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Qualitative and Quantitative Differences in the Operant Runway Behavior of Rats Working for Cocaine and Heroin Reinforcement

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ETTENBERG, A. AND T. D. GEIST. *Qualitative and quantitative differences in the operant runway behavior of rats working for cocaine and heroin reinforcement.* PHARMACOL BIOCHEM BEHAV 44(1) 191–198, 1993.—Animals were trained to traverse a straight alley for drug reinforcement consisting of five IV injections of either 0.75 mg/kg/injection cocaine (n = 6) or 0.06 mg/kg/injection heroin (n = 6). Testing involved single daily trials during which the latency to leave the start box and the time required to traverse the alley were recorded for each animal. In addition, input from 12 pairs of infrared photocell detector/emittors placed along the length of the alley provided information on the precise location of the animal at 0.1-s intervals throughout the course of each trial. This information was recorded by computer and provided the basis for construction of graphic representations of each trial in the form of *spatiotemporal records* that revealed the precise route the subject took in getting to the goal box. The experiment revealed substantial differences in the runway behavior of heroin and cocaine animals. While the heroin group exhibited typical patterns of operant performance in that both start latency and goal times decreased gradually over the course of the experiment, cocaine animals were reliably slower than heroin subjects to leave the start box and exhibited a progressive *increase* in goal times over trials. The latter effect appeared to be a consequence of a "stop and retreat" behavior that was observed in all six cocaine subjects and increased in frequency as the experiment progressed. Because the runway behaviors exhibited here were emitted *prior* to delivery of the drug reinforcer, they suggest that the motivational state underlying drug-seeking behavior is qualitatively different for heroin- and cocaine-reinforced animals.

Cocaine Heroin Conditioned place preference Self-administration Psychomotor stimulants Opiates Operant behavior Runway Drug reinforcement

INVESTIGATIONS of the reinforcing properties of psychoactive drugs have relied almost exclusively upon the use of two distinct behavioral methodologies: the operant self-administration procedure and the conditioned place preference (CPP) test [e.g., see reviews by (6,25,26,38,54)]. In the self-administration model, drug delivery is made contingent upon the emission of an operant response with the drug's reinforcing efficacy determined by its ability to serve as a positive reinforcer. While there are procedural variations between laboratories in the use of this technique, by far the most typical self-administration experiment uses a lever-press operant in conjunction with an IV drug reinforcer. In contrast to self-administration, the conditioned place test does not involve the use of an operant response. Animals receive experimenter-delivered drug injections followed by placement into one of two distinctive environments. Within-subject control procedures involve placing the same animal into a second environment (clearly distinguishable from the first) following non-drug vehicle injections. After multiple exposures to each of the two environments, a behavioral test is conducted in which the nondrugged animal is afforded a choice between the two conditioning environments (6). A reliable preference for the drug-paired environment (or a shift in preference toward that environment compared to a preconditioning baseline) provides an index of some positive attribute of the administered drug. Note, however, that because the place preference test does not employ an operant response (during either conditioning or preference testing) it may be inappropriate to employ the term *reinforcement* in this context. For this reason, some researchers have preferred the term "drug reward" to describe the underlying process responsible for the shifts in CPP behavior observed in their studies (50,52).

It is, of course, unclear at this point whether the differences in the terms "drug reward" and "drug reinforcement" are purely operational in nature or whether they describe different neuronal processes within the CNS (49,50). However, there

