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Haloperidol Does Not Attenuate Conditioned Place Preferences or Locomotor Activation Produced by Food- or Heroin-Predictive Discriminative Cues

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MCFARLAND, K. AND A. ETTENBERG. *Haloperidol does not attenuate conditioned place preferences or locomotor activation produced by food- or heroin-predictive discriminative cues.* PHARMACOL BIOCHEM BEHAV **62**(4) 631–641, 1999.—The present study examined whether a discriminative cue previously predictive of food or heroin reinforcement could activate and direct behavior in an environment that had never been paired with primary reinforcement. Olfactory cues, predicting the availability (S+) or unavailability (S−) of either heroin (0.1 mg/kg IV) or food (45 mg Noyes food pellets) reinforcement in the goal box of a straight-arm runway, were later tested in a separate environment for their ability to elicit locomotion (activate behavior) or induce a conditioned place preference (direct behavior). Presentation of the S+, but not the S−, resulted in a reliable increase in spontaneous locomotor activity that was not blocked by pretreatment with the dopamine receptor antagonist, haloperidol. Similarly, subjects displayed a preference for a novel location in which the S+, but not the S−, was placed. This preference was also unaltered by pretreatment with haloperidol. These data suggest that discriminative cues can profoundly affect behavior, even in environments that have themselves never been associated with primary reinforcement. Additionally, the conditioned motivational quality of these cues is unaltered by treatment with the same dopamine receptor antagonist shown in previous work to attenuate the primary reinforcing properties of heroin and food. © 1999 Elsevier Science Inc.

Conditioned locomotion Conditioned place preference Behavioral activation Discriminative stimulus Motivation Dopamine Food Heroin Haloperidol

ONE of the defining characteristics of behavior is the degree to which it is guided by contextual and environmental cues. Features of the environment that are repeatedly associated with biologically significant events (e.g., food, water, sex, or drugs of abuse) come to exert a profound influence on behavior. In clinical studies of human drug abuse, stimuli that are predictive of drug availability increase self-reports of craving and the motivation to consume drugs [e.g., (22,67,68,71)]. In addition, drug-paired cues have been shown to increase drug-seeking and self-administration in humans (10,27,58), and have been implicated in relapse (22,37). Environmental control of drug-taking behavior has also been demonstrated in animal models of drug-seeking and self-administration. Stimuli paired with drug delivery or availability have been shown to increase responding for drug reward, to maintain responding when the drug reinforcement is removed, and to produce a reinstatement of drug-seeking behavior following extinction [e.g., (24,25,26,40,61,62,76)].

Drug-related behavior is not alone in its susceptibility to stimulus control. Laboratory studies of human and animal feeding behavior demonstrate the importance of food-related cues in determining food intake. For example, in rats trained to lever press for food, presentation of contextual cues or conditioned stimuli increases operant responding in both hungry and satiated animals (50,57,84,85). Additionally, food-paired cues can reinstate responding following a period of extinction

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(2,29), and have been shown to elicit the desire to eat in both hungry and satiated humans (16,54). Thus, it seems that a prerequisite for understanding goal-directed behavior (e.g., food and drug seeking) is an analysis of the neural mechanisms through which environmental cues elicit their behavioral effects.

Midbrain dopamine systems have been implicated in the reinforcing consequences of both food and drugs of abuse [for reviews, see (30,52,53,88)]. These systems have, therefore, been a primary target for studies of the environmental control of motivated behavior. The underlying notion here is that primary reinforcers may influence future behavior by increasing the behavior-activating or response-eliciting properties of neutral stimuli with which they are repeatedly paired (6,12,13,17, 20,23). Presumably, contextual or environmental cues associated with reinforcement are also paired with the dopaminergic activation such reinforcers elicit. Research has demonstrated that, via such pairings with primary reinforcement, conditioned cues can come to elicit activation of midbrain dopamine neurons (15,28,41,51,69,75). Although some have suggested that this activation represents the neural mechanism by which conditioned cues activate goal-directed behavior (14,72,80), the functional significance of conditioned dopamine release for behavior remains unclear [e.g., see (15,28,32, 69,74); but see also (4,5,18,66,83)].

To examine the role of environmental stimuli in goal-directed motivated behavior, we have recently employed a discrimination procedure in rats trained to traverse an operant runway for either food (61) or heroin (62,63) reinforcement. In this situation olfactory discriminative stimuli are presented to signal the availability (S+) or unavailability (S−) of goal box reinforcement. Subjects come to traverse the alley rapidly when presented with the S+ but more slowly when presented with the S−. Thus, goal-directed behavior is facilitated by environmental cues that are predictive of reinforcer availability, contingent upon the performance of the appropriate action (i.e., the discriminative cues set the stage for motivated behaviors such as food or drug seeking). This work has demonstrated the ability of discriminative cues to maintain extremely reliable food- and heroin-seeking behavior. Notably, dopamine receptor antagonism with haloperidol was not able to block either food or heroin seeking elicited by presentation of the S+ (61,62). Additionally, haloperidol pretreatment did not block a reinstatement of drug-seeking produced by reintroduction of the S+ following a period of drug abstinence (63). Thus, it seems that normal dopaminergic function is not necessary for the production of many aspects of goal-directed behavior.

