Pharmacology Biochemistry & Behavior, Vol. 33, pp. 281–283. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

PCP and Conditioned Place Preferences

SANDRA H. MARGLIN, WILLIAM C. MILANO, MARK E. MATTIE AND LARRY D. REID[1]

Department of Psychology, Rensselaer Polytechnic Institute, Troy, NY 12180-3590

Received 31 May 1988

MARGLIN, S. H., W. C. MILANO, M. E. MATTIE AND L. D. REID. *PCP and conditioned place preferences.* PHARMACOL BIOCHEM BEHAV 33(2) 281–283, 1989.—Phencyclidine (PCP), in doses of 0.25, 0.35, and 0.45 mg/kg, was administered systemically to male Sprague-Dawley rats in order to determine if a positive conditioned place preference (CPP) could be achieved. Other subjects received systemic injections of morphine, 4.0 mg/kg, as a standard for comparison. At testing, rats receiving 0.45 mg/kg PCP showed a positive CPP compared to controls, as did rats receiving morphine. Previous research had shown that larger doses of PCP and prolonged times after PCP administration produced aversion as indexed by CPP testing. The narrow dose range and short time span in which PCP's positively reinforcing properties are apt to emerge may be related to PCP's psychotomimetic potential and to its ability to sustain its own intake even though aversive effects are often manifest.

Phencyclidine PCP Conditioned place preference

THE essence of reinforcement from a drug's effects is that somehow the drug effect subsequently moves the subject to the place of a potential repetition of the drug experience and then to a repetition of the act of drug taking itself. We have a number of ways of indexing this complex phenomena we call drug reinforcement, the most salient of which is the repetition of the act of drug taking. Another way to index a feature of reinforcement from drugs is to measure a drug's ability to establish a conditioned place preference (CPP), a potential index of facets of this complex phenomenon (2,14). Testing for CPPs associated with administration of a drug has some advantages over other indices (9) and, therefore, it is a procedure of choice for certain kinds of studies.

Phencyclidine [1-(1-phenylcyclohexyl)piperidine; PCP] is taken recreationally by people, but has considerable psychotomimetic toxicity. Consequently, PCP is of interest from a number of points of view. PCP is self-administered orally (4) and intravenously (5,7), but the initial attempts (1, 10, 11) to establish a CPP using systemic injections of PCP failed to show that PCP elicited effects indicative of a conditionable positive affective state. In fact, the initial studies indicated that PCP elicited an aversive state. Yet, there is a report (8) indicating that an infusion of PCP into the accumbens nucleus sustains a CPP.

As we inspected the reports of studies of CPP using PCP, it was noticed that smaller doses were more apt to produce a positive CPP. Also, it was noticed that when conditioning times were restricted to a period shortly after injections that a positive CPP was more apt to emerge. Consequently, in our laboratory, some pilot studies were done using a range of doses of PCP and some variety of times and conditioning periods. From those studies, it was concluded that doses smaller than 0.125 mg/kg were not apt to be positive, i.e., similar to saline, and doses of 1.25 and 2.0 mg/kg were apt to be aversive.

Specifically, our pilot work confirmed (10) that 2 mg/kg of PCP, subcutaneously given (SC), with putative conditioning (numbers of pairings of PCP with side of putative conditioning = 6; of saline with other side = 6) beginning just after injections and lasting 10 min, produced reliable signs of aversion. The dose of 0.5 mg/kg, with the same parameters of conditioning, produced reliable signs of a positive CPP. With another procedure (4 pairing of PCP with putative side and 4 of saline with other side) with injections of PCP just before putative conditioning and lasting 15 min, we even observed reliable signs of aversion with doses of 1.0 and 1.25 mg/kg, SC. The only signs of positivity seen in pilot studies were with a dose of 0.5 mg/kg of PCP given just before the start of a 10-min conditioning session; but with other procedures using this dose, the result was not always positive. When putative conditioning encompassed periods greater than 30 min after injections, there were few signs of conditioning indicative of positivity.