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have been instances where qualitatively different results have been obtained from studies of the same drugs using self-administration and place preference methodologies. For example, while lesions of the mesolimbic dopaminergic system and dopamine (DA) receptor antagonist drugs have both been demonstrated to interfere with IV self-administration of cocaine (12,17,39), these same treatments do not attenuate the place preferences produced by SC administered cocaine (33,44). Although this discrepancy disappears when cocaine is administered IV in the place preference test (46), the vast majority of CPP studies employ SC or IP routes of administration (6). As a result, some concerns continue to linger about the comparability of the underlying processes being measured in these two test paradigms when different routes of drug delivery are employed. For example, the mixed opiate agonist-antagonist buprenorphine has been proposed as a putative treatment for both heroin and cocaine abuse on the basis of results obtained in IV self-administration experiments (32). However, in CPP studies it has recently been reported that buprenorphine and cocaine act synergistically and that small doses of one can potentiate the size of CPPs produced with the other (4). In other work, DA antagonist drugs or 6-hydroxydopamine (6-OHDA) lesions of the mesolimbic DA system prevented the establishment of conditioned preferences produced by IP injections of heroin or morphine [(29,36,45), but see also (31)]. However, these same DA manipulations have been demonstrated to be ineffective at reliably altering IV opiate self-administration (17,20,35). Finally, IV phencyclidine (7) and pentobarbital (23) are readily self-administered in animals but produce aversions when injected IP in the CPP test (2,34).

In addition to differences in the typical route of drug administration in CPP and self-administration studies, some of the discrepancies in results from these two procedures might also be accounted for by the degree of "subject control" over drug administration. There is, for example, a substantial literature demonstrating that animals find the identical reinforcing stimulus more preferred when its presentation is made contingent upon an operant response compared to when it is passively administered (5,16,18,40). Contingent and noncontingent cocaine administration have also been differentially associated with drug toxicity. Dworkin et al. (13) observed that yoked-control animals having received noncontingent cocaine at the same time, rate, and dose as animals self-administrating cocaine had a dramatically increased risk of drug-induced lethality. In our own work, animals demonstrated stronger place preferences for an environment associated with contingently administered amphetamine over one associated with noncontingent amphetamine injections (28). It would seem then that even when the employed dose and route of drug administration are comparable, place preference (noncontingent) and self-administration (contingent) methods may be sensitive to qualitatively different drug experiences. This does not mean that the results from CPP and self-administration methodologies are consistently at odds with one another. In fact, in the majority of cases the data derived from these two test procedures yielded consistent results (6). However, when discrepancies do exist it may be because the two procedures are sensitive to different, albeit overlapping, subsets of drug action.

In an attempt to overcome some of the potential interpretive problems with integrating the results from place preference and self-administration experiments, we employed a behavioral paradigm that incorporates procedural aspects of both methodologies (14,15). Animals were trained to emit an operant response (alley running) to enter a distinctive place (the goal box) where IV drug reinforcement is administered. An additional procedurally unique characteristic of this work is that animals are tested on only a single trial per day. This ensures that all the behavioral data are collected prior to the delivery of the drug reinforcer. The data cannot, therefore, be easily attributed to some nonspecific or motoric consequences of the drug reinforcer. More significantly, the one-trial-per-day testing protocol provides a unique index of the *pre*drugged state of the animal, thereby addressing how *motivated* the animal is to seek out the drug reinforcer each day. We successfully employed this methodology for the study of SC amphetamine (14) and IV cocaine (15) and hereby extend our investigation to the comparative effects of cocaine and heroin.

METHOD

Subjects

Subjects were 12 male, albino Sprague-Dawley rats (weighing 350–375 g at the time of surgery) obtained from Charles River Laboratories. Each animal was individually housed in metal wire hanging cages located within a temperature-controlled (23°C) 12 L : 12 D vivarium environment (lights on at 0700 h). Throughout the course of the experiment, animals were provided with continuous access to food and water in their home cages. Subjects were individually handled and weighed once each day for 2 weeks prior to catheter implantation.

Surgery

Each subject was surgically implanted with a chronic silastic jugular catheter under deep 50 mg/kg sodium pentobarbital (Nembutal) anesthesia [as we have previously described: (17,27,35)]. One end of the catheter was intravenously implanted and the other end passed subcutaneously to a threaded stainless steel guide cannula (Plastic Products Co., Roanoke, VA; Item C313G) that was in turn affixed to a polyethelene (PE) assembly mounted on the animal's back. This permitted the animal to be disconnected from the drug delivery when behavioral testing was not being conducted. During the first 5 days after catheterization, the system was flushed daily with heparinized (1,000 IU/ml) physiological saline to help protect against the formation of embolisms in the vein. The first training day commenced 7–10 days after surgery.