From early in the century when the term "motivation" was first coined, scholars have consistently described both "activation" and "direction" as key components of motivated states (11,42,47,55,77,90). From this perspective, stimuli in the environment predictive of reinforcement have the ability to motivate behavior by producing a generalized increase in activity and serving to direct behavior toward a to-be-obtained goal. Thus, contextual cues paired with primary reinforcement have been shown to support conditioned locomotion. That is, when animals are placed in environments previously paired with either food (43,44,46,56,70) or drugs of abuse (7,8,48,73,82), they exhibit locomotor activation. Additionally, in conditioned place preference experiments, environmental cues have been shown to direct behavior. In such experiments, a distinctive environment that has been paired with food or drug administration is preferred to one that has not been paired with reinforcement [e.g., (49,59,64,78,79,81)].

If the use of discriminative cues is to provide a useful model of the role of environmental stimuli in the production of motivated behavior such as food and drug seeking, then presentation of such cues should engender the well-documented behavioral effects of reinforcer associated stimuli (i.e., they should be able to activate and direct behavior). For this reason, the present study examined the ability of olfactory discriminative cues (predictive of either food or heroin reinforcement) to elicit locomotor activation (to activate behavior) and to produce conditioned place preferences (to direct behavior). Subjects were trained using an operant straight-arm runway in which one cue predicted the presence (S+) and the other the absence (S−) of goal box reinforcement. The S+ cue was then tested for its ability to produce locomotor activation or a place preference in an environment never previously paired with primary reinforcement. Additionally, the role of dopaminergic substrates in the production of the resulting conditioned locomotion and conditioned place preferences was assessed by pretreatment challenge with the dopamine receptor antagonist, haloperidol.

METHOD

Subjects

The subjects for the experiment were 96 male Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA), weighing 275–325 g upon arrival. Animals were individually housed in wire suspension cages located within a temperature-controlled (23°C) vivarium that operated on a 12 L:12 D cycle (lights on at 0700 h). Subjects were allowed ad lib access to food (Purina Rat Chow) and water for 1 week, during which time they were weighed and handled daily.

Reinforcement Conditions

Following 1 week of daily handling, subjects were divided into two groups: one that received heroin reinforcement (a single 0.1 mg/kg infusion delivered over 5 s, $n = 46$) and one that received food reinforcement (33 45-mg Noyes food pellets, $n = 50$), on each trial during behavioral training. Animals assigned to receive heroin reinforcement were implanted with indwelling IV catheters (see details below) then allowed 7–10 recovery days before beginning discrimination training in the runway.

Animals assigned to the food reinforcement condition were food-restricted to and maintained at 90% of their free-feeding body weight. These subjects began food restriction 5 days prior to beginning discrimination training. Heroin reinforced subjects continued to receive free access to food for the duration of the experiment.

Surgery

Following 1 week of daily handling, the heroin reinforcement subjects were implanted with chronic Silastic catheters under sodium pentobarbital (Nembutal) anesthesia (55 mg/kg IP). One end of the catheter was inserted into the right jugular vein and sutured in place to the underlying muscle tissue. The other end was passed subcutaneously to a threaded guide cannula (Plastic Products Co., Roanoke, VA; Item C313G) that was embedded in a silicon assembly and secured on the animal's back. The silicon assembly was placed under the skin between the subject's shoulder blades, and the protruding end of the guide cannula exited via a dermal biopsy hole (3 mm). The guide cannula was then closed with a male internal dummy cannula. During behavioral testing, the internal dummy can-

nula was removed, and subjects were attached to the drug delivery apparatus. To help maintain catheter patency, the internal tubing was flushed with 0.1 ml heparinized saline (1000 IU/ml) every other day.

Operant Runway Apparatus

All discriminative training was conducted in a straight-arm wooden runway, where subjects were trained to traverse the alley for either heroin or food reinforcement. The runway consisted of two wooden boxes (24 × 27 × 38 cm) separated by a straight alley (150 × 11 × 38 cm). One box served as the start box, while the other served as the goal box. Both boxes could be closed off from the alley by means of wooden doors. On trials where subjects were to receive food reinforcement, a food trough was secured in one corner of the goal box and filled with 33 Noyes food pellets. Before each heroin trial, a subject was connected to the drug delivery tubing via a male internal infusion cannula inserted into the guide cannula on the animal's back. The tubing ran from the animal's back to a swivel assembly hanging over the runway and then to a drug-filled syringe. The swivel had a donut shaped collar around it that permitted its placement between two parallel magnetic rails that ran along the length of the alley. Affixed to the bottom of the swivel was a small magnet whose polarity was aligned to repel the polarity of the two magnetic rails. This arrangement allowed the swivel to float over the runway, while remaining within the track formed by the bar magnets. Thus, very little resistance was produced as subjects pulled the drug delivery swivel along with them as they traversed the length of the runway. For a more detailed description of the runway apparatus the reader is referred to Geist and Ettenberg (38).

Procedure

Discrimination training. All subjects were trained in the operant runway to discriminate two olfactory cues: one predicting the availability (S+) and one predicting the unavailability (S−) of reinforcement in the goal box. Schilling Pure Almond and Pure Orange food extracts served as the discriminative cues. Subjects were assigned to counterbalancing conditions such that half of them were presented with the almond cue during S+ trials, while the other half were presented with the orange cue. The remaining scent served as the S− stimulus. Olfactory cues (3 ml of extract changed every third day) were administered from lidded glass containers that were opened and placed under the runway (one container under the start and goal boxes and one halfway along the length of the alley) during behavioral training. At the beginning of each trial, a subject was placed in the start box with the door to the alley closed. After 10 s the door to the start box was opened, and subjects were allowed access to the entire runway. Crossing an infrared photobeam located at the entrance to the alley triggered a timer that ran until the subjects interrupted a second beam located 8 cm inside the door to the goal box (i.e., the timer measured run time—the length of time required for subjects to traverse the alley). Crossing the second photobeam resulted in closure of the door to the goal box, thus confining the animal within. For heroin-reinforced subjects crossing the second photobeam also resulted in the delivery of an intravenous infusion of either heroin (S+ trials) or saline (S− trials). Heroin-reinforced subjects remained in the goal box for 5-min postinfusion before being removed. Upon completion of a trial, each subject's catheter was flushed with 0.1 ml 0.9% physiological saline to clear the internal tubing. Food-reinforced subjects remained in the goal box for three minutes, during which time they consumed the Noyes food pellets available therein.

For the first 3 days of training, subjects experienced a single trial per day in which they were presented with the S+ followed by goal box reinforcement. Beginning on the fourth day of behavioral training, subjects experienced two trials per day: one S+ trial where reinforcement was available in the goal box and one S− trial where it was not. Subjects continued this discrimination training until they met an arbitrary criterion that required the average run time on three consecutive S+ trials to be five times faster than the average run time on the corresponding S− trials. Once all subjects had met this criterion, they were tested for the ability of the drug-predictive cue to elicit either locomotor activation or a conditioned place preference.

Treatment conditions. Animals were randomly assigned to participate in either the locomotor activity ($n = 49$) or conditioned place preference ($n = 47$) test. Half of each group consisted of animals for whom the orange extract had served as the S+ and half consisted of animals for whom the almond extract was the S+. To assess the role of dopaminergic substrates in the ability of the discriminative cues to produce either locomotor activation or a cue induced place preference, subjects were randomly assigned to a subgroup that was pretreated with a single dose of haloperidol, a dopamine receptor antagonist. In the locomotor activity group there were four haloperidol pretreatment conditions (0.0, 0.075, 0.15, or 0.30 mg/kg), while in the conditioned place preference experiment there were three (0.0, 0.15, or 0.30 mg/kg). All haloperidol injections were made intraperitoneally 45 min prior to behavioral testing. Vehicle animals (0.0 mg/kg haloperidol) were injected with 0.2 M lactic acid vehicle. All injections were made in a volume of 1 ml/kg.

Locomotor activity. To measure the locomotor activity exhibited upon presentation of the discriminative cues (either S+ or S−), subjects were placed into one of 16 wire hanging cages (36 × 26 × 20 cm) located within a sound-attenuated and temperature-controlled (23°C) room. One cm from the floor of each cage were two pairs of infrared photocells, each of which contained one infrared emitter and one detector. The two pairs were aligned perpendicular to the long axis of the cage, such that one pair of photocells was 8 cm from the front wall and the other was 8 cm from the rear wall. Each interruption of a photobeam was recorded at 1-min intervals.

Prior to behavioral testing, subjects were placed in the locomotor chambers and allowed to acclimate to the environment over night. Forty-five minutes prior to the start behavioral testing (i.e., following 17 h and 15 min of acclimation), subjects received their assigned haloperidol pretreatment and were then immediately replaced into the locomotor chambers for an additional 45 min of acclimation. Data were collected beginning 45 min postinjection. The first 5 min were used to determine a spontaneous locomotor activity baseline for each subject. Then, one of the two olfactory stimuli was introduced (one open container of scent was placed underneath and midway between each set of two locomotor cages). One minute was allowed for introduction of the stimuli and then another 5 min of S+ or S− locomotor activity data were recorded. Because only one olfactory cue could be presented per test session, animals were randomly divided into two groups and tested on consecutive days. Half of each group consisted of subjects for whom the presented cue served as the S+ and half for whom it served as the S−. Following the first locomotor test, subjects were returned to the runway for an additional 5 days of discrimination training. They then underwent

a second locomotor test in which they experienced the same pretreatment condition, but were presented with the alternate discriminative cue. Thus, all subjects were presented, in a counterbalanced fashion, with both discriminative cues under the same dose of haloperidol.

Conditioned place preference procedure. The place preference apparatus consisted of three distinct wooden chambers: a center compartment (30 × 30 × 60 cm) with the walls painted gray, and two larger compartments (60 × 30 × 60 cm), one of which was painted white and the other black. The floor of the black chamber was covered with Plexiglas, while the floor of the white chamber was covered with a thin layer of wood chips. Once a subject had been placed into the chamber, a perforated Plexiglas covering was lowered over the apparatus, forming a ceiling over the entire chamber. The chamber was fitted with 15 infrared photocells, each consisting of an emitter-detector pair. The pairs were located 1 cm from the floor and spaced at equal intervals along the long axis of the chamber. An IBM compatible computer timed the sessions and recorded the location of a subject within the chamber in real time by continuous monitoring of the output of the infrared emitter-detector pairs.

Following discrimination training in the runway, subjects were each placed in the place preference chamber for a single 10 min acclimation session, during which no data were recorded. On the following day a Baseline trial was conducted. Subjects were individually placed into the central gray region and allowed free access to the entire place preference chamber. The amount of time each subject spent in each of the three compartments was recorded over a 5 min session. Twenty-four hours later, a 5-min test session was conducted in the identical manner as baseline. Forty-five minutes prior to test, subjects were injected with their assigned haloperidol pretreatment. In addition, prior to the test, the discriminative cues were added to the chamber. The S+ was placed on one side and the S− on the other (2 ml of extract in a shallow container at the base of the wall farthest from the central gray compartment). For half of the subjects the S+ was introduced in the more-preferred side from the baseline trial, while for the other half of subjects the S+ was introduced on the less-preferred side. Of the 47 rats run in the conditioned place preference portion of the study, 26 had an initial preference for the black side of chamber, while 21 initially preferred the white compartment. Thus, there was not a large bias in the baseline preferences, and a comparable number of subjects experienced the S+ on the black ($n = 24$) and white ($n = 23$) sides during the test trial.

