 mg/kg) of PCP in mice [7].

EXPERIMENT 4

Since in humans PCP can produce alterations in food and water intake [1,2], it was important to test whether PCP disrupted water intake in rats.

Subjects

Twelve naive male Long-Evans rats, initially weighing 325–450 g, were used as subjects. They were maintained on a 23 hr water deprivation schedule.

Procedure

After establishing a stable water intake baseline across a one week period, animals were injected with either saline (n=2), 4 mg/kg PCP (n=2), 8 mg/kg PCP (n=2), 12 mg/kg PCP (n=2), 16 mg/kg PCP (n=2), or 24 mg/kg PCP (n=2). Thirty minutes later they were given water. Total water intake was measured every 15 min.

RESULTS AND DISCUSSION

The effects of PCP on average water intake for the first 15 min and for 1 hour is shown in Table 3. Low doses of PCP (4, 8, 12 mg/kg) had no effect on water intake, while reduced water consumption appeared at 16 mg/kg and no water consumption at 24 mg/kg. Thus, a motivational state change as indexed by water intake does not manifest itself until the animal has been exposed to high doses of PCP. The reasons for this reduction in water intake were not investigated, but taste aversion can be ruled out as a contributing factor. More likely the lack of motor coordination might have contributed significantly.

GENERAL DISCUSSION

In conclusion, there appear to be clear dose-response effects of PCP upon a variety of behavioral functions. At low doses of PCP (4 mg/kg) there were no major effects on sensory and motor function, emotionality, motivation, and taste aversion. The only observed effect was an increase in activity level which was assumed to be a secondary consequence of inefficient functioning of response habituation. At 8 mg/kg some disruption of sensory and motor function can be observed as well as a depression of activity level. No effect can

be seen on emotionality, taste aversion or motivation. At 12–16 mg/kg major impairments of sensory and motor function are observed including stereotypic motor movements. Finally at doses of 24 mg/kg there were, in addition to impairment of sensory and motor function, also motivational impairments, but no effects on development of taste aversion.

These data are important for at least two reasons. First, it

appears that on a qualitative basis PCP produces in rats changes in sensory and motor functions, activity level and motivation similar to what has been described in humans. Thus, the rat could perhaps serve as a useful animal model to test the neurobiological effects of PCP. Second, these data should aid in the selection of appropriate doses to study the effects of PCP on more complex behavioral processes including learning and memory.

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