Runway Apparatus

All trials were conducted in a wooden straight-arm runway (155 × 15 × 40 cm) located within a small, sound-attenuated room. A start box (24 × 25 × 40 cm) was attached at one end of the runway and a goal box of the same dimensions attached at the opposite end. The floor of the apparatus consisted of small-diameter steel rods arranged in parallel approximately 1.2 cm apart along the entire length of the alley including the start and goal boxes. A sliding door provided access from the start box to the runway. Opening this door initiated the start of a trial, the timing of which terminated when the animal interrupted an infrared photocell beam detecting its presence in the goal box. An additional 12 pairs of infrared photodetector emitters were set into the walls of the runway in such a way as to subdivide the alley into 12 equally sized subregions. The output from these photodetectors was monitored in real time by an IBM-AT computer programmed to

record the precise location of the animal within the alley at 0.1-s time intervals. This provided a detailed analysis of the runway behavior of animals after leaving the start box but before entering the goal box.

As each animal traversed the alley, it pulled a swivel assembly along between a track consisting of two magnetic rails aligned in parallel and suspended 53 cm above and along the entire length of the alley. The swivel assembly was in essence a commutator-like device that permitted an animal to move and turn freely without getting its lead tubing twisted. One end of the swivel was connected by PE tubing to the rat and the other end to the drug-filled syringe that delivered the reinforcer. The originality of this design is reflected in the fact that the carriage assembly to which the swivel was attached remained suspended a few centimeters above the track. This was accomplished by placing the swivel through the center hole of a doughnut-shaped pot magnet whose magnetic poles were appropriately aligned to repel the magnetic charge of the tracks. Thus, the entire swivel-carriage assembly appeared to float slightly above the tracks. The extremely low friction afforded by the magnetic repulsion between the swivel's pot magnetic and the opponent tracks permitted animals to wander through the runway essentially unfettered. For a more detailed description of the apparatus, the reader is referred to Geist and Ettenberg (21).

Procedure

For behavioral testing, each animal was removed from its home cage and connected to the drug-delivery system. This was accomplished by manually threading a male internal cannula into the external threaded guide cannula mounted on the animal's back. The internal cannula was itself connected by PE 20 tubing, through the swivel assembly, to a 10-ml syringe containing a solution of either cocaine HCl (Sigma Chemical Co., St. Louis, MO) or diacetylmorphine (NIDA, Rockville, MD) prepared in a vehicle of 0.9% physiological saline. The syringe resided within a Razel (Stamford, CT) Model A syringe pump adjusted to deliver a 0.1 ml volume of drug over a 4-s period. Once connected to the drug-delivery system, the animal was placed in the start box and, after 10 s, the start box door was lifted and the trial thereby initiated. Upon traversing the alley and arriving in the goal box, the goal box door was closed (to prevent retracing) and a reinforcer consisting of five IV injections (applied at 30-s intervals) was provided. Half the animals were administered 0.75 mg/kg/injection cocaine and the remaining half 0.06 mg/kg/injection diacetylmorphine (heroin). These doses were selected for comparability to those employed in our own previous lever-press IV self-administration work and the published reports of others (12,17,35,47,55). Similarly, the use of five successive injections was also chosen on the basis of previous self-administration research demonstrating that when drug-reinforcer availability is limited to a few hours each day subjects typically make numerous responses during the first few minutes (presumably to elevate blood/brain drug levels to some homeostatic value) before more paced and regular responding is exhibited (17,53).

After the drug reinforcer was delivered, each animal remained in the goal box for a total of 5 min, after which it was removed from the apparatus and returned to its home cage. Testing continued in this manner (a single trial per day) for 21 consecutive days, the first 3 of which were used to shape the operant response and habituate animals to the test procