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Conditioned Taste Aversions as a Behavioral Baseline for Drug Discrimination Learning: An Assessment With Phencyclidine

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MASTROPAOLO, J. P., K. H. MOSKOWITZ, R. J. DACANAY AND A. L. RILEY. *Conditioned taste aversions as a behavioral baseline for drug discrimination learning: An assessment with phencyclidine.* PHARMACOL BIOCHEM BEHAV 32(1) 1–8, 1989.—When PCP was given prior to the pairing of saccharin with LiCl (and the PCP vehicle prior to a nonpoisoned exposure to the same saccharin solution), rats rapidly acquired the discrimination, avoiding saccharin consumption following PCP and consuming saccharin following the vehicle after only three conditioning trials. Conversely, when the PCP vehicle was given prior to the saccharin-LiCl pairing and PCP prior to a nonpoisoned exposure to saccharin, other subjects avoided saccharin consumption following the vehicle injection and readily consumed saccharin after an injection of PCP. During dose substitution sessions, animals displayed greater drug-appropriate responding as the dose of PCP increased. When a range of doses of ketamine was given in place of PCP prior to saccharin access, subjects displayed dose-dependent PCP-appropriate responding. When a range of doses of d-amphetamine was substituted for PCP, subjects displayed vehicle-appropriate responding at all doses. The relative efficacy of the taste aversion procedure as a baseline for drug discrimination learning is discussed.

Conditioned taste aversions Drug discrimination learning Phencyclidine Rats

OVER the past 25 years, the major focus of research on conditioned taste aversions (CTAs) has been on its empirical assessment and theoretical implications [see (12, 31, 32, 35)]. Recently, CTAs have also been utilized as a tool in the investigation of a range of applied issues. For example, within the last 10 years CTAs have been applied to the study of the dietary preferences of cancer patients (2,23), the control of predation (14) and the etiology and treatment of alcohol abuse (1, 11, 24).

CTAs have also been used as a pharmacological tool, e.g., in the assessment of drug dependence and tolerance (19, 24, 25, 42), drug toxicity (21, 26, 33) and pharmacological antagonism (13, 18, 34, 40). One area of research in behavioral pharmacology in which the taste aversion design might be applied is in the area of drug discrimination learning [for reviews, see (7–9, 25), for recent bibliographies, see (37,38)]. In typical research on drug discrimination learning [see (38)], an animal is trained to respond differentially as a function of the presence or absence of a drug. Based on whether various drugs substitute for the training drug once discrimination has been established, one can use the drug discrimination design in drug classification and receptor differentiation (7, 38, 39). In drug discrimination learning utilizing the conditioned taste aversion design, a drug would be administered prior to a taste/toxin pairing while its vehicle would be given prior to the pairing of the taste with a control injection (or the vehicle would be given prior to the taste/toxin pairing while the drug would be given prior to the pairing of the taste with a control injection). Discrimination would be evidenced if consumption was differentially suppressed following administration of the stimulus (drug or vehicle) that signalled the taste/toxin pairing.

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Although the taste aversion design has been widely used in pharmacological research, there has been no assessment of the ability of drugs to serve a simple discriminative function within the taste aversion paradigm. The present experiment addressed this issue. Specifically, phencyclidine (PCP) was examined for its effectiveness as a stimulus whose presence or absence signalled a saccharin-LiCl pairing. Following the acquisition of the discrimination (Phase I) and an assessment of the dose-response relationship for PCP (Phase II), a drug from a class similar to PCP (ketamine; Phase III) and a drug from a class different from PCP (d-amphetamine; Phase IV) were substituted for the training dose to test for generalization to the PCP stimulus.

METHOD

Subjects and Apparatus

The subjects were 24 experimentally naive, Long-Evans hooded female rats, approximately 120 days of age at the beginning of the experiment. The subjects were housed in individual wire-mesh cages and maintained on a 12-hr-light/12-hr-dark cycle and at an ambient temperature of 23°C.

Drugs

All drugs were dissolved in distilled water and were injected intraperitoneally (IP) in a volume of 1.0 ml/kg with the exception of lithium chloride (LiCl) which was injected in a volume of 12.0 ml/kg. Phencyclidine hydrochloride and d-amphetamine sulfate were generously supplied by The National Institute on Drug Abuse, Rockville, MD. Ketamine hydrochloride (Ketalar) was purchased from Veterinary Products (Bristol Laboratories, Syracuse, NY). All doses are expressed in terms of the salt of the drug.

Procedure

Phase I: Conditioning. Following water deprivation, all subjects were given 20-min access to water once a day for 13 consecutive days. On Days 14–16, a novel saccharin solution (0.1% w/v sodium saccharin, Fisher Purified) replaced water during the daily 20-min fluid-access period. On these days, differential treatment was administered to two groups of subjects matched on water consumption over the three preceding days (i.e., Days 11–13). Subjects in Group W (n=12) were injected with 1.8 mg/kg of PCP (in a volume of 1 ml/kg of body weight) 10 min prior to 20-min access to saccharin. Subjects in Group P (n=12) were given an equivolume injection of distilled water (i.e., the PCP vehicle). No injections were given following saccharin access.

