*Pharmacology Biochemistry & Behavior*, Vol. 18, pp. 611–617, 1983. © Ankho International Inc. Printed in the U.S.A.

# Drug Discrimination in Rats: Evidence for Amphetamine-Like Cue State Following Chronic Haloperidol

ROBERT J. BARRETT AND LARRY R. STERANKA

*Veterans Administration Medical Center, Departments of Psychology and Pharmacology*
*Vanderbilt University, Nashville, TN 37203 and*
*Departments of Pharmacology and Physiology, Northwest Center for Medical Education*
*Indiana University, Gary, IN 46408*

Received 29 July 1982

BARRETT, R. J. AND L. R. STERANKA. *Drug discrimination in rats: Evidence for amphetamine-like cue state following chronic haloperidol.* PHARMACOL BIOCHEM BEHAV 18(4) 611–617, 1983.—Two groups of male Sprague-Dawley rats were trained to discriminate which of two levers to press for milk reinforcement on a VI-20 sec schedule of reinforcement on the basis of whether they were injected intraperitoneally with d-amphetamine (0.50 mg/kg or 1.50 mg/kg) or saline 15 min prior to daily 30 min training sessions. Following acquisition of the discrimination, dose-response functions were generated for both training-dose groups during 5 min test sessions. All subjects were then injected with 1.0 mg/kg of haloperidol for ten consecutive days and retested on either saline or intermediate doses of amphetamine on days 1, 2, 4 and 7 following the final haloperidol injection. The results indicated that chronic haloperidol enhanced the discriminative stimulus properties of amphetamine in both training groups. More importantly, when tested on saline, subjects in both training groups made significantly more responses on the d-amphetamine lever than observed prior to chronic haloperidol. On the basis of linear regression analysis of the dose-response curves it was shown that rats in both groups responded as though they had been injected with 0.18 mg/kg of d-amphetamine. In a second experiment this increase in amphetamine-lever responding when animals were tested with saline following chronic haloperidol was replicated and in addition it was observed that chronic amphetamine had the opposite effect on this measure.

Drug discrimination  Amphetamine  Haloperidol  Dopamine supersensitivity  Chronic drug

A CONSIDERABLE number of previous studies have demonstrated that amphetamine-produced cues can be used as discriminative stimuli to learn a two-choice discrimination task [1, 5, 9, 12, 20]. Furthermore there is considerable evidence to suggest that dopamine is involved in mediating the amphetamine related stimuli which control the choice behavior. For example, Schechter and Cook [19] as well as Colpaert *et al.* [5] have shown that haloperidol, a dopamine receptor blocker, disrupts amphetamine discrimination while $\alpha$- and $\beta$-adrenergic receptor blockers do not [19]. Other evidence for dopamine involvement is provided by the demonstration that apomorphine, a direct dopamine receptor agonist, will substitute for the discriminative stimulus properties of amphetamine [19,25]. A separate literature composed of ligand binding [2,16] electrophysiological [7,23] and behavioral [8,24] studies have reported evidence for dopamine receptor supersensitivity following treatment with chronic neuroleptics. The behavioral experiments have demonstrated enhanced amphetamine and apomorphine-induced locomotor activity [10] as well as enhanced apomorphine-induced stereotypy following chronic injections of haloperidol [24].

The purpose of the present experiment was to determine whether following chronic haloperidol rats would be more sensitive to the discriminative stimulus properties of amphetamine. Since the drug discrimination paradigm provides a behavioral assay system which is not directly influenced by rate of responding, enhanced amphetamine discrimination following chronic haloperidol treatment would suggest changes in dopaminergic function in systems other than those directly involved in control of motor behavior.

An additional question of interest concerned the extent to which treatment with chronic haloperidol might alter discrimination in the non-drug (saline) state. Previous behavioral studies using measures of stereotyped activity have not been able to demonstrate spontaneous stereotypy following chronic treatment with neuroleptics. Rather, the demonstration of dopaminergic supersensitivity has relied on showing enhanced stereotypy following challenge with either dopaminergic or anticholinergic drugs [24]. If the discrimination of amphetamine from saline is dependent on dopaminergic neuronal activity and if chronic haloperidol results in increased neuronal function in this transmitter system, it seemed reasonable to predict that when tested with saline following chronic haloperidol, animals might respond as though administered a small dose of amphetamine.

## METHOD

### *Subjects*

Subjects were 12 male Sprague-Dawley rats (Zivic Miller Laboratories) weighing approximately 275–325 g at the beginning of the experiment, housed in individual cages and food deprived to 75–80% of their ad lib weight. They were maintained on a 12-hr light-dark cycle (7:00 a.m. – 7:00 p.m. light) and given enough food immediately following test sessions and over weekends to maintain control weight throughout the experiment. The animals were tested at the same time each day 5 days a week.

### *Apparatus*

Three commercially available chambers (BRS/LVE Model No. RTC-022) each housed in a sound attenuating chamber were used for training rats on the discriminative stimulus task. Two response levers 4.92 cm above the floor were mounted on the front panel and required a 24 g force to activate. Reinforcements (Borden's condensed milk diluted with water) were delivered by a liquid feeder (0.06 ml) centered between the two levers. Electromechanical programming and recording equipment was located in an adjacent room. White noise was used in the experimental room to mask extraneous auditory stimuli.

### *Procedure*

*Training procedure and acquisition of the amphetamine-saline discrimination.* Rats were trained to lever press during daily 30 minute sessions on a continuous schedule of reinforcement (CRF). They were given training on alternate days to each of two levers. Following acquisition of the lever press response the reinforcement contingency was changed to a variable-interval 20 sec (VI-20″) and discrimination training was initiated. Rats were divided (n=6) into two training-dose groups (0.50 and 1.50 mg/kg d-amphetamine sulfate) and were injected intraperitoneally (IP) 15 minutes prior to the start of each training session with either the drug or saline. For half the subjects in each group the right lever was designated the amphetamine-correct lever and the left lever the saline-correct one. This was reversed for the remaining subjects. The correct lever was alternated on consecutive training sessions which according to Extance and Goudie [6] precludes the animals using inter-animal cues to identify the correct lever. The first 2.5 minutes of each session consisted of an extinction period during which no lever presses were reinforced which allowed for daily monitoring of discrimination learning unconfounded by reinforcement. During the remaining 27.5 minutes of the session responses were reinforced on the correct lever with the exception that responses on the incorrect lever were punished by imposing a 20 sec-delay before reinforcements were again available. Training was continued in this manner until the groups consistently averaged at least 80% correct-lever responding following both amphetamine and saline injections. Throughout training, drug-saline sessions were alternated with the exception that once every 10 sessions two consecutive saline or drug sessions were scheduled to ensure that the rats were responding to the drug-related cues rather than the temporal sequence of drug-saline injections. Inspection of the 2.5 minute data from these sessions of consecutive saline or drug pre-injection indicated that the rats did not respond to the order of injections. Discrimination training sessions were conducted 5 days per week (Monday to Friday).

*Amphetamine dose-response functions.* Following discrimination training, dose-response functions were determined for the two training-dose groups during 5 min extinction sessions. No reinforcement was available during these test sessions to prevent the animals from receiving discrimination training to a new drug dose which might disrupt the original baseline discrimination. Immediately following the 5 min test session the rats were returned to their home cages and given their daily allotment of food. The doses of amphetamine tested were 0.25, 0.50, 0.75, 1.0 and 1.5 mg/kg for the 1.5 mg/kg training-dose group and 0.10, 0.15, 0.25, 0.35 and 0.50 mg/kg for the 0.50 mg/kg training-dose group. Order of the one test session at each dose was counterbalanced within each group. One test session was administered each week, generally on Wednesday, so that a drug and saline training day both preceded and followed each test session. This schedule of events resulted in one third of the animals receiving saline training and two thirds amphetamine training on the day prior to each test dose. Although a previous report [11] indicated that the nature of the pre-test training session might effect discrimination, analysis of the present data with respect to this variable found no differences.

Following completion of the dose-response function all subjects were injected IP with chronic haloperidol (1.0 mg/kg) once a day for 10 consecutive days. On day 1 following the final injection all subjects were given a saline training session including the 2.5 min extinction period at the beginning of the session. On days 2, 4 and 7 subsequent to the chronic regimen, subjects from the two training groups were tested following an injection of either 0.35 mg/kg or 0.50 mg/kg d-amphetamine for the 0.50 mg/kg and 1.50 mg/kg training groups, respectively. These doses were selected on the basis of the dose-response data which showed that prior to chronic haloperidol they resulted in 50–60% amphetamine-lever responding.

*Drugs.* The drugs used in this experiment were d-amphetamine sulfate purchased from Sigma Chemical Co. and haloperidol (Haldol), in solution, provided by McNeil Laboratories, Fort Washington, PA. Haloperidol was diluted in distilled water and amphetamine dissolved in a 0.9% saline solution so that the desired dose per kg was contained in a volume of 1.0 ml. All injections were administered IP. The dose of d-amphetamine refers to the salt.