RESULTS

Discrimination Data

Heroin reinforcement. Figure 1A depicts the performance of heroin-reinforced subjects during discrimination training. To ensure that subjects had learned the olfactory discrimination (i.e., their run times were reliably faster when presented with the S+ than when presented with the S−), a three-way trial × stimulus condition (S+/S−) × scent (orange/almond) ANOVA was computed on the data from the final 3 days of runway discrimination (i.e., the data used to ensure subjects met criterion performance before being moved on to either the place preference or locomotor activity tests) . The analysis revealed a highly significant effect of stimulus condition, $F(1, 44) = 316.52$, $p < 9.001$, indicating that subjects traversed the alley more quickly when presented with the S+ than when presented with the S−. There was no effect of trial, $F(2, 88) = 1.59$, $p > 0.05$, and no trial × stimulus condition interaction, $F(2, 88) = 2.04$, $p > 0.05$, suggesting that the operant behavior of subjects was stable across the final 3 days of discrimination training. Additionally, there was no effect of scent, $F(1, 44) = 0.01$, $p > 0.05$; no scent × trial interaction, $F(2, 88) = 0.32$, $p > 0.05$; no scent × stimulus condition, $F(1, 44) = 0.004$, $p > 0.05$; and no scent × stimulus condition × trial interaction, $F(2, 188) = 0.15$, $p > 0.05$. The lack of all of these effects provides evidence that differences in the nature of the S+ cue (either almond or orange) did not inherently influence the operant runway behavior of subjects. For this reason, the data from the two S+ scents were pooled for all subsequent analyses.

Food reinforcement. As can be seen in Fig. 1B, food- and heroin-reinforced subjects performed similarly during discrimination training. In fact, the pattern of results obtained from a three-way trial × stimulus condition (S+/S−) × scent (orange/almond) ANOVA computed on the data from on the final 3 days of food discrimination training (i.e., the days in which these subjects were found to meet the criterion performance requirement) exactly parallel those previously described for the heroin group: a highly significant main effect of stimulus condition, $F(1, 48) = 224.24$, $p < 0.0001$, but no reliable effect of either trial, $F(2, 96) = 0.15$, $p > 0.05$; or scent, $F(1, 48) = 0.14$, $p > 0.05$; stimulus condition × scent, $F(1, 48) = 0.31$, $p > 0.05$, trial × scent, $F(2, 96) = 0.84$, $p > 0.05$; stimulus

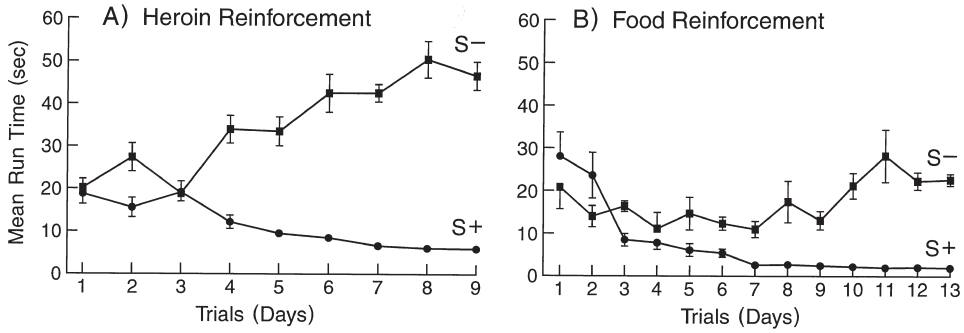

FIG. 1. Mean (±SEM) run times during discrimination training of subjects that earned either heroin (A) or food (B) reinforcement in the goal box of a straight-arm runway. Note that with training, subjects came to reliably traverse the alley more quickly in the presence of the cue predicting reinforcer availability (S+) compared to performance in the presence of the cue predicting no reinforcer availability (S−).

condition × trial, $F(2, 96) = 0.16$, $p > 0.05$; or stimulus condition × trial × scent, $F(2, 96) = 0.75$, $p > 0.05$. Thus, as was the case for heroin, food-reinforced subjects ran faster during S+ than S− trials, and did so independent of the precise S+ cue. For this reason, data were once again pooled across scent condition for all subsequent analyses.

Locomotor Activity

Heroin reinforcement. This part of the experiment was conducted to determine the effect of dopamine receptor blockade on the ability of reinforcement-predictive stimuli to elicit locomotor activation. The left-hand panels of Fig. 2 depict the mean response of subjects to presentation of a stimulus predictive of either heroin (S+, A) or saline (S−, C) administration. A two-way dose × condition (prestimulus vs. poststimulus presentation) ANOVA computed on the S+ data shown in A revealed a significant effect of pre- vs. poststimulus condition, $F(1, 20) = 111.00$, $p < 0.0001$, indicating that presentation of the S+ produced a highly reliable increase in spontaneous locomotor activity. There was also a significant effect of dose, $F(3, 20) = 3.73$, $p < 0.03$, resulting from decreases in activity as the dose of haloperidol was increased. However, it is important to note there was no condition × dose interaction, $F(3, 20) = 0.07$, $p > 0.05$. Hence, haloperidol's activity-reducing effects were equally present both prior to and after S+ presentation. The animals still responded to the presentation of the S+ in the presence of haloperidol, which served as a general depressant to locomotor activity. A similar analysis was computed on the S− data (shown in Fig. 2C). This ANOVA revealed no significant effect of condition, $F(1, 20) = 1.05$, $p > 0.05$, or dose, $F(3, 20) = 2.57$, $p > 0.05$, and no condition × dose interaction, $F(3, 20) = 0.14$, $p > 0.05$. This pattern of results suggests that presentation of a cue that had not previously been predictive of reinforcement was not sufficient to produce locomotor activation. Although haloperidol produced a dose-dependent decrease in locomotor activity, this effect did not reach statistical significance.