On Day 17, conditioning began. On this day, subjects again received 20-min access to saccharin. Subjects in Group P were injected with 1.8 mg/kg of PCP 10 min prior to saccharin access. Subjects in Group W were given an injection of distilled water. Immediately following saccharin access, each of these two groups was further divided into two groups (n=6 per group matched on saccharin consumption on Day 17) and injected with 1.8 mEq, 0.15 M LiCl (Groups PL and WL) or distilled water (the LiCl vehicle; Groups PW and WW). The first letter of each group represents the compound administered before saccharin consumption (P: PCP or W: Distilled Water) and the second letter represents the compound administered immediately following saccharin consumption (L: LiCl or W: Distilled Water). On the next three recovery days (Days 18–20), subjects in Groups PL and PW were injected with distilled water (the PCP vehicle) 10 min prior to 20-min access to saccharin, while subjects in Group WL and WW were given an injection of 1.8 mg/kg PCP at this time. Immediately following saccharin access, all groups were injected with distilled water. This alternating procedure of conditioning and recovery was repeated until all animals had received five complete cycles (see Table 1).

TABLE 1

GENERAL PROCEDURE FOR EACH GROUP DURING THE ACQUISITION OF THE DRUG DISCRIMINATION

		Groups			
Day	Procedure	PL	PW	WL	WW
14–16	H	W-S-W	W-S-W	P-S-W	P-S-W
17	C	P-S-L	P-S-W	W-S-L	W-S-W
18–20	R	W-S-W	W-S-W	P-S-W	P-S-W

H—Saccharin habituation; C—Conditioning day; R—Recovery day; P—PCP injection; W—Distilled water injection; S—20″ Access to saccharin; L—Lithium chloride injection.

Note that the alternating procedure of conditioning (Day 17) and recovery (Days 18–20) was repeated for five complete cycles.

Phase II: Dose substitutions. Following the final recovery session in Phase I, a dose-response relationship was determined for PCP. The procedure during this phase was identical to that described above, i.e., a single conditioning trial followed by three recovery sessions, with the following exception. On the second recovery day following each conditioning trial, one of a range of doses of PCP (0.32, 0.56, 1.0 and 3.2 mg/kg) was administered to all subjects 10 min prior to saccharin access. Doses were given in a mixed order across dose substitution sessions, and LiCl was not administered following any of these probes. All doses were administered twice with the exception of 0.32 mg/kg which was given only once.

Phase III: Ketamine substitution. Following the final recovery session in Phase II, a dose-response relationship was determined for ketamine. The procedure during this phase was identical to that for Phase II with the exception that on the second recovery day, one of a range of doses of ketamine (3.2, 5.6, 10.0 and 18.0 mg/kg) was administered to all subjects 10 min prior to saccharin access. Doses were given in a mixed order across substitution sessions, and LiCl was not administered following any of these probes. Doses of 5.6 and 10.0 mg/kg were administered twice, while only a single administration of 3.2 and 18.0 mg/kg was given.

Phase IV: d-Amphetamine substitutions. Following the final recovery session in Phase III, a dose-response relationship was determined for d-amphetamine. The procedure during this phase was identical to that for Phase III with the exception that on the second recovery session, one of a range of doses of d-amphetamine (0.18, 0.32, 0.56, 1.0 and 1.8 mg/kg) was administered to all subjects 10 min prior to saccharin access. Doses were given in a mixed order across substitution sessions, and LiCl was not administered following any of these probes. All doses were administered twice with the exception of 1.8 mg/kg which was given only once.

RESULTS

Acquisition data, i.e., consumption of saccharin over the five conditioning trials, were analyzed using a Kruskal-

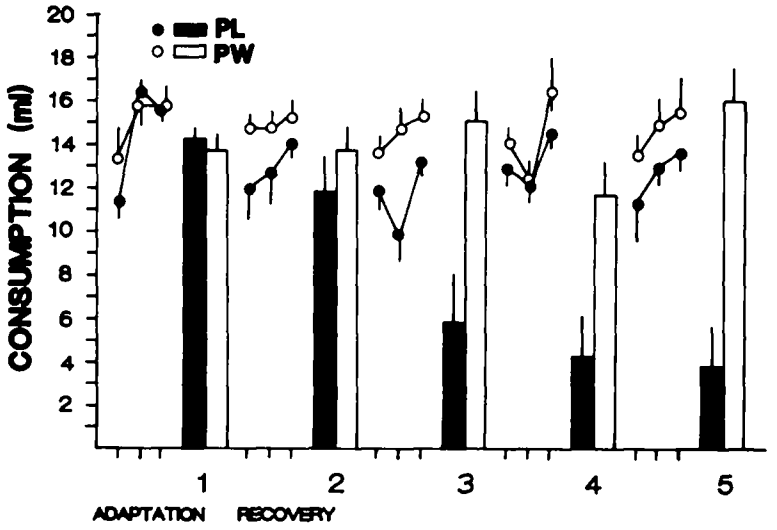

FIG. 1. Mean absolute saccharin consumption for subjects in Groups PL and PW during adaptation and throughout the conditioning/recovery cycles of Phase I.