From inspection of our pilot data and the results of work of others (1, 8, 10, 11), we reasoned that a positive CPP with PCP would only be observable when the doses were relatively small (say 0.5 mg/kg or less) and conditioning occurred shortly after injections (i.e., the effects of drugs paired with environmental cues before the passage of 30 min). PCP, at larger doses, seems to be aversive across all tests. Given some confusion concerning the possibility of a putative CPP with PCP, and given the consensus that large doses were aversive (as indexed by CPP testing), we did the following experiment using a range of smaller doses.

METHOD

Subjects

Sixty male Sprague-Dawley rats, purchased from Taconic Farms when they weighed between 175–200 g, served as subjects.

[1]Requests for reprints should be addressed to L.D. Reid.

When they arrived at the laboratory, they were housed individually in standard cages in a room having 12 hr of artificial light/day (lights on at 0800 hr) and a constant temperature of 24°C. Subjects had food (standard laboratory blocks) and water always available in their home cages.

Apparatus

The alleys used to assess CPPs were 12 nearly identical rectangular boxes, 65 × 17 × 33 cm, each of which was enclosed in a larger sound-attenuating box having a ventilating fan. Each alley had two distinctive sides. One side's walls were gray; the other's walls were black and white stripes. The floor of the striped side was a grid with the stainless steel rods running perpendicular to the length of the alley. The floor of the gray side had rods running parallel to the length.

Each alley was suspended by an axle running through the middle of the top of the alley, so that the alley tilted slightly to one side when a rat was in that side. When the alley tilted, it closed a circuit, producing signals that were read into an IBM PC. The software of the PC tabulated the rats' cumulative time spent on each side of an alley.

Over the clear Plexiglas ceiling of the alley (which also served as the door) there were lights, one over each side. Brightness of the light was adjusted so that, in general, rats did not show a preference for one side over the other prior to conditioning. Across 15 previous experiments, and the same apparatus, the mean percentage of time that rats spent on the striped side was 49.2% at baseline, indicating that rats have no particular preference for a side prior to conditioning (13).

During part of the procedures, rats were confined to only one side of the alley by placing a barrier between the striped and gray sides. The side of the barrier facing the striped side was also striped and the other side was gray. On all days of the procedure, the alleys were washed with a detergent after their use to minimize odors that may have been due to a rat's occupancy. The rats were moved from the room containing their cages to the room of the alleys with the aid of a rolling cart having 12 cages.

Injections

Subjects always received subcutaneous injections, given 10 min prior to the start of conditioning sessions. Immediately after injections, rats were returned to their home cages and, after all injections were given, they were put into the cart for transport to the apparatus. The time of injection was noted so that rats were put into the chambers 10 min after injections. Morphine sulfate was given in doses of 4.0 mg/kg, prepared with a vehicle of physiological saline. PCP hydrochloride was given in doses of 0.25, 0.35, and 0.45 mg/kg, in a physiological saline vehicle. Placebo injections were always of vehicle. Injection volumes for all solutions were 1 ml/kg.

Procedure

Ten days after the rats arrived in the laboratory, they began the procedures of CPP testing. Across the next 3 days, rats received special handling in order to ensure they were accustomed to being handled. On the next day, they were placed into the alley (no barrier) for 30 min to habituate them to the apparatus. On the next day, rats' times on each side of the alley were tabulated during a 30-min period, and these scores served as a baseline, preconditioning, index of rats' preferences for a side. With baselines tabulated, conditioning began. Conditioning involved putting the subject into only one side of the alley (barrier in place) while it experienced the effects of an injection.

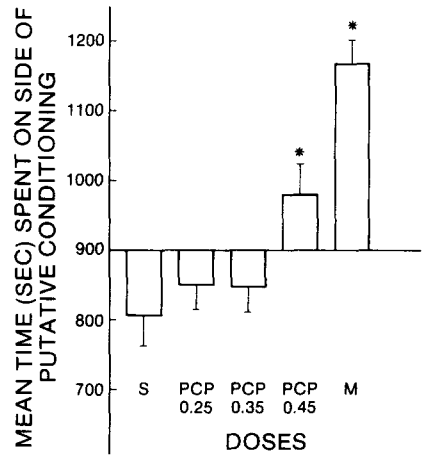

FIG. 1. Values shown are means of times (sec) spent on side of putative conditioning on test day across 1800 sec. Bars represent the standard error of the mean. Mean sec on side of putative conditioning (all subjects) at baseline was 888.30. During conditioning, subjects received injections 10 min prior to being placed into a side for 20 min. S refers to the group that received saline; PCP 0.25, PCP 0.35, PCP 0.45 refer to the groups that received phencyclidine (and the doses in mg/kg); M to the group that received morphine. An asterisk indicates that the mean is reliably different ($p<0.05$) than the mean of the control group (leftmost value).

Rats were randomly assigned to 5 different groups, 12 rats a group as well as randomly assigned to receive putative conditioning either on the striped or gray side. One group had saline injections before every conditioning session, i.e., a control group. One group was given injections of morphine on those days designated as days of putative conditioning, and of vehicle on the other conditioning days. Prior experiments in our apparatus using very similar procedures have produced reliable CPPs with this dose of morphine (13). These animals were included in the experiment, therefore, merely as a basis of comparison, or a standard, with which to test the general efficiency of the procedure. The subjects of the three other groups each received injections of one of the three different doses of PCP on days of putative conditioning, and of vehicle on the alternative days.

Across 12 days, conditioning sessions occurred once a day, beginning 10 min postinjection and lasting for 20 min, i.e., the pairing of the alley with a drug experience was limited to drug effects occurring 10 to 30 min after injections. Conditioning followed a pattern of 3 days of putative conditioning followed by a day of alternative conditioning. Previous experiments with our CPP apparatus have revealed that this approach (more pairings of the effects of drug injections with the putative side of conditioning than pairings of the effects of placebo injections with the alternative side of conditioning) is a conservative assessment of a drug's effects since rats receiving only placebos have a propensity, at testing, to spend the most time in the place where they have been the least (13).

On the last day of the procedure, the test, subjects were not given injections but were placed in the alleys (without the barrier in place) for 30 min and time spent on each side of the chamber throughout the session was tabulated. Previous results suggest that 30 min is an optimal period to index morphine's CPP (13).

Statistics and Data Reduction

The rats' performances at baseline (mean time on side of putative conditioning = 49.35% of total time) were very similar to those of previously tested rats. It follows, therefore, the mean time

spent on side of putative conditioning at testing reflects a group's experiences with drug during conditioning. Previous research (13) indicates that this schedule of conditioning under only placebo often results in slightly less time on the side of putative conditioning at testing, an expectation met by the subjects receiving saline. Previous research (13) also indicates that rats getting morphine on side of putative conditioning, on the same schedule, will spend more time on the side of putative conditioning at testing, an expectation met in this experiment. Side of putative conditioning, striped or gray, is also of little consequence in this or previous experiments (13). Given these considerations, the design dissolves into a one-way analysis of variance (ANOVA) of scores (sec on side of putative conditioning) at testing. The comparison of interest is that between scores of placebo and of 0.45 mg/kg of PCP, which previous work indicated was apt to be an effective dose, a comparison assessed by way of a *t*-test for independent samples.

RESULTS

The results are summarized in Fig. 1. ANOVA of the data of the figure yields an, $F(4,55)=5.26$, $p=0.0012$. The scores of subjects getting morphine are reliably different than those getting saline, $t(22)=5.54$, $p<0.001$. The scores of those getting 0.45 mg/kg of PCP are reliably different from those getting saline, $t(22)=2.35$, $p<0.05$, whereas the scores of subjects getting the other two doses of PCP are not. Notice, however, that the most effective dose of PCP was not as effective as the dose of morphine used as a standard, however, smaller doses of morphine produce less signs of a positive CPP (13).

DISCUSSION

PCP can be used to establish a positive CPP when PCP is given in smaller doses (about 0.5 mg/kg, SC) and when the time of conditioning is shortly after administration (across 30 min after injections). PCP at larger doses (e.g., 2.0 mg/kg, SC) is aversive as indexed by CPP testing [pilot studies mentioned in Introduction, (10,11)].

PCP can be added to the list of agents that will be self-administered by laboratory subjects, taken recreationally by people, and will establish a CPP. The conditions of PCP's positive CPP, however, are revealing. PCP established a positive CPP only at one dose of the doses tested in this and previously published studies indicating that PCP's positivity is apt to be limited to a very narrow span of doses.

There is an apparent paradox associated with PCP's effects; i.e., it is taken recreationally, yet often produces effects that seem to be aversive. This apparent paradox is resolved, in part, by knowing that smaller doses are apt to be positive shortly after being administered, whereas larger doses are apt to be aversive. Also, the aversive effects are apt to be delayed. The condition of positivity first, followed by aversiveness, is a condition sustaining an operant, even with very harsh delayed aversiveness (3, 6, 12). Although there may be considerable folklore among people using PCP recreationally concerning optimal dosing, the narrow range of doses that apparently are positive is apt to be missed. This circumstance of being unable to always select optimal doses but often selecting doses having a positive effect shortly after administration is just the circumstance for there to be considerable usage with adverse effects.

ACKNOWLEDGEMENTS

The authors thank Yizhao Hui, Jean S. Bestle and Elizabeth A. Osganian for their assistance. The research was funded, in part, through Grant AA06212 from the National Institute on Alcohol Abuse and Alcoholism and Grant DA04440 from the National Institute on Drug Abuse.

REFERENCES

1. Barr, G. A.; Paredes, W.; Bridger, W. H. Place conditioning with morphine and phencyclidine: dose dependent effects. Life Sci. 36: 363–368; 1985.
2. Bozarth, M. A. Conditioned place preference: a parametric analysis using systemic heroin injections. In: Bozarth, M. A., ed. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987:241–273.
3. Buckwalter, M. M.; Gibson, W. E.; Reid, L. D.; Porter, P. B. Combining positive and negative intracranial reinforcement. J. Comp. Physiol. Psychol. 65:329–331; 1967.
4. Carroll, M. E. A quantitative assessment of phencyclidine dependence produced by oral self-administration in rhesus monkeys. J. Pharmacol. Exp. Ther. 242:405–412; 1987.
5. Carroll, M. E.; France, C. P.; Meisch, R. A. Intravenous self-administration of etonitazene, cocaine and phencyclidine in rats during food deprivation and satiation. J. Pharmacol. Exp. Ther. 217:241–247; 1981.
6. Casper, N. J.; Reid, L. D. Complex contingencies. Physiol. Psychol. 3:9–13; 1975.
7. Collins, R. J.; Weeks, J. R.; Cooper, M. M.; Good, P. I.; Russell, R. R. Prediction of abuse liability of drugs using IV self-administration by rats. Psychopharmacology (Berlin) 82:6–13; 1984.
8. Giovino, A. A.; Glimcher, P. W.; Mattei, C. A.; Hoebel, B. G. Phencyclidine (PCP) generates conditioned reinforcement in the nucleus accumbens (ACC) but not in the ventral tegmental area (VTA). Soc. Neurosci. Abstr. 9:120; 1983.
9. Hunter, G. A.; Reid, L. D. Assaying addiction liability of opioids. Life Sci. 33(Suppl. 1):393–396; 1983.
10. Iwamoto, E. T. Place-aversion conditioned by phencyclidine in rats: development of tolerance and pharmacologic antagonism. Alcohol Drug Res. 6:265–276; 1986.
11. Marquis, K. L.; Moreton, E. Place conditioning with phencyclidine (PCP): effects of route and drug experience. Fed. Proc. 45:1085; 1986.
12. Miller, D. E.; Reid, L. D.; Porter, P. B. Delayed punishment of positively reinforced bar presses. Psychol. Rep. 22:1073–1077; 1967.
13. Reid, L. D.; Marglin, S. M.; Mattie, M. E.; Hubbell, C. L. A system for measuring positive affect induced by injections of opioids. Pharmacol. Biochem. Behav.; submitted.
14. van der Kooy, D. Place conditioning: a simple and effective method for assessing the motivational properties of drugs. In: Bozarth, M. A., ed. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987:229–240.