## RESULTS AND DISCUSSION

### *Acquisition of the Amphetamine-Saline Discrimination*

Subjects in both training groups were given 32 sessions of d-amphetamine-saline discrimination at which time both groups were consistently averaging greater than 80% correct-lever responding. The data from the 2.5 min extinction period at the beginning of each session averaged across the final two training sessions (one saline and one amphetamine) showed that the 0.50 mg/kg and 1.50 mg/kg groups averaged 83 and 96% correct-lever responding, respectively.

### *Amphetamine Dose-Response Functions*

Figure 1 shows the dose-response data for the two training-dose groups. As can be seen the percentage of amphetamine-lever responding was dependent not only on the test dose but also the training dose. Thus, for example, subjects trained on 0.50 mg/kg averaged 83% drug-lever responding when tested on 0.50 mg/kg of d-amphetamine while

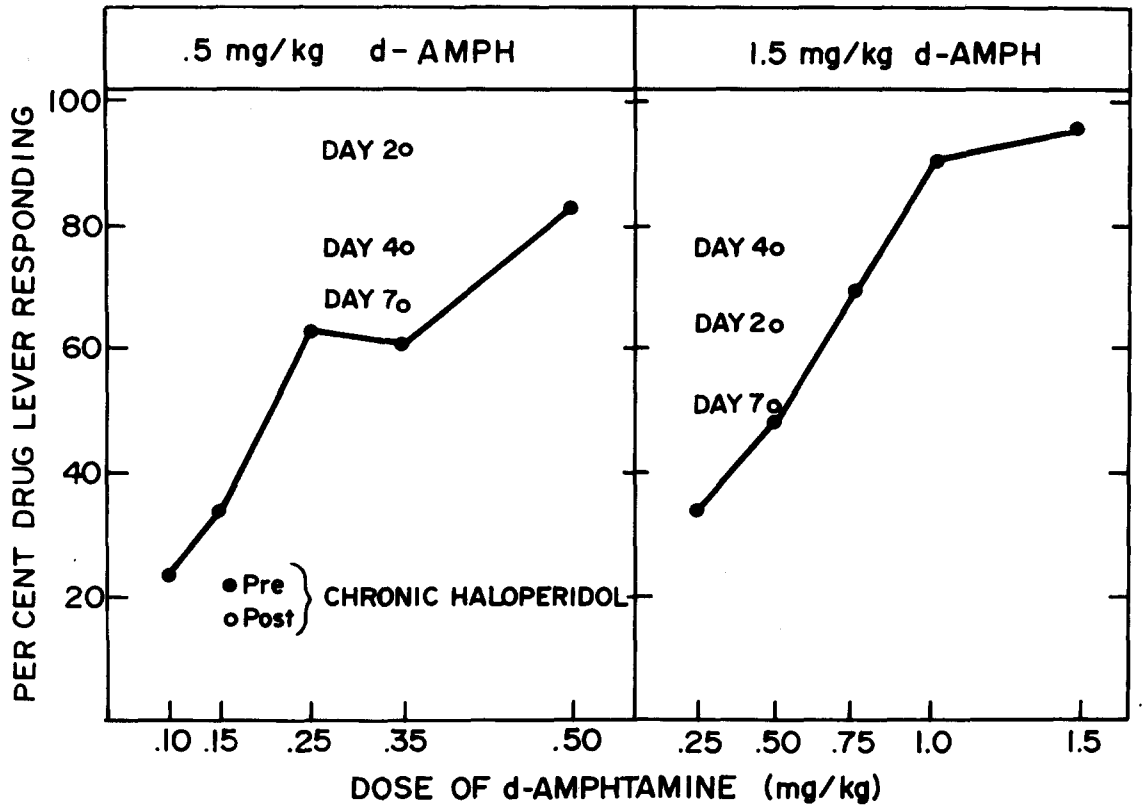


FIG. 1 Percentage of responding on the amphetamine-correct lever as a function of five test doses of amphetamine for each of the two training-dose groups. Data points labelled Day 2, Day 4 and Day 7 are the results of the three post-chronic haloperidol test sessions and can be compared to the results of testing with the same doses (0.25 and 0.35 mg/kg for the 0.50 and 1.50 mg/kg training-dose groups, respectively) prior to treatment with chronic haloperidol.

the same dose administered to the 1.50 mg/kg group resulted in only 49% responding on the drug-lever. The effect of training dose is further illustrated by comparing the $ED_{50}$ values for the two groups. The $ED_{50}$ was estimated for each animal from linear equations describing the relationship between percentage drug-lever responding and log-dose of amphetamine. The average $ED_{50}$ values were 0.23 mg/kg for the animals trained on 0.50 mg/kg of d-amphetamine and 0.39 mg/kg for the animals trained on 1.50 mg/kg of d-amphetamine. Similar effects of training dose on dose-response functions have previously been reported [1, 15, 26].

*Test for Supersensitivity to the Discriminative Stimulus Properties of Amphetamine*

In Figure 1 it can be seen that following chronic haloperidol, subjects in both training-dose groups showed supersensitivity to the discriminative cue properties of amphetamine. One-tailed t-tests for correlated means indicated that drug-lever responding was significantly greater on Day 2, $t(5)=2.3$, $p<0.05$, for the 0.50 mg/kg group and on Day 4, $t(5)=2.7$, $p<0.02$, for the 1.5 mg/kg group than observed for the same test doses prior to the chronic haloperidol drug regimen. The 0.50 mg/kg group averaged 93% drug-lever responding on Day 2 compared to 62% prior to chronic haloperidol when tested on the 0.35 mg/kg d-amphetamine test dose. This was even higher than the 82% which had been observed following testing with the 0.50 mg/kg training dose. The 1.50 mg/kg group made 49% of their responses on the amphetamine lever prior to chronic haloperidol and 75% on Day 4 following the chronic regimen. Every animal in the 0.50 mg/kg and 1.50 mg/kg groups showed increased drug lever responding on Day 2 and Day 4 for the two groups, respectively. Except for one animal this was also true of the 1.50 mg/kg group on Day 2.

*Saline Tests Following Chronic Haloperidol*

On Day 1 following chronic haloperidol subjects in both groups were given a regular training session on saline including the 2.5 min extinction period at the beginning of the session. The 2.5 min data showed that both groups significantly ($p<0.05$) increased their percentage of amphetamine-lever responding compared to pre-haloperidol levels (from 6% to 44% for the 0.50 mg/kg group and from 2% to 23% for the animals trained on 1.50 mg/kg of d-amphetamine). These data suggested that, even in the absence of amphetamine challenge, there is an increase in dopaminergic function following chronic haloperidol which results in interoceptive cues similar to those produced by a small dose of amphetamine. By substituting for Y (% amphetamine-lever responding) and solving for X (drug dose) in each group's dose-response linear equation, it was possible to compute the theoretical dose of amphetamine that would normally

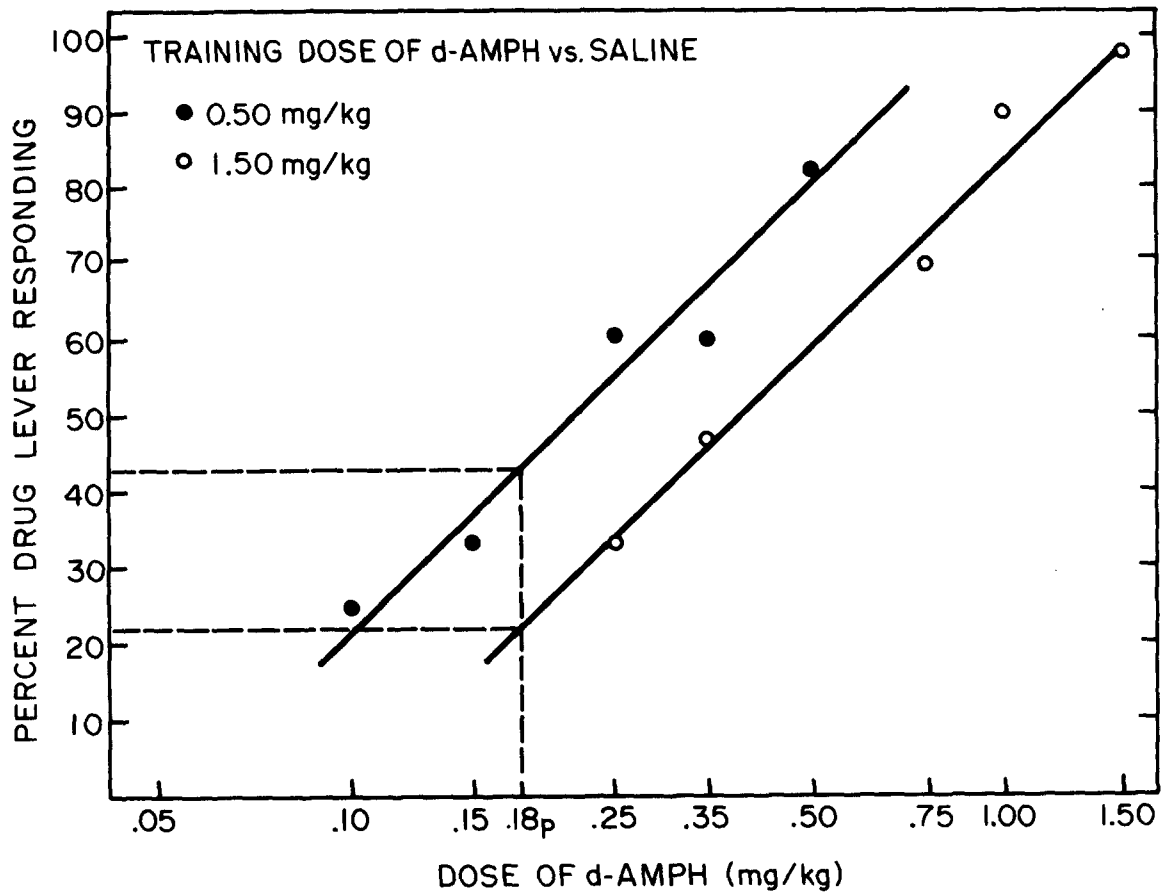


FIG. 2. Linear dose-response relationships observed prior to chronic haloperidol treatment for animals trained on either 0.50 mg/kg or 1.50 mg/kg of d-amphetamine. Also shown is that when these animals were tested on saline following chronic haloperidol they responded as though injected with doses of amphetamine (predicted "p" from the linear regression equations) equivalent to 0.183 and 0.188 mg/kg of d-amphetamine for the 0.50 and 1.50 mg/kg training-dose groups, respectively.

result in 44% and 23% drug-lever responding for the 0.50 and 1.50 mg/kg training-dose groups, respectively. Figure 2 shows the results of these computations. The theoretical dose of amphetamine which would normally result in 44% and 23% drug-lever responding was 0.183 mg/kg and 0.188 mg/kg for the low and high dose training groups, respectively. Thus, these results indicate that the chronic haloperidol regimen used in this experiment resulted in neuronal activation equivalent to that normally produced by 0.18 mg/kg of amphetamine, at least with respect to those systems which mediate the cue properties of amphetamine. The finding that the theoretical dose of amphetamine was virtually the same (0.18 mg/kg) for both groups is consistent with the fact that they received identical chronic haloperidol regimens.

## EXPERIMENT 2

The purpose of the second experiment was to replicate the finding that, following chronic haloperidol, animals respond as though administered a small dose of amphetamine when tested without drug in a two-lever drug-discrimination task. To control for any effects the ten day injection regimen, during which training was suspended, might have had on discrimination in the first experiment, an independent group of rats was included in this experiment which received chronic injections of saline. In addition, a third group was included which received chronic amphetamine injections during the ten day injection regimen. It was predicted that these animals would make fewer responses on the amphetamine lever when tested in the no-drug (saline) state following the chronic regimen.

### METHOD

*Subjects*

The subjects were 24 male Sprague-Dawley rats weighing approximately 300–350 g at the beginning of the experiment. They were food deprived and maintained in exactly the manner described for the first experiment.

*Apparatus and Procedure*

The apparatus and training procedures were the same as those described in the first experiment with the exception that only one training dose of amphetamine (1.0 mg/kg) was used and the saline-amphetamine training sessions were