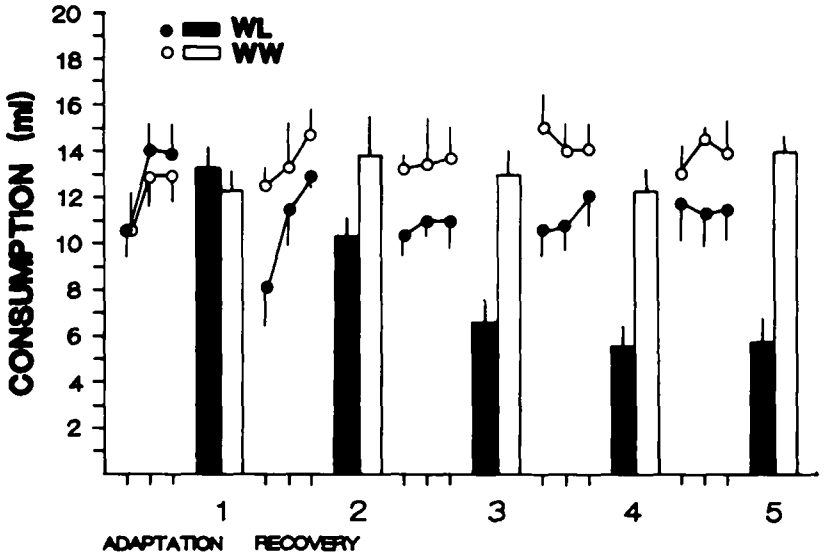

FIG. 2. Mean absolute saccharin consumption for subjects in Groups WL and WW during adaptation and throughout the conditioning/recovery cycles of Phase I.

Wallis. Subsequent to finding significant differences, group comparisons were determined using nonparametric contrasts.

Phase I: Conditioning

Figure 1 illustrates the mean absolute consumption of saccharin for subjects in Groups PL and PW throughout the conditioning/recovery cycles of Phase I. As illustrated, there were no significant differences in saccharin consumption between subjects in Groups PL and PW during adaptation, each group consuming a mean of approximately 15 ml of saccharin. On the first conditioning trial (Day 17), both groups continued to consume saccharin at high levels with no differences between groups. On the second conditioning trial (Day 21), subjects in Group PL displayed a slight, but nonsignificant, decrease in saccharin consumption in relation to subjects in Group PW. This difference between groups was significant by the third conditioning trial. On this day, subjects in Group PL drank a mean of 6 ml while subjects in Group PW drank approximately 15 ml of saccharin. This difference in consumption was maintained over the subsequent conditioning trials.

There were no significant differences between Groups PL and PW over recovery sessions. Both groups drank saccharin at levels not significantly different from that consumed

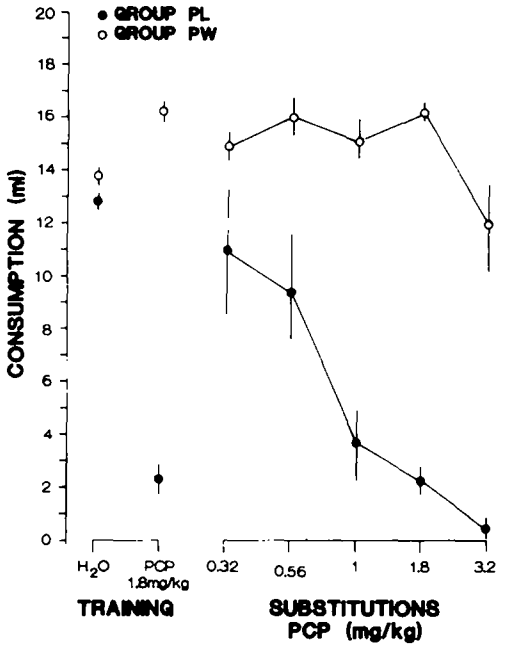

FIG. 3. Dose-response relationship for PCP for subjects in Groups PL and PW. The data for the dose substitutions are plotted on a log scale with the ordinate displaying the doses. The abcissa is saccharin consumption in ml. Note that the data obtained for 1.8 mg/kg PCP on the conditioning sessions during this phase are also included in the dose-response presentation.

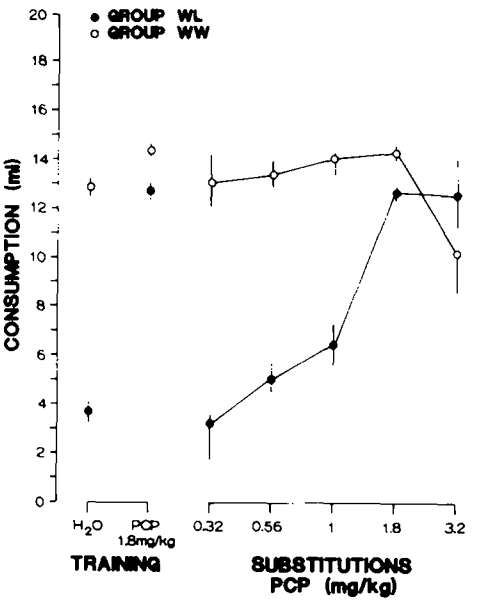

FIG. 4. Dose-response relationship for PCP for subjects in Groups WL and WW. Note that the data obtained for 1.8 mg/kg PCP on the conditioning sessions during this phase are also included in the dose-response presentation.

during adaptation. For subjects in Group PL, the amount consumed during recovery was significantly different from that consumed on the third, fourth and fifth conditioning trials. There were no differences in consumption during recovery and conditioning for subjects in Group PW.

Figure 2 illustrates the mean absolute consumption of saccharin for subjects in Groups WL and WW throughout the conditioning/recovery cycles of Phase I. As illustrated, there were no significant differences in saccharin consumption between subjects in Groups WL and WW during adaptation, each group consuming a mean of approximately 13 ml of saccharin. On the first conditioning trial (Day 17), both groups continued to consume saccharin at high levels with no differences between groups. On the second conditioning trial (Day 21), subjects in Group WL displayed a slight, but nonsignificant, decrease in saccharin consumption in relation to subjects in Group WW. This difference between groups was significant by the third conditioning trial. On this day, subjects in Group WL drank a mean of 6.5 ml while subjects in Group WW drank approximately 14 ml of saccharin. This difference in consumption was maintained over the subsequent conditioning trials.

There were no significant differences between Groups WL and WW over recovery sessions. Both groups drank saccharin at levels not significantly different from that consumed during adaptation. For subjects in Group WL, the amount consumed during recovery was significantly different from that consumed on the third, fourth and fifth conditioning trials. There were no differences in consumption during recovery and conditioning for subjects in Group WW.

Phase II: Dose-Response Relationship for PCP

Figure 3 illustrates the mean absolute consumption of saccharin for subjects in Groups PL and PW during PCP dose substitution sessions and following the administration of the training stimuli (i.e., 1.8 mg/kg PCP and distilled water). As illustrated, for Group PL saccharin consumption following the administration of 1.8 mg/kg PCP (i.e., the stimulus that signalled the saccharin/LiCl pairing during conditioning) was reduced relative to consumption following the administration of distilled water (the stimulus that signalled the saccharin/distilled water pairing during conditioning). Further, for these subjects, the dose-response relationship revealed that saccharin consumption was inversely related to the dose of PCP. Specifically, consumption tended to decrease with increasing doses. For the control subjects (Group PW), for which neither 1.8 mg/kg PCP nor distilled water signalled a saccharin/LiCl pairing, saccharin was consumed at high levels under both injection conditions (i.e., following an injection of either 1.8 mg/kg PCP or distilled water). The dose-response relationship revealed that consumption for these subjects was unaffected until the highest dose of PCP was administered (i.e., 3.2 mg/kg).

Figure 4 illustrates the mean absolute consumption of saccharin for subjects in Groups WL and WW during PCP dose substitution sessions and following the administration of the training stimuli. As illustrated, for Group WL saccharin consumption following the administration of distilled water (i.e., the stimulus that signalled the saccharin/LiCl pairing during conditioning) was reduced relative to saccharin consumption following the administration of 1.8 mg/kg PCP (i.e., the stimulus that signalled the saccharin/distilled water pairing during conditioning). Further, the dose-response relationship revealed that saccharin consumption

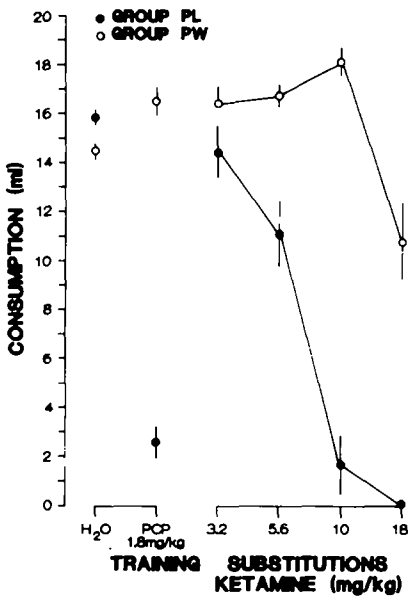

FIG. 5. Dose-response relationship for ketamine for subjects in Groups PL and PW (presented as in Fig. 3).

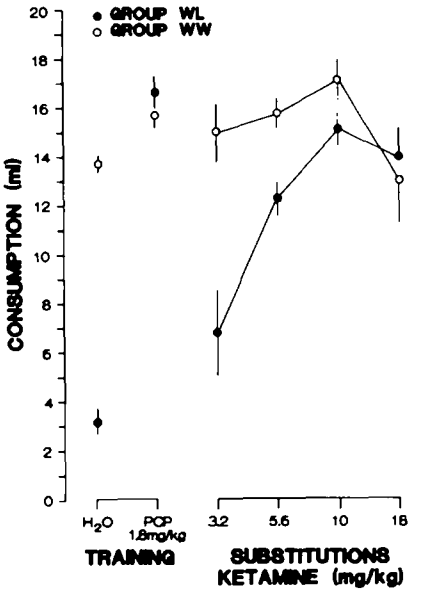

FIG. 6. Dose-response relationship for ketamine for subjects in Groups WL and WW (presented as in Fig. 3).

was directly related to the dose of PCP. Specifically, consumption tended to increase as the dose of PCP increased. For the control subjects (Group WW), for which neither distilled water nor 1.8 mg/kg PCP signalled a saccharin/LiCl pairing, saccharin was consumed at high levels under both injection conditions (i.e., following an injection of either distilled water or 1.8 mg/kg PCP). The dose-response relationship revealed that consumption for these subjects was unaffected until the highest dose of PCP was given (i.e., 3.2 mg/kg).

