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Pharmacological Specificity of the Phencyclidine Discriminative Stimulus in Rats

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MANSBACH, R. S. AND R. L. BALSTER. *Pharmacological specificity of the phencyclidine discriminative stimulus in rats.* PHARMACOL BIOCHEM BEHAV **39**(4) 971–975, 1991.—The discriminative stimulus effects of phencyclidine (PCP), pentobarbital and the competitive N-methyl-D-aspartate antagonist 3-([±]-2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) were examined in rats trained to discriminate PCP from saline under a 2-lever, food-maintained operant schedule. Dose-response curves were obtained for all three drugs at a PCP training dose of 1.25 mg/kg; subsequently, rats were retrained to discriminate either 0.56 or 3.0 mg/kg PCP. The dose-response to PCP was not substantially changed by raising or lowering the training dose. However, doses of pentobarbital and CPP produced augmented levels of substitution when the training dose was lowered and decreased substitution when it was raised. The changes in PCP training dose were, therefore, effective in either diminishing or amplifying the pharmacological specificity of the PCP stimulus. Under conditions where specificity was high (high training dose), neither pentobarbital (0.1–17 mg/kg) nor CPP (1–17 mg/kg) produced appreciable PCP-like stimulus effects, supporting evidence that competitive NMDA antagonists may be no more PCP-like than are barbiturates. These data provide additional evidence for differences in the behavioral effects of noncompetitive and competitive NMDA antagonists.

Phencyclidine NMDA CPP Drug discrimination

PHENCYCLIDINE (PCP) and PCP-like drugs have been shown in numerous studies to produce discriminative stimulus effects in animals (2). The cellular basis for most of PCP's biochemical and pharmacological effects has been ascribed to its actions at the PCP receptor, which may be a site within the cationic channel of the N-methyl-D-aspartate (NMDA) receptor complex, and efforts to elucidate the basis for PCP's behavioral effects have largely supported the in vitro findings [see reviews (11,12)]. Drugs which bind to the PCP receptor produce PCP-like stimulus effects with a potency directly related to their affinity for the site, and drugs of most other pharmacological classes tend not to produce PCP-like effects in the drug discrimination model unless they also bind to the PCP receptor (2,23).

The pharmacological specificity of the PCP stimulus has been less clear in PCP-trained animals tested with competitive NMDA antagonists or CNS depressants. While some reports describe common stimulus effects of these compounds with PCP or PCP analogs (5, 14, 19), other investigators report only partial generalization or no generalization in PCP- or ketamine-trained animals injected with the competitive NMDA antagonists 3-([±]-2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), NPC 12626, and CGS 19755 (7, 8, 13, 20). Partial generalization was also reported in PCP-trained animals tested with various barbiturates, illustrating that stimulus effects produced by competitive NMDA antagonists may be no more PCP-like than CNS depressants with little pharmacological activity at the NMDA receptor complex (7, 15, 20, 23). In fact, some evidence suggests that competitive NMDA antagonists may produce a discriminative stimulus more benzodiazepine- or barbiturate-like than PCP-like (4,22).

Of the many factors known to influence the likelihood of substitution in drug discrimination studies, the magnitude of the training-drug dose has on several occasions been shown to be particularly important. Training animals to discriminate low doses of a drug generally results in a wider range of compounds that will produce training-drug-appropriate behavior, and can also increase the apparent potency of drugs in doing so (6, 17, 18). On the other hand, high training doses can produce greater pharmacological specificity and lower sensitivity when other drugs are tested for generalization. If this relationship were to apply to the PCP discriminative stimulus, then it might be possible to more clearly assess the degree to which competitive NMDA antagonists and barbiturates produce PCP-like effects and thereby aid in understanding the pharmacological basis for PCP's unique psychoactive effects.

Three published studies have manipulated training dose in examining the discriminative stimulus effects of PCP (3, 10, 14). Results from each of these experiments suggest some evidence of an increased sensitivity of animals injected with PCP-like drugs to produce PCP-appropriate behavior when the training dose was relatively low. However, neither of the two studies examining drugs other than PCP (10,14) revealed a difference in pharmacological specificity of the PCP stimulus (i.e., generalization when tests with competitive NMDA antagonists or com-

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pounds of other drug classes were conducted) as a function of training dose. Although these results would suggest that cross-generalization between PCP and competitive NMDA antagonists is not sensitive to training dose, the low dose in the Jackson and Sanger study was not particularly low for the rat (i.e., 2 mg/kg), and the other study was conducted in pigeons, a species which may produce a different profile of NMDA antagonist effects.

The present study was an attempt to identify conditions under which the selectivity of the PCP stimulus can be altered. Generalization tests were conducted with pentobarbital and the competitive NMDA antagonist CPP before and after an increase or decrease in the PCP training dose. It was hypothesized that rats trained to discriminate low doses of PCP would be likely to emit PCP-like behavior when tested with these two drugs. Similarly, rats trained to discriminate a high dose of PCP would be more likely to demonstrate specificity for the PCP stimulus. Such a result would add support to suggestions that competitive and noncompetitive NMDA antagonists produce different subjective effects. If competitive antagonists could be demonstrated not to have appreciable PCP-like stimulus effects under high training-dose conditions, then this class of compounds might offer a decided advantage over PCP receptor ligands in a variety of disorders thought to be amenable to treatment with NMDA antagonists (16).

METHOD

Subjects and Apparatus

Twelve adult male Sprague-Dawley rats (Charles River), weighing between 300–400 g, served as subjects. Rats were maintained in an AAALAC-accredited animal facility and provided with ad lib access to water. An initial period of food restriction was imposed in which subjects' weights were reduced to 80–85% of their free-feeding weights. After training, these weights were allowed to slowly increase over the course of the experiment. Weights were maintained throughout the experiment by postsession supplemental feedings of Purina Rat Chow.

Daily (Monday–Friday) 30-min behavioral sessions were conducted in two-lever operant chambers (Coulbourn Instruments) equipped with a houselight and a food dispenser which delivered 45-mg pellets (Noyes). Sessions were controlled by a computer located in an adjacent room.

Training Procedure and Initial Dose-Response Curves

Subjects were initially trained to press each of the two levers under a fixed-ratio 1 (FR1) schedule of food reinforcement. Once this behavior was well-established, the ratio was slowly increased to 32 and then drug discrimination training was begun. Rats were injected 10 min before the session with either saline or PCP (1.25 mg/kg). For each of the rats, one lever was designated correct after PCP injection and the other as correct after saline injection. Lever-pressing produced food only on the injection-appropriate lever for that day; incorrect presses reset the response requirement on the correct lever. During the initial phase of discrimination training, injections preceding successive sessions alternated daily (i.e., PCP, saline, PCP, saline). After approximately 6 sessions, a double alternation procedure was followed (PCP, PCP, saline, saline).

Generalization testing began once the subject met the following criteria: 1) at least 80% of the total responses were made on the correct lever during four consecutive training sessions; and 2) the first 32 consecutive responses were completed on the correct lever during each of these sessions. After these initial training conditions were met, generalization tests occurred on Tuesdays and Fridays provided that the subject met the 80%-correct/first-FR-correct rule on the day before testing. On test days, responding on either lever was reinforced for the entire 30-min session. As on training days, however, all reinforced response runs had to consist of 32 consecutive responses on one lever. Overall response rates (in responses/s) were also collected for each session. On test days, the overall percentage of PCP-lever selection was considered to be valid data only if the overall response rate for the session was 0.05 responses/s or greater. Therefore, data presented for higher doses do not always reflect observations for the entire group. The response rate data are presented in either case. Each dose-response curve was preceded by test days on which the training dose of PCP or saline was administered. These data, presented to the left of each dose curve in Figs. 1–3, serve as a reference for the degree of stimulus control exerted by PCP and saline under test conditions. Dose-response curves were generated first for PCP (0.1–5.6 mg/kg), then for pentobarbital (0.3–17 mg/kg) and CPP (1–30 mg/kg), with all doses given in ascending order.

Change in Training dose and Redetermination of Dose-Response Curves

Following completion of the initial dose-response curves for PCP, pentobarbital, and CPP, animals were assigned to the "high" or "low" training dose group. Because individual rats reached this phase of training at different times, and because previous work has shown that only a subset of subjects tend to produce PCP-lever selection when injected with CPP or pentobarbital, an attempt was made to create groups that performed equally on the initial dose-response curves. Accordingly, rats were assigned scores based on their test-drug performances. A point was assigned to the subject if it produced at least 50% PCP-lever responding at any dose of pentobarbital or CPP; therefore, a minimum of 0 (>50% with neither drug) and maximum of 2 points (>50% with both drugs) was possible. As rats finished these dose-response curves, an attempt was made to assign equal numbers of subjects with scores of 0, 1 or 2 to the two training-dose conditions.

PCP training-dose changes took place in two phases. The dose for "low" training dose rats was first lowered to 0.75 mg/kg; once subjects met the standard training criteria, successful consecutive tests with 0.75 mg/kg PCP and saline allowed the subject to be moved to the new training dose of 0.3 mg/kg. Acceptable performances at 0.3 mg/kg could not be established in the first 3 rats tested, so a new training dose of 0.56 mg/kg was selected as the new "low" training dose. The remaining rats assigned to this group were moved to 0.56 mg/kg after completing training at 0.75 mg/kg. The PCP dose assigned to the "high" training-dose group was initially raised to 1.75 mg/kg; after completing successful tests as outlined above, the PCP dose was raised again to 3.0 mg/kg. After meeting similar criteria the training dose for two rats was raised to 5.6 mg/kg. This dose produced consistently low response rates in both subjects, and the attempt to establish performances under this training dose was, therefore, abandoned. Thereafter, 3.0 mg/kg served as the "high" training dose in all subjects.

After subjects met training criteria at their final training dose, PCP, pentobarbital, and CPP dose-response curves were redetermined in the same order as before. An additional dose (0.1 mg/kg) was administered in the pentobarbital curve. One rat (S8)

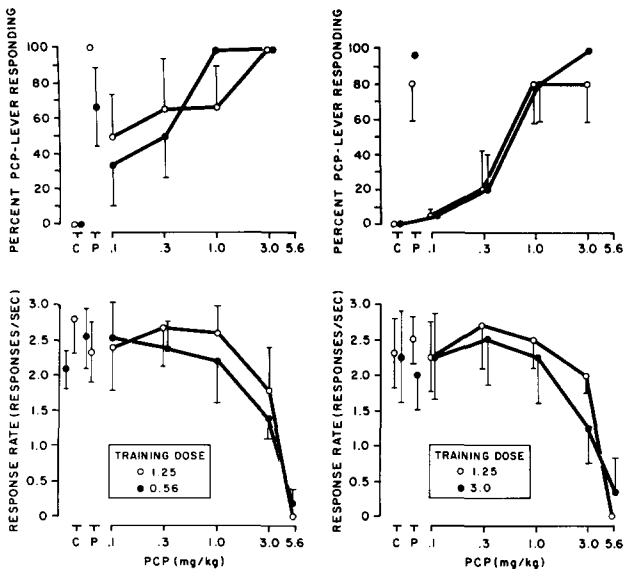

FIG. 1. Effects of training dose on PCP-lever selection (upper panels) and response rate (lower panels) in rats trained to discriminate PCP from saline. The left panels present PCP generalization test results (±S.E.) in 6 rats whose training dose was lowered from 1.25 to 0.56 mg/kg PCP. The right panels present data collected from 5 rats whose training dose was increased from 1.25 to 3.0 mg/kg. The unconnected points on the left side of each graph present test results in sessions where saline control ("C") or the training dose of PCP ("P") was administered.

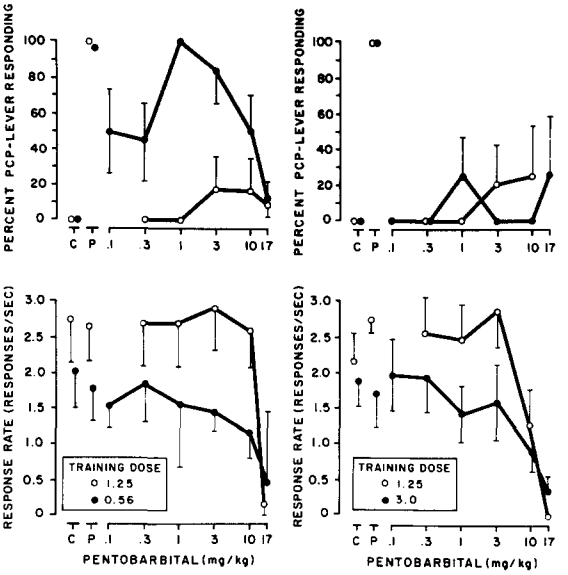

FIG. 2. Effects of PCP training dose on PCP-lever selection and response rate in rats tested with pentobarbital. Details are as described for Fig. 1.

became unhealthy and could not complete all conditions. Data for this subject are not presented.

Drugs

PCP HCl (National Institute on Drug Abuse) and pentobarbital Na (Sigma Chemical, St. Louis) were dissolved in saline and administered IP 10 min before behavioral testing. Doses of these compounds are expressed as the salt. CPP (Research Biochemicals Inc., Wayland, MA) was dissolved in equimolar NaOH to form a stock solution of 10 mg/ml and diluted with saline to appropriate concentrations. This compound was administered 60 min prior to behavioral testing. All drug doses were injected in a volume of 1 ml/kg.

RESULTS

Effects of PCP

At a training dose of 1.25 mg/kg, PCP produced a reliable discriminative stimulus in all subjects. Figure 1 (left panel: open circles) shows the effects of PCP in those subjects (S1, S2, S3, S4, S6, S10) later selected for the low training-dose group. The filled circles present the effects of the same animals later trained to discriminate 0.56 mg/kg PCP from saline. The dose-response to PCP was not appreciably different under the two training-dose conditions, although poorer performance on the PCP control test for rats discriminating 0.56 mg/kg of PCP may reflect somewhat weaker stimulus control at this training dose. PCP produced response-rate decreases at doses above 1 mg/kg under both training-dose conditions.

The right-hand panel of Fig. 1 presents the effects of PCP in those subjects selected for the high training-dose condition (S5, S7, S9, S11, S12). Increasing the training dose of PCP from 1.25 to 3.0 mg/kg did not greatly alter the sensitivity or efficacy of PCP in producing PCP-appropriate responding or in reducing response rates. As in the low-dose group, however, performance during the PCP training-dose control test was superior at the higher training dose.

Effects of Pentobarbital

In contrast to PCP, pentobarbital produced differing levels of generalization in rats trained to discriminate low or high doses of PCP. As shown in the top panels of Fig. 2 (open circles), the maximum amount of PCP-lever selection produced by pentobarbital was initially very similar in the groups of rats subsequently chosen for high and low training doses. However, rats subsequently trained to discriminate 0.56 mg/kg PCP produced much higher levels of PCP-lever responding when injected with pentobarbital than at the original training dose of 1.25 mg/kg. Pentobarbital produced 100% PCP-lever responding in all subjects at 1 mg/kg, with decreasing amounts of generalization at higher doses. In the high-dose group, pentobarbital did not produce markedly different levels of PCP-lever responding under the 3 mg/kg training dose condition than those at the original 1.25 mg/kg training dose. Pentobarbital produced less than 30% PCP-lever selection at all doses under the high-dose condition. Control response rates were higher during testing when 1.25 mg/kg was the training dose than when the training dose was lowered (Fig. 2, lower left panel) or raised (lower right panel). Considering these differences in control rates of responding, the effects of pentobarbital on response rate were not altered by changes in the PCP training dose. Severe response-rate decreases were produced in both groups at 17 mg/kg of pentobarbital.

Effects of CPP

As in a previous experiment (7), CPP produced partial generalization in rats trained to discriminate 1.25 mg/kg PCP from

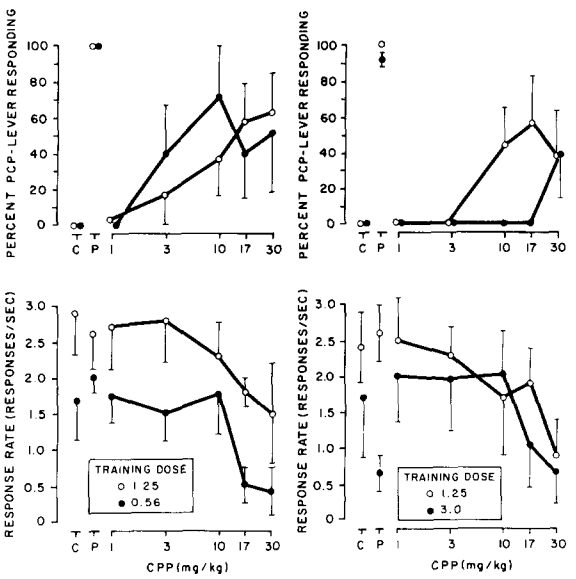

FIG. 3. Effects of PCP training dose on PCP-lever selection and response rate in rats tested with CPP. Details are as described in Fig. 1.

saline (Fig. 3). When the training dose of PCP was altered, generalization from PCP was not greatly affected at the highest dose tested (30 mg/kg), but at the intermediate doses of 3–17 mg/kg differences were apparent. When the training dose of PCP was lowered to 0.56 mg/kg, the mean PCP-lever selection increased at 3 and 10 mg/kg CPP (Fig. 3, upper left-hand panel). Increasing the training dose to 3.0 mg/kg decreased the amount of generalization to 0 percent in all subjects at CPP doses below 30 mg/kg.

DISCUSSION

The results of the present experiment suggest that training dose can, under some circumstances, be an important determinant in the pharmacological specificity of the PCP discriminative stimulus. Greater levels of substitution were produced by pentobarbital and CPP after the PCP training dose was lowered to 0.56 mg/kg than after it was raised to 3.0 mg/kg. Interestingly, changes in the PCP training dose had less of an effect on the sensitivity to PCP itself as measured by changes in the PCP dose-effect curve during substitution tests. Although greater levels of PCP-lever responding were produced by low doses of PCP in the low-dose group than in the high-dose group, these differences were also apparent before training-dose changes were made. Animals selected for placement in the low training-dose group tended to display a greater sensitivity to low PCP doses under original testing conditions than the group selected for the high-dose condition (Fig. 1). Another reason for a lack of increased sensitivity to PCP at the low training dose is that the two doses are not very different (about 2-fold). In the experiment by Beardsley et al. (3), sensitivity differences to PCP were observable at some doses when there was a 2-fold change in training dose, but dramatic differences were most clearly seen when there was a 4- or 8-fold difference in training dose. Similarly, in the Jackson and Sanger experiment (10), a 2-fold training-dose difference revealed only slight changes in sensitivity to PCP or dizocilpine, but Koek et al. (14) reported an approximate one-half-log shift in dose-response to PCP with a 3-fold difference in training dose. Thus selection of an initial training dose (i.e., 1.25 mg/kg) that could not be easily lowered may have made it inherently difficult to demonstrate increased sensitivity of the PCP stimulus to PCP or other drugs in the present experiment.

Generalization tests with pentobarbital revealed a clear training-dose effect (Fig. 2). Under initial training conditions neither group of rats emitted greater than a mean of 26% PCP-lever responding when any dose of pentobarbital was administered. In contrast, there was a substantial level of generalization in the low training-dose group at 5 of the 6 pentobarbital test doses administered, including complete generalization at the 1 mg/kg dose, but relatively little change was evident in the high training-dose group. Koek et al. (13) also observed little generalization to pentobarbital or chlordiazepoxide in rats trained to discriminate 2.5 mg/kg PCP—a dose close to the present "high" training dose.

There was a marked decrease in the level of generalization at the highest two doses of pentobarbital relative to lower doses under the low training-dose condition. This may have occurred because these higher doses were more salient and, therefore, more easily distinguished from the PCP stimulus, or perhaps the high doses produced some loss of stimulus control which accompanied the observed decreases in response rate.

Generalization tests with CPP also resulted in some evidence of training-dose-dependent behavior in rats trained to discriminate PCP, but in this case the clearest effects occurred in the high training-dose group. In agreement with previous experiments (7,20), an intermediate level of generalization was observed with CPP in both groups at the 1.25 mg/kg PCP training dose. In the present study at a PCP training dose of 3.0 mg/kg, CPP occasioned no PCP-lever responding at any dose below 30 mg/kg. In the low training-dose group, there was some evidence of an increase in sensitivity to CPP at intermediate doses (3 and 10 mg/kg).

Taken together, the present results with pentobarbital and CPP illustrate the importance of training dose in drug discrimination experiments. In general, there appeared to be less pharmacological specificity for the PCP stimulus at the low training dose, especially at low and intermediate doses of test compounds. These findings are in general agreement with those in experiments studying training-dose effects of opioids, in which low training doses of morphine led to considerable generalization when kappa agonists or stimulants were tested (6, 17, 18). The present finding that pentobarbital and CPP produce partial generalization in rats trained to discriminate PCP supports earlier results (7,20). The lower levels of generalization observed when the training dose of PCP was high exemplifies the principle that when animals are trained to produce behavior under very powerful stimulus control, even stimuli closely related to the training stimulus can be clearly distinguished (9).

The results of this study provide additional evidence for differences in the behavioral effects of the noncompetitive and competitive NMDA antagonists [see (23) for review]. Doses of CPP (1–17 mg/kg) that have previously been shown to have NMDA antagonist effects in rats, as evidenced by antagonism of the discriminative stimulus effects of NMDA (21) and by substitution in animals trained to discriminate the competitive NMDA antagonist, NPC 12626 (24), produced no evidence of PCP-like effects in this study under high training dose conditions. Indeed, CPP was no more similar to PCP than was pentobarbital, a drug with CNS depressant effects but no evidence of PCP-like abuse liability. Because PCP-receptor agonists, competitive NMDA antagonists and barbiturates share many common CNS depressant actions (1, 23, 25), it may not be altogether surprising that these classes of compounds should share some common stimulus effects as well. The present evidence that dif-

ferences among them can be amplified by altering the training dose provides a basis for placing these commonalities in perspective and for further exploring the conditions where similarities and differences can be demonstrated. The increasing evidence in animal studies for differences in the discriminative stimulus effects of noncompetitive and competitive NMDA antagonists suggests that each class may have a unique profile of acute effects in humans as well.

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