Food reinforcement. The right-hand panels of Fig. 2 show the locomotor response of food-reinforced subjects prior to and after either S+ (B) or S− (D) presentation. Again, the pattern of results paralleled those seen in the heroin-reinforced groups. The ANOVA computed on the data from Fig. 2B revealed a highly significant effect of pre/postcondition, $F(1, 21) = 121.58$, $p < 0.0001$, confirming that S+ presentation produced a reliable increase in locomotor activity. There was also a significant behavior-attenuating effect of haloperidol dose, $F(3, 21) = 6.32$, $p < 0.004$, but no reliable condition × dose interaction, $F(3, 21) = 0.20$, $p > 0.05$. Thus, as with heroin-reinforced subjects, pretreatment with haloperidol produced a general depression of locomotor activity but did not prevent the increase in locomotor behavior caused by presentation of the food-predictive cue. Figure 2D illustrates the locomotor behavior of subjects upon presentation of the S− cue. There was a reliable dose-dependent depressant effect of haloperidol dose, $F(3, 21) = 3.18$, $p < 0.05$, but no effect of condition, $F(1, 21) = 2.32$, $p > 0.05$, and no condition × dose interaction, $F(3, 21) = 0.31$, $p > 0.05$. Once again, as is clearly

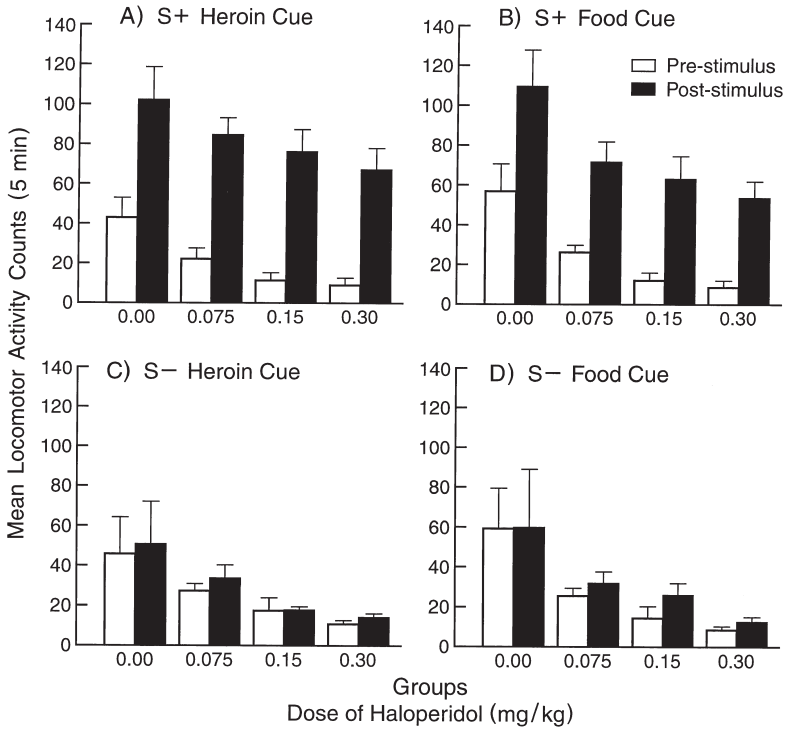

FIG. 2. Mean (±SEM) locomotor activity counts of heroin-reinforced subjects (left) and food-reinforced subjects (right) before (white bars) and after (black bars) introduction of the S+ (top, A and B) or S− (bottom, C and D). Subjects were pretreated with 0.0, 0.075, 0.15, or 0.30 mg/kg of haloperidol 45 min prior to behavioral testing. Although haloperidol had a general suppressant effect on locomotor behavior, it did not prevent the behavioral activating response to heroin- or food-predictive stimuli.

seen from Fig. 2, these results confirm that the S− cue was insufficient to produce locomotor activation, and that this pattern was unaffected by dose of haloperidol.

Conditioned Place Preference Data

Heroin reinforcement. Figure 3A depicts the performance of heroin-reinforced subjects in the conditioned place-preference apparatus. Introduction of the olfactory cues (S+ on one side and S− on the other) increased the amount of time subjects spent in the environment into which the S+ was placed. A two-way condition (baseline test) × dose (0.0, 0.15, or 0.30 mg/kg haloperidol) ANOVA revealed a significant effect of condition, $F(1, 19) = 60.56, p < 0.001$, but no significant effect of dose, $F(2, 19) = 0.01, p > 0.05$, and no condition × dose interaction, $F(2, 29) = 0.26, p > 0.05$. This pattern of results suggests that introduction of the heroin-predictive cue significantly increased the amount of time subjects spent in the compartment where that cue was applied. This tendency was unaffected by haloperidol pretreatment. Although subjects were spending an increased amount of time in the S+ compartment, there was no reliable change in the time they spent in the central gray region, $F(1, 21) = 0.87, p > 0.05$, suggesting that there was a compensatory decrease in the time subjects were willing to spend in the presence of the S−.

Additionally, although pretreatment with haloperidol did not change the ability of the S+ to produce a place preference, it did dose dependently decrease the overall activity levels of subjects during the place preference test trial (see Fig. 4A). An analysis of the number of photobeams interrupted provided a measure of subjects' locomotor activity under each of the three doses of haloperidol. A two-way condition (baseline test) × dose ANOVA revealed significant main effects of both condition, $F(1, 19) = 22.98, p < 0.001$, and dose, $F(2, 19) = 12.36, p < 0.001$, as well as a dose × condition interaction, $F(2, 19) = 24.49, p < 0.001$. This pattern of results suggest that while subjects were comparable in their activity levels during baseline, haloperidol produced a reliable decrease in locomotor behavior during the test trial. Despite the fact that behaviorally active doses of the drug were administered (as indicated by the decrease in spontaneous locomotor activity), haloperidol did not block the ability of the heroin-predictive cue to elicit a place preference (Fig. 3A).

Food reinforcement. As revealed in Figs. 3B and 4B, the pattern of behavior exhibited by food-reinforced subjects was analogous to that of heroin-reinforced subjects. A two-way condition (baseline test) × dose ANOVA on the data from Fig. 3B confirmed a significant main effect of condition, $F(1, 22) = 23.27, p < 0.001$; the S+ cue reliably increased the time spent in that compartment—an effect unaltered by haloperidol pretreatment [i.e., there was no effect of dose, $F(2, 22) = 0.18, p > 0.05$, and no dose × condition interaction, $F(2, 22) = 0.005, p > 0.05$]. Once again, the preference for the S+ side was the result of a shift away from the S− side, because there was no reliable difference in the amount of time food-reinforced subjects spent in the neutral gray compartment between baseline and test, $F(1, 24) = 0.02, p > 0.05$.

An analysis of the locomotor activity data presented in Fig. 4B confirmed a dose dependent haloperidol-induced decrease in locomotor activity during test relative to baseline [i.e., the ANOVA revealed significant effects of condition, $F(1, 22) = 48.80, p < 0.001$, dose, $F(2, 22) = 17.02, p < 0.001$, and a reliable condition × dose interaction, $F(2, 22) = 47.71, p < 0.001$]. Thus, as was the case for heroin reinforced subjects, haloperidol produced decreases in locomotion while having no effects on the ability of the food-predictive S+ cue to elicit place preferences.

DISCUSSION

As indicated in the introduction of this article, theories of motivation have historically identified two important at-

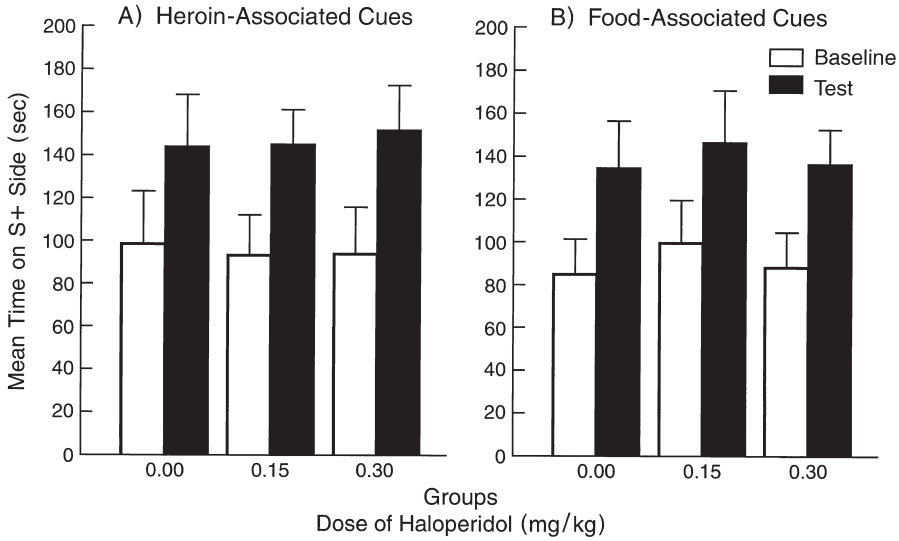

FIG. 3. Mean (±SEM) time spent in the S+ side of the conditioned place preference box for subjects that had been trained to traverse the alley for either heroin (A) or food (B) reinforcement. No discriminative cues were present on the baseline trial (white bars), however, during the test trial (black bars) the S+ cue was placed on one side and the S− cue on the other. Subjects receiving injections of either 0.0, 0.15, or 0.30 mg/kg of haloperidol 45 min prior to test performed comparably in their preference for the S+ side of the test apparatus.