Phase III: Dose-Response Relationship for Ketamine

Figure 5 illustrates the mean absolute consumption of saccharin for subjects in Groups PL and PW during ketamine drug substitution sessions and following the administration of the training stimuli.

As illustrated, for Group PL, saccharin consumption following the administration of 1.8 mg/kg PCP was reduced relative to consumption following the administration of distilled water. The dose-response relationship for ketamine revealed that for Group PL saccharin consumption tended to decrease with increasing doses. For the control subjects (Group PW), saccharin was consumed at high levels under both injection conditions (i.e., following an injection of either 1.8 mg/kg PCP or distilled water). For these subjects, there was no relation between the dose of ketamine and saccharin consumption. Only at the highest ketamine dose (18.0 mg/kg) was saccharin consumption affected.

Figure 6 illustrates the mean absolute consumption of saccharin for subjects in Groups WL and WW during ketamine drug substitution sessions and following the administration of the training stimuli. As illustrated, for Group WL, saccharin consumption following the administration of distilled water was reduced relative to consumption following the administration of 1.8 mg/kg PCP. The dose-response relationship for ketamine revealed that for Group WL saccharin consumption tended to increase with increasing doses of ketamine until the highest dose of ketamine was administered (i.e., 18 mg/kg). For the control subjects (Group WW), saccharin was consumed at high levels under both injection conditions (i.e., following an injection of either distilled water or 1.8 mg/kg PCP). During the drug substitution sessions, consumption for these subjects was unaffected until the highest dose of ketamine was given (i.e., 18 mg/kg).

Phase IV: d-Amphetamine Dose-Response Relationship

Figure 7 illustrates the mean absolute consumption of saccharin for subjects in Groups PL and PW during d-amphetamine drug substitution sessions and following the administration of the training stimuli. For Group PL, saccharin consumption following the administration of 1.8 mg/kg PCP was reduced relative to consumption following the administration of distilled water. The dose-response relationship for d-amphetamine revealed that for Group PL saccharin consumption tended to decrease with increasing doses. For the control subjects (Group PW), saccharin was consumed at high levels under both injection conditions (i.e., following an injection of either 1.8 mg/kg PCP or distilled water). For these subjects, saccharin consumption also tended to decrease with increasing doses of d-amphetamine.

Figure 8 illustrates the mean absolute consumption of saccharin for subjects in Groups WL and WW during d-amphetamine drug substitution sessions and following the administration of the training stimuli. As illustrated, for Group WL, saccharin consumption following the administration of distilled water was reduced relative to consumption following the administration of 1.8 mg/kg PCP. The dose-response relationship for d-amphetamine revealed that for Group WL there was no relation between saccharin consumption and the dose of d-amphetamine. In fact, consump-

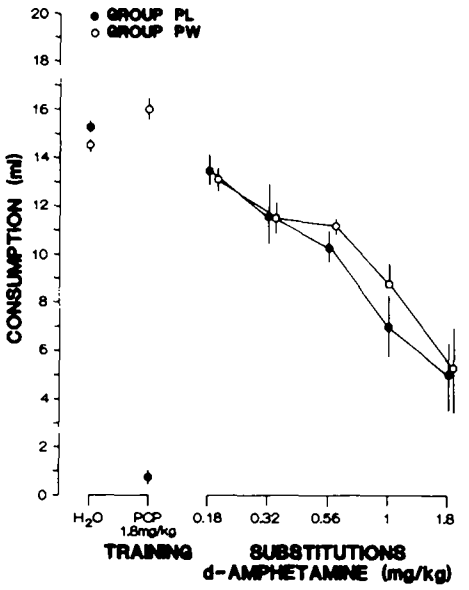

FIG. 7. Dose-response relationship for d-amphetamine for subjects in Groups PL and PW (presented as in Fig. 3).

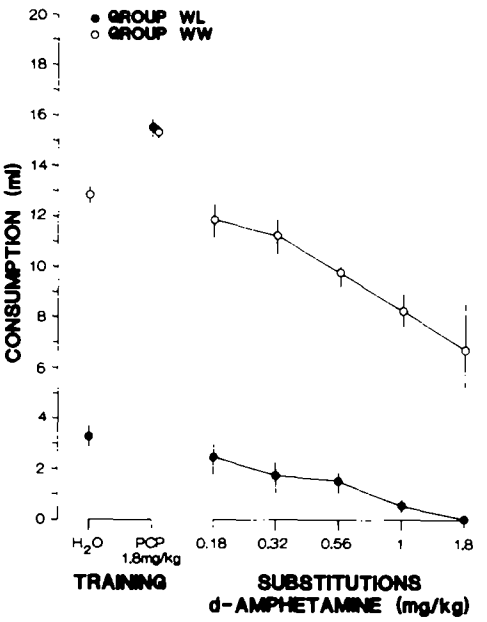

FIG. 8. Dose-response relationship for d-amphetamine for subjects in Groups WL and WW (presented as in Fig. 3).

tion was suppressed at all doses. For the control subjects (Groups WW), saccharin was consumed at high levels under both injection conditions (i.e., following either distilled water or 1.8 mg/kg PCP). For this group, saccharin consumption tended to decrease with increasing doses of d-amphetamine.