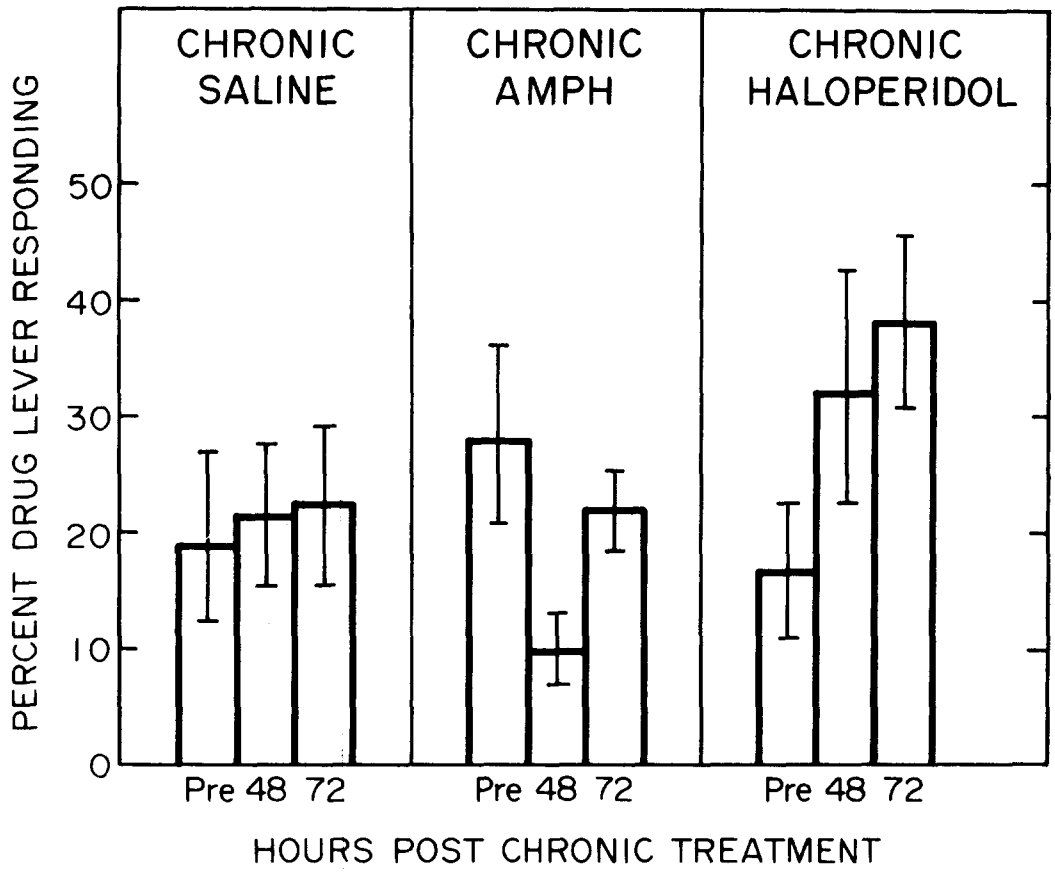


FIG. 3. Percent responding on the amphetamine lever when animals were tested with saline prior (PRE) and subsequent to (48 and 72 hr) chronic injections of either saline, amphetamine or haloperidol.

scheduled on a double rather than single alteration sequence, i.e. SS, DD, SS, DD, etc. Training continued until subjects were averaging at least 80% correct lever choice during the initial 2.5 min extinction period at the beginning of both drug and saline trainins essions.

Following discrimination acquisition the subjects were divided into three groups on the basis of whether they received daily IP injections of haloperidol (1.0 mg/kg), d-amphetamine sulfate (10 mg/kg) or saline (1 ml/kg) during the 10 day injection regimen. All subjects were then tested on saline 48 and 72 hr after the last chronic injection. As in the first experiment reinforcement was withheld during the 5 min test sessions.

## RESULTS

After 36 training sessions (18 amphetamine and 18 saline) the animals averaged at least 80% correct-lever responding during the 2.5 min extinction period at the beginning of each session on both saline and amphetamine sessions.

The data presented in Fig. 3 show the results from the 5 min saline test sessions administered both before (PRE) and subsequent (48 and 72 hr) to the chronic injection regimens. As can be seen in the left-hand panel, chronic saline injections had no effect on percent choice of the drug-lever at either the 48 or 72 hr test interval. The data presented in the right-hand panel replicate the finding reported in the first experiment that following chronic haloperidol there is an increase in responding on the amphetamine-lever even in the no-drug (saline) state. Thus, when tested on saline 48 and 72 hr following the last haloperidol injection, the subjects made 32 and 39% of their responses on the amphetamine lever compared to 17% on the pre-regimen test. One-tailed $t$-tests for correlated means indicated that the 72 hr mean was significantly, $t(8)=1.81$, $p<0.05$, greater than the pre-regimen value. In the middle panel of Fig. 3 it can be seen that there was a significant, $t(5)=1.86$, $p<0.05$, (one-tailed test) decrease in percent drug lever responding at the 48 hr test interval (10%) following chronic amphetamine when compared to the pre-regimen value (28%) and that by 72 hr (22%) there was some recovery to the pre-chronic treatment level. Since it was hypothesized that there would be a decrease in drug-lever responding when animals were tested in the saline state following chronic amphetamine injections, animals with somewhat higher (28%) drug-lever responding were assigned to this group compared to the chronic saline (18%) and chronic haloperidol (17%) groups.

## DISCUSSION

The enhanced cue value of d-amphetamine following a pharmacological treatment known to induce dopamine re-

ceptor supersensitivity adds to previous evidence [5, 17, 19] indicating that a dopaminergic substrate is involved in mediating the stimulus properties of amphetamine. Furthermore, the finding that when animals were tested on saline following chronic haloperidol, they responded as though administered a small dose of amphetamine, indicates that even in the absence of challenge with dopamine agonists, dopamine-related behavioral supersensitivity can be demonstrated with the drug discrimination paradigm. This finding is in contrast to previous demonstrations of behavioral supersensitivity following treatment with chronic neuroleptics [14,24]. In those studies behavioral evidence for dopamine receptor supersensitivity (increased locomotor or stereotyped activity) required challenge with dopamine agonists since these behaviors do not spontaneously increase following chronic neuroleptic treatment. The results of a more recent study [18] demonstrating haloperidol-induced supersensitivity to apomorphine discrimination are in agreement with the results presented here with regard to amphetamine. However, in contrast to the present study, in the previous article it was concluded that chronic haloperidol had no effect on responding following saline administration, since the animals still 'selected' the saline lever as defined by the lever on which 10 responses were first accumulated. However, an additional measure employed in that study involved continuing a test session until 10 responses had also been made on the non-selected lever. The data of interest here were the total number of responses made on the selected lever before 10 responses accumulated on the second lever. This procedure was developed to increase the sensitivity of detecting differences in cue strength which might not be apparent by the 'first selected lever' criterion. The data on this measure indicated that when tested on saline prior to chronic haloperidol, animals averaged 125 responses on the saline lever before completing 10 on the apomorphine lever. Similar tests on days 1, 7 and 11 post-haloperidol resulted in only 54.5, 69.8 and 61.8 saline lever responses for the three test days, respectively. In fact, using this measure it is apparent that the behavior on these post-haloperidol saline tests was more similar to the behavior following administration of .02 mg/kg apomorphine than observed following saline when these tests were given prior to chronic haloperidol. Thus, although the author does not discuss these data, they would seem to confirm the findings from the present study indicating that the drug discrimination paradigm can detect changes in dopaminergic function which is not dependent on drug challenge.

The second experiment replicated the finding that animals increase their percent responding on the amphetamine-lever when tested on saline following chronic haloperidol. The additional finding that following chronic amphetamine animals decreased their percent amphetamine-lever responding when tested on saline, suggests diminished dopaminergic function. This shift in the no-drug baseline also has interesting implications for understanding the nature of the mechanisms mediating the previously reported [1] tolerance to amphetamine's cue properties and also suggests an explanation for those studies reporting a failure to detect tolerance to the cue properties of a drug [3,4]. This explanation proposes that the effect of administering the cue drug chronically is not necessarily to diminish the discriminability between the drug and no-drug states, but rather to shift the position of this difference to the left on the continuum representing the drug's cue properties. Whether this shift would result in a discrimination decrement (tolerance) would theoretically depend on whether or not animals had continued to receive training during the chronic regimen. Continued training would be expected to gradually transfer the discrimination to the altered cues without markedly disrupting discrimination. However, if no training was administered during chronic drug treatment, subjects would not have had the opportunity to adjust their choice behavior to the changing cue state and a decrement in discrimination (tolerance) would be predicted when animals were tested following chronic drug administration. This explanation would account for the apparent discrepancy between studies on cue tolerance since only studies which have discontinued training during chronic drug administration have reported tolerance [1, 13, 21].

Furthermore, with respect to amphetamine, if the discriminative stimulus properties of the drug are based on its euphoria or rewarding effects, then the shift in the no-drug baseline might be a useful model to understand the biochemical changes responsible for producing the post-amphetamine depression often observed in humans following termination of chronic amphetamine use [22].

In summary, the results from the two experiments demonstrate the value of measuring changes in drug-lever selection when animals are tested in the no-drug (saline) state following chronic drug treatment. Althoug a variety of adaptive processes involving both pre- and post-synaptic mechanisms are known to occur as a result of chronic drug administration, it is generally not possible to predict what net effect these regulatory processes will have on the resulting functional state of the particular neurotransmitter system involved. It is this information that the data from the saline tests following chronic drug treatment would seem to provide. Specifically, in the present experiment the changes in lever selection on the saline tests provided behavioral evidence for both enhanced (following chronic haloperidol) and diminished (following chronic amphetamine) dopaminergic function.

ACKNOWLEDGEMENTS

The authors acknowledge the expert technical assistance of Ms. Vicky Feinstein who was responsible for the data collection. This work was supported by the Veterans Administration and the Tennessee Department of Mental Health and Retardation.

## REFERENCES

1. Barrett, R. J. and N. J. Leith. Tolerance to the discriminative stimulus properties of d-amphetamine. *Neuropharmacology* **20**: 251–255, 1981.
2. Burt, D., I. Creese and S. H. Snyder. Antischizophrenic drugs: Chronic treatment elevates dopamine receptor binding in brain. *Science* **196**: 326–328, 1977.
3. Colpaert, F., J. J. M. D. Kuyps, C. J. E. Niemegeers and P. A. J. Janssen. Discriminative stimulus properties of fentanyl and morphine tolerance and dependence. *Pharmacol Biochem Behav* **5**: 401–408, 1976.
4. Colpaert, F. C., J. E. Niemegeers and P. A. J. Janssen. Studies on the regulation of sensitivity to the narcotic cue. *Neuropharmacology* **17**: 705–713, 1978.

5. Colpaert, F. C., J. E. Niemegeers and P. A. J. Janssen. Discriminative stimulus properties of cocaine and d-amphetamine, and antagonism by haloperidol: A comparative study. *Neuropharmacology* **17**: 937–942, 1978.
6. Extance, K. and A. J. Goudie. Inter-animal olfactory cues in operant drug discrimination procedures in rats. *Psychopharmacology* **73**: 363–371, 1981.
7. Gallagher, D. W., A. Pert and W. E. Bunney. Haloperidol induced presynaptic dopamine supersensitivity is blocked by lithium. *Nature* **273**: 309–312, 1978.
8. Gianutsos, G., J. E. Thornburg and K. F. Moore. Dopaminergic supersensitivity in striatum and olfactory tubercle following chronic administration of haloperidol or clozapine. *Life Sci* **20**: 1585–1592, 1977.
9. Harris, R. T. and R. L. Balster. Discriminative control by d, l-amphetamine and saline of lever choice and response patterning. *Psychonom Sci* **10**: 105–106, 1968.
10. Heal, D. J., A. R. Green, D. J. Bullin and D. G. Grahame-Smith. Single and repeated administration of neuroleptic drugs to rats: effects on striatal dopamine-sensitive adenylate cyclase and locomotor activity. *Psychopharmacology* **49**: 287–300, 1976.
11. Koek, W. and J. L. Slangen. The role of fentanyl training dose and of the alternative stimulus condition in drug generalization. *Psychopharmacology* **76**: 149–156, 1982.
12. Kuhn, D. M., J. B. Appel and I. Greenberg. An analysis of some discriminative properties of d-amphetamine. *Psychopharmacologia* **39**: 57–66, 1974.
13. Miksic, S. and H. Lal. Tolerance to morphine-produced discriminative stimuli and analgesia. *Pharmacology* **54**: 217–221, 1977.
14. Muller, P. and D. Seeman. Dopaminergic supersensitivity after neuroleptics: Time course and specificity. *Psychopharmacology* **60**: 1–11, 1978.
15. Overton, D. A. Experimental methods for the study of state-dependent learning. *Fed Proc* **33**: 1800–1813, 1974.
16. Pert, A., J. F. Rosenblatt and C. Sivit. Long-term treatment with lithium prevents the development of dopamine receptor supersensitivity. *Science* **201**: 171–173, 1978.
17. Schechter, M. D. Effect of neuroleptics and tricyclic antidepressants upon d-amphetamine discrimination. *Pharmacol Biochem Behav* **12**: 1–5, 1980.
18. Schechter, M. D. Haloperidol-induced supersensitivity to the discrimination of apomorphine. *Eur J Pharmacol* **74**: 343–346, 1981.
19. Schechter, M. D. and P. O. Cook. Dopaminergic mediation of the interoceptive cue produced by d-amphetamine in rats. *Psychopharmacologia* **42**: 185–193, 1975.
20. Schechter, M. D. and J. A. Rosencrans. D-amphetamine as a discriminative cue: Drugs with similar properties. *Eur J Pharmacol* **21**: 212–216, 1973.
21. Shannon, H. E. and S. G. Holtzman. Evaluation of the discriminative effects of morphine in the rat. *J Pharmacol Exp Ther* **198**: 54–65, 1976.
22. Shick, J. F. E., D. E. Smith and D. R. Wesson. An analysis of amphetamine toxicity and patterns of use. In: *Uppers and Downers*, edited by D. E. Smith and D. R. Wesson. Englewood Cliffs: Prentice-Hall, 1973.
23. Siggins, G. R., B. J. Hoffer and V. Ungerstedt. Electrophysiological evidence for involvement of cyclic adenosine monophosphate in dopamine responses of caudate neurons. *Life Sci* **15**: 779–784, 1974.
24. Tarsy, D. and R. J. Baldessarini. Behavioral supersensitivity to apomorphine following chronic treatment with drugs which interfere with the synaptic function of catecholamines. *Neuropharmacology* **13**: 927–940, 1974.
25. White, D. K. and R. J. Barrett. The effects of electroconvulsive shock on the discriminative stimulus properties of d-amphetamine and apomorphine: Evidence for dopamine receptor alteration subsequent to ECS. *Psychopharmacology* **73**: 211–214, 1981.
26. White, J. F. and J. B. Appel. The role of dopamine and serotonin in the discriminative stimulus effects of lisuride. *J Pharmacol Exp Ther* **221**: 421–427, 1982.