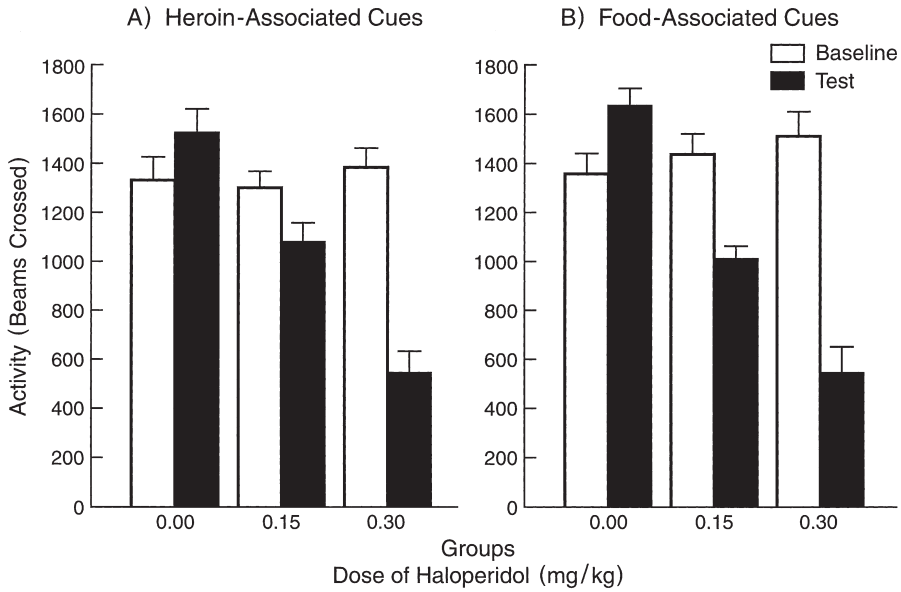

FIG. 4. The effect of haloperidol treatment on locomotor mean (±SEM) behavior measured in the conditioned place preference test. The white bars depict locomotor counts during the baseline trial when no pretreatment was given, and the black bars show mean locomotor counts during the test trial, when subjects pretreated with 0.0, 0.15, or 0.30 mg/kg haloperidol produced dose-dependent reductions in spontaneous locomotor activity.

tributes of motivational stimuli: that their presentation results in behavioral activation, and that they serve to direct or channel the organism's behavior in a goal-directed manner (11,42, 47,55,77,90). In the present study, an S+ predictive of either food or heroin reinforcement was tested for its motivational properties (i.e., its ability to activate and direct behavior). Subjects were initially trained in a straight-arm operant runway to discriminate an olfactory cue predicting the availability of reinforcement (S+) from another stimulus predicting its unavailability (S−). Then, the S+ was assessed for its ability to produce conditioned locomotion (i.e., behavioral activation) and to establish a place preference (i.e., behavioral direction).

During discrimination training, all subjects came to traverse the alley reliably more quickly in the presence of the S+ (predictive of either food or heroin) than in the presence of the S−. Presumably, these results indicate that subjects' goal-directed behavior was facilitated in the presence of an environmental stimulus associated with prior presentations of the reinforcer. Put another way, the S+ might be seen as reliably activating motivational substrates associated with the attainment of food and/or heroin reinforcement. Once the S+ had acquired this capacity, it was tested for its ability to produce conditioned locomotor activation. Presentation of the S+, but not the S−, caused a reliable increase in the spontaneous activity of subjects previously reinforced with either heroin or food. Furthermore, pretreatment with the dopamine receptor antagonist haloperidol did not affect the ability of the S+ to produce locomotor activation, although it did decrease basal activity in a manner consistent with its well-documented motor attenuating properties [e.g., (1,3,31,45)]. Thus, subjects pretreated with haloperidol moved less than those pretreated with vehicle, both before and after introduction of the S+ stimulus. However, the increase in locomotion exhibited upon S+ presentation was consistent across all doses, indicating that the behavioral activating effects of the S+ stimulus remained intact (see Fig. 2A and B).

In the place preference test, we examined the ability of the S+ stimulus to establish a preference for an environment never paired with reinforcement. When the S+ was placed in one compartment and the S− was placed in the other, subjects spent reliably more time in the S+ compartment than they had during a baseline trial when no scents were present. The addition of the discriminative cues produced an increased preference for the S+ side, regardless of whether it was initially preferred or unpreferred. This ability of the S+ stimulus to elicit the place preference was unaffected by pretreatment with haloperidol (see Fig. 3). Note that haloperidol treatment produced a decrease in the spontaneous activity of subjects during the test, indicating that behaviorally active doses of the drug were administered (see Fig. 4). Thus, it seems that not only can a discriminative cue influence choice behavior in a novel environment, but that this ability is not altered by the dopamine receptor antagonist actions of haloperidol. The fact that haloperidol did not block the tendency of subjects to prefer an environment in which the S+ was placed, despite the fact that the environment itself had never been paired with reinforcement, suggests that the motivational (or behavioral directing) properties of the cue remained intact.

The present finding that environmental stimuli predictive of reinforcement maintain their ability to direct and control behavior during dopamine receptor antagonist challenge is consistent with previous research. Horvitz and Ettenberg (46) demonstrated that a conditioned stimulus repeatedly paired with food delivery retained its ability to activate behavior in the presence of pimozide, another dopamine receptor antagonist. As in the present study, there was a drug-induced attenuation of general locomotor activity, but no associated disruption in the ability of the CS to induce behavioral activation. Similarly, it has been demonstrated that pretreatment with ei-

ther haloperidol or pimozide (dopamine receptor antagonist drugs) does not prevent the expression of conditioned locomotion when subjects are placed in environments that had been previously paired with either cocaine or amphetamine [e.g., (7,8,60,86)]. In a parallel manner, expression of conditioned hyperactivity produced by a morphine-paired environment has been shown to be much more resistant to pimozide pretreatment than to naloxone pretreatment (65). In fact, the deficit in conditioned locomotion produced by pimozide could not be adequately dissociated from a general deficit in locomotor behavior produced by neuroleptic drugs. Additionally, Carey (21) demonstrated that haloperidol is unable to block the conditioned rotation exhibited by animals with unilateral 6-OHDA lesions when placed in environments paired with apomorphine injection. In contrast to these findings, Blackburn et al. (14) reported that pimozide blocks the "conditioned incentive properties" of CSs paired with food. However, in this study, the behavior of animals under the influence of pimozide was compared to behavior during nondrugged periods. Thus, there was no control for the motor impairments produced by dopamine receptor antagonist treatment. It seems possible, therefore, that this one contradictory finding results from the motoric demands of the behavior examined, rather than from a lessening of the motivational properties of the conditioned cues.

The finding that the conditioned motivational properties of discriminative stimuli are not blocked by pretreatment with haloperidol is also consistent with previous findings from our laboratory examining the role of dopamine substrates in the production of motivated behavior. The authors have previously demonstrated that both food- and heroin-seeking behavior, exhibited upon presentation of an S+, remain intact during dopamine receptor antagonist challenge (61,62). In these studies, as in the present one, subjects were trained in an olfactory discrimination that required them to traverse a straight alley in order to receive either food or heroin reinforcement in the goal box. Pretreatment with haloperidol did not lengthen the time required for subjects to reach the goal box when presented with the S+. Furthermore, haloperidol did not prevent the reinstatement of previously extinguished drug-seeking instigated by reintroduction of the heroin-predictive cue (63). Taken together, these data suggest that the S+ must have maintained its capacity to activate goal-directed behavior during dopamine receptor blockade.

Our conclusion, that motivational capacity is maintained during haloperidol-induced dopamine receptor antagonist challenge, is also supported by observations of neuroleptic-treated subjects engaged in operant responding for reinforcement [e.g., (33,35,36,39,56,89)]. In such studies, the administration of a dopamine receptor antagonist produces a within-session decline in operant behavior, similar to the "extinction curves" that result from removal of the reinforcer. Subjects begin the session responding at normal or near normal levels and only reduce their rates of operant behavior as the session progresses. The fact that animals initiate responding, and do so with normal (or near normal) response latencies, suggests that the motivation of these subjects to engage in goal-oriented behavior is very much intact. It is only after experiencing the reinforcer in the presence of the antagonist drug that subjects typically reduce their operant responding—a pattern of behavior suggestive of a primary deficit in the reinforcing consequences of reinforcer administration, and not in the motivational state or capacity of the treated subjects.

Franklin and McCoy (35) trained animals to press a lever in order to receive electrical brain stimulation. They demonstrated that when subjects were pretreated with pimozide, animals showed an extinction-like pattern of responding. However, presentation of a CS previously paired with ICSS reward successfully reinstated operant responding. Thus, subjects maintained their motivational responsivity to a reward-paired stimulus, despite the reinforcement decrement that presumably led to the progressive decline in responding through the initial course of the session. Similarly, Gallistel et al. (36) and Franklin (34) showed that although dopamine antagonists elevated reward thresholds for intracranial stimulation in a runway paradigm, they did not prevent the motivational effects of "priming" stimulation that incited animals to run the alley in the first place.

The inability of dopamine receptor antagonism to block the motivational properties of the discriminative stimuli in the present experiment is also consistent with the results of neurochemical studies examining dopaminergic function in the presence of conditioned cues. Research has failed to find an increase in dopamine turnover in subjects returned to an environment previously paired with cocaine when compared with subjects for whom the environment had no prior association with the drug (4). Similarly, no increase has been found in either dopamine release (18) or dopamine overflow (66) within the nucleus accumbens following presentation of cocaine-paired stimuli. In vivo microdialysis measurements within the nucleus accumbens have also failed to demonstrate an increase in DA release during the anticipatory component of feeding behavior, while they showed large increases during the actual consumption of food (87). Likewise, a food-predictive stimulus that successfully elicited behavioral responses, failed to modify extracellular DA in the nucleus accumbens (5). Additionally, although conditioned neuronal activation elicited by presentation of cocaine-paired stimuli (measured via Fos expression) has been shown in many limbic regions, it is conspicuously absent from the nucleus accumbens and dorsal striatum (19). Although there has been a report of increased DA overflow in the nucleus accumbens following placement in a cocaine-paired environment (32), it should be noted that interpretation of this result is complicated by the fact that subjects received cocaine injections prior to measurement. Thus, the results were not purely an indicator of conditioned DA response; instead, they were an index of the interaction between the neural consequences of cocaine administration and the environment. When considered in conjunction with the behavioral evidence, data from these neurochemical studies of DA function are consistent with the notion that reinforcement-predictive cues do not rely on the activation of DA mechanisms to produce their behavioral activating (i.e., motivating) effects.

The present data have particular relevance for our understanding of goal-directed behavior. They provide further support for the view that discriminative cues can be used to produce reliable goal-oriented behavior. Because many environmental cues are not passively paired with reinforcement, but rather are signals indicating that particular behaviors will produce desired outcomes, an understanding of the neural mechanisms through which discriminative stimuli elicit their behavioral effects seems crucial for any adequate account of goal-directed behavior. The present data also suggest that such cues, once established, have the ability to influence behavior that is not restricted to the training environment, but can be transferred to novel ones. These two pieces of evidence have particular relevance for the understanding of addictive behavior and relapse. It suggests that one possible reason for the frequent failure of drug abuse treatments that rely on the extinction of

classically conditioned cues is their failure to appreciate 1) that many of the cues have discriminative properties, and 2) that extinguishing such cues in the clinical setting may not have an effect on their ability to influence behavior in the drug-paired environment or prevent the transfer of these cues to new contexts. Finally, the present study, in agreement with many prior ones, suggests that the motivational properties of discriminative cues are not disrupted by pretreatment with dopamine receptor antagonist drugs. There is abundant evidence implicating dopaminergic substrates in reinforcement, or in the process by which environmental cues acquire their motivational properties (6,9,24,30,88). However, once such properties are acquired, it seems that their ability to influence behavior relies on a separate, dopamine independent process.

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