DISCUSSION

As reported, when PCP was given prior to the pairing of saccharin with LiCl and its vehicle prior to the same saccharin taste but not paired with LiCl toxicosis (i.e., Group PL), rats rapidly acquired the discrimination, avoiding saccharin consumption following PCP and consuming saccharin following the vehicle. Conversely, when the PCP vehicle was given prior to the saccharin-LiCl pairing and PCP prior to a nonpoisoned exposure to saccharin (i.e., Group WL), rats avoided saccharin consumption following the distilled water injection and readily consumed saccharin after an injection of PCP. Control animals, for which neither PCP nor its vehicle served as a stimulus predicting LiCl toxicosis (i.e., Group PW and WW), drank saccharin following both the PCP and distilled water injections. Given this differential control of saccharin consumption by PCP and distilled water in conditioned subjects, it is clear that the taste aversion design can serve as a baseline for drug discrimination learning. It is also clear that control of the aversion can be established independent of whether the presence or absence of PCP signals the saccharin-toxicosis pairing.

The results using the taste aversion baseline display interesting similarities to and differences from more traditional procedures used in indexing drug discrimination learning [see (25)]. In relation to similarities, PCP was an effective cue in controlling responding whether as a signal for a saccharin-LiCl pairing or as a signal for a nonpoisoned exposure to saccharin [see (4–6, 10, 15–17, 20, 22, 41)]. Further, when various doses of PCP were administered as probes, animals displayed a pattern of responding similar to that with PCP within more traditional paradigms, i.e., the greater the dose of the drug, the more drug appropriate responding (4, 15, 17). In the case where PCP signalled the saccharin-LiCl pairing, the greater the dose of PCP the stronger the aversion. In the case where PCP signalled a saccharin-distilled water pairing, the greater the dose of PCP the weaker the aversion and the greater the amount of saccharin consumed. When ketamine (a compound from the same class as PCP) was substituted for PCP, subjects displayed drug appropriate responding [see (4, 6, 15, 41)]. Again, this substitution was evident independent of whether PCP signalled the saccharin-LiCl or saccharin-distilled water pairing. It is also interesting in this comparison that similar to other reports higher doses of ketamine were required to produce responding comparable to that produced by the training dose of PCP. In the present experiment, a dose of 10 mg/kg ketamine produced drug appropriate responding similar to the training dose of PCP, i.e., 1.8 mg/kg. Finally, when d-amphetamine (a compound from a class different from PCP) was substituted for PCP, subjects displayed vehicle appropriate responding [see (20, 22, 41)], i.e., subjects for which PCP signalled the saccharin-LiCl pairing drank saccharin following d-amphetamine administration while subjects for which PCP signalled the saccharin-distilled water pairing avoided saccharin after injections of each of the doses of d-amphetamine. That ketamine substituted for PCP and amphetamine failed to do so suggests that subjects were responding to some specific stimulus produced by PCP and not responding nonspecifically.

Although there were these similarities between the taste aversion procedure and the more traditional drug discrimination designs, there were differences as well, the most obvious being the rate of the acquisition of the discrimination. As reported, by the third conditioning trial

subjects were clearly discriminating the presence and absence of PCP. Specifically, subjects in Group PL decreased saccharin consumption following PCP administration and consumed the same saccharin solution following administration of the vehicle. Conversely, subjects in Group WL decreased saccharin consumption following the distilled water injection and readily consumed saccharin following the administration of PCP. Although the rate of acquisition of a drug discrimination varies as a function of a range of factors [see (25)], e.g., drug dose, whether the discrimination involves training with or without another drug, and even the specific criterion used for assessing the discrimination, the speed with which the discrimination in the present experiment was acquired appears very rapid in relation to other reports with PCP. For example, White and Holtzman (41) noted that an average of 35 days was required for the acquisition of a discrimination between PCP (2.0 mg/kg) and saline. Similarly, Jarbe *et al.* (17) reported that after 20 days of training on a water escape t-maze task only 1 of 6 animals had reached criterion responding on a PCP (2.0 mg/kg) vs. saline discrimination. The basis for this rapid acquisition within the taste aversion paradigm remains unknown, although the rate of acquisition of a drug discrimination does appear to vary with the specific task [see (17,25)].

Given the fact that drug discrimination was produced in the taste aversion procedure and that the data were quite similar to those previously reported in other designs (see above), it is somewhat surprising that such learning has not been generally reported within the taste aversion literature, especially given the rate of acquisition of the discrimination. There have only been three reports that address the use of drugs as stimuli within this baseline, none of which demonstrated the efficacy of the taste aversion design in drug discrimination learning. Two of these reports [see (3,29)] functionally assessed state dependent (and not drug discrimination) learning. That is, the animals were given a compound prior to the taste-toxin pairing but were never given the same taste in the absence of the drug. Under these conditions, there was no opportunity for the drug to predict differentially that the taste would be followed by toxicosis. In a third report, Revusky, Coombes and Pohl (30) attempted to establish a conditional discrimination using drugs as one of the cues predicting toxicosis. Specifically, in the Revusky *et al.* (30) procedure, Drug A predicted that Taste A was followed by toxicosis, while the combination of Drug A and Taste B was safe. Conversely, in the same animals, Drug B predicted that Taste B was followed by toxicosis while the combination of Drug B and Taste A was safe. In other words, neither the drug nor the taste alone was predictive of toxicosis. The predictive relationship was conditional on a specific drug/taste combination. As noted, there was little evidence that animals could learn this discrimination. It remains unclear if this failure reflects the difficulty of drug discrimination learning within the taste aversion design or the difficulty of acquiring conditional discriminations in general. The fact that the drug discrimination was so rapidly acquired in the present experiment is clearly support for the latter position.

Although PCP was able to gain control of responding in the present study, the mechanism underlying this control is not yet determined. Several possibilities exist. For example, it is possible that PCP altered the taste of the saccharin in such a way that following the PCP administration subjects were actually sampling a different taste than that consumed on days without the PCP injection. Although possible, this is unlikely given the substitution data with ketamine. It would have to be argued that ketamine effected a similar change in taste. Another account for the discrimination could be that the animals learned that saccharin was aversive when preceded by an injection of PCP. In other words, PCP signals that saccharin is aversive. Preliminary data from our lab suggest that this too is unlikely. Specifically, after extensive training with PCP vs. distilled water, animals were injected with PCP but were given sodium chloride to drink instead of the usual saccharin. In this case, sodium chloride was also avoided. Controls readily consumed the sodium chloride following PCP. These data seem to suggest that the animal learns that any solution which follows PCP administration is aversive, not just saccharin. This evidence, however, is preliminary and more work must be done before attempting to account for the basis of the discrimination.

Independent of its basis, it is clear that the taste aversion design can index drug discrimination learning. Given the speed with which the discrimination was established, the parallels in the data between the aversion procedure and other designs as well as the general low cost nature of taste aversion work, this procedure appears to be a useful design in investigating drug discrimination learning. However, the design must be assessed with other compounds and with various modifications before statements as to its relative efficacy and sensitivity can be made [see (33)].

ACKNOWLEDGEMENTS

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REFERENCES

1. Baker, T. B.; Cannon, D. S. Alcohol and taste-mediated learning. Addict. Behav. 7:221–230; 1982.
2. Bernstein, I. L. Learned food aversions in the progression of cancer and its treatment. Ann. NY Acad. Sci. 443:365–380; 1985.
3. Best, M. R.; Domjan, M. Characteristics of the lithium-mediated proximal US-preexposure effect in flavor-aversion conditioning. Anim. Learn. Behav. 7:433–440; 1979.
4. Brady, K. T.; Balster, R. L. Discriminative stimulus properties of ketamine stereoisomers in phencyclidine-trained rats. Pharmacol. Biochem. Behav. 17:291–295; 1982.
5. Brady, K. T.; Balster, R. L.; May, E. L. Stereoisomers of N-allylnormetazocine: Phencyclidine-like behavioral effects in squirrel monkeys and rats. Science 215:178–180; 1982.
6. Browne, R. G.; Welch, W. M. Stereoselective antagonism of phencyclidine's discriminative properties by adenosine receptor agonists. Science 217:1157–1158; 1982.
7. Colpaert, F. C. Drug discrimination: Behavioral, pharmacological, and molecular mechanisms of discriminative drug effects. In: Goldberg, S. R.; Stolerman, I. P., eds. Behavioral analysis of drug dependence. New York: Academic Press; 1986.

8. Colpaert, F. C.; Rosecrans, J. A., eds. Stimulus properties of drugs: Ten years of progress. Amsterdam: Elsevier/North Holland Biomedical; 1978.
9. Colpaert, F. C.; Slangen, J. L., eds. Drug discrimination: Applications in CNS pharmacology. Amsterdam: Elsevier/North Holland Biomedical; 1982.
10. Cunningham, K. A.; Appel, J. B. Discriminative stimulus properties of cocaine and phencyclidine: Similarities in the mechanism of action. In: Colpaert, F. C.; Slangen, J. L., eds. Drug discrimination: Applications in CNS pharmacology. Amsterdam: Elsevier/North Holland Biomedical; 1982.
11. Elkins, R L. Aversion therapy for alcoholism: Chemical, electrical, or verbal imaginary? Int. J. Addict. 10:157–209; 1975.
12. Garcia, J.; Ervin, F. R. Gustatory-visceral and telereceptor-cutaneous conditioning: Adaptation in internal and external milieus. Commun. Behav. Biol. 1:389–415; 1968.
13. Grupp, L. A. Effects of pimozide on the acquisition, maintenance and extinction of an amphetamine-induced taste aversion. Psychopharmacologia 53:235–242; 1977.
14. Gustavson, C. R.; Gustavson, J. C. Control of predation using conditioned food aversion methodology: Theory, practice and implications. Ann. NY Acad. Sci. 443:348–356; 1985.
15. Holtzman, S. G. Phencyclidine-like discriminative properties of psychotomimetic opioids. Ann. NY Acad. Sci. 398:230–240; 1982.
16. Holtzman, S. G. Discriminative stimulus properties of opioids that interact with mu, kappa and PCP/sigma receptors. In: Seiden, L. S.; Balster, R. S., eds. Behavioral pharmacology: The current status. New York: Alan R. Liss; 1985.
17. Jarbe, T. U. C.; Johansson, J. O.; Henrikksson, B. G. Drug discrimination in rats: The effects of phencyclidine and Ditran. Psychopharmacologia 42:33–39; 1975.
18. LeBlanc, A. E.; Cappell, H. Antagonism of morphine-induced aversive conditioning by naloxone. Pharmacol. Biochem. Behav. 3:185–188; 1975.
19. Le Magnen, J.; Marfaing-Jallat, P.; Miceli, D. A bioassay of ethanol dependence in rats. Pharmacol. Biochem. Behav. 12:701–704; 1980.
20. McMillan, D. E.; Wenger, G. R. Bias of phencyclidine discrimination by the schedule of reinforcement. J. Exp. Anal. Behav. 42:51–66; 1984.
21. MacPhail, R. C. Studies on the flavor aversions induced by triakyltin compounds. Neurobehav. Toxicol. Teratol. 4:225–230; 1982.
22. Massey, B. W.; McMillan, D. E. Effects of body weight on discriminative-stimulus control by phencyclidine in the pigeon. J. Exp. Anal. Behav. 47:233–239; 1987.
23. Mattes, R .D.; Arnold, C.; Borass, M. Learned food aversions among cancer chemotherapy patients. Cancer 60:2576–2580; 1987.
24. Nathan, P. E. Aversion therapy in the treatment of alcoholism: Success and failure. Ann. NY Acad. Sci. 443:357–364; 1985.
25. Overton, D. A.; Leopard, W. R.; Merkle, D.A. Methods for measuring the strength of discriminable drug effects. Neurosci. Biobehav. Rev. 10:251–263; 1986.
26. Parker, L. A.; Hutchison, S.; Riley, A. L. Conditioned flavor aversions: A toxicity test of the anticholinesterase agent, physostigmine. Neurobehav. Toxicol. Teratol. 4:93–98; 1982.
27. Parker, L. F.; Failor, A.; Weidman, K. Conditioned preferences in the rat with an unnatural need state: Morphine withdrawal. J. Comp. Physiol. Psychol. 82:294–300; 1973.
28. Parker, L. F.; Radow, B. L. Morphine-like physical dependence: A pharmacological method for drug assessment using the rat. Pharmacol. Biochem. Behav. 2:613–618; 1974.
29. Rabin, B. M.; Hunt, W. A.; Lee, J. State-dependent interactions in the antihistamine-induced disruption of a radiation-induced conditioned taste aversion. Radiat. Res. 90:621–627; 1982.
30. Revusky, S.; Coombes, S.; Pohl, R. W. Drug states as discriminative stimuli in a flavor-aversion learning experiment. J. Comp. Physiol. Psychol. 96:200–211; 1982.
31. Revusky, S.; Garcia, J. Learned associations over long delays. In: Bower, G.; Spence, J., eds. Psychology of learning and motivation: Advances in research and theory. New York: Academic Press; 1970.
32. Riley, A. L.; Tuck, D. L. Conditioned food aversions: A bibliography. Ann. NY Acad. Sci. 443:381–437; 1985.
33. Riley, A. L.; Tuck, D. L. Conditioned taste aversions: A behavioral index of toxicity. Ann. NY Acad. Sci. 443:272–292; 1985.
34. Romano, J. A.; King, J. M. Conditioned taste aversion and cholinergic drugs: Pharmacological antagonism. Pharmacol. Biochem. Behav. 27:81–85; 1987.
35. Rozin, P.; Kalat, J. Specific hungers and poison avoidance as adaptive specializations of learning. Psychol. Rev. 78:459–486; 1971.
36. Stolerman, I. P.; Baldy, R. E.; Shine, P. J. Drug discrimination procedure: A bibliography. In: Colpaert, F. C.; Slangen, J. L., eds. Drug discrimination: Applications in CNS pharmacology. Amsterdam: Elsevier/North Holland Biomedical; 1982.
37. Stolerman, I. P.; Shine, P. J. Trends in drug discrimination research analyzed with a cross-indexed bibliography. Psychopharmacology (Berlin) 86:1–11; 1985.
38. Stolerman, I. P.; Stephenson, J. D.; Rauch, R. J. Classification of opioid and 5-hydroxytryptamine receptors by means of discriminative drug effects. Neuropharmacology 26:867–875; 1987.
39. Ukai, M.; Holtzman, S. G. Morphine-like discriminative stimulus effects of opioid peptides: Possible modulatory role of d-Ala-a-Leu-enkephalin (DADL) and dynorphin A (1–13). Psychopharmacology (Berlin) 94:32–37; 1988.
40. van der Kooy, D.; Phillips, A. G. Temporal analysis of naloxone attenuation of morphine-induced taste aversion. Pharmacol. Biochem. Behav. 6:637–641; 1977.
41. White, J. M.; Holtzman, S. G. Three-choice drug discrimination: Phencyclidine-like stimulus effects of opioids. Psychopharmacology (Berlin) 80:1–9; 1983.
42. Zellner, D. A.; Dacanay, R. J.; Riley, A. L. Opiate withdrawal: The result of conditioning or physiological mechanisms? Pharmacol. Biochem. Behav. 20:175–180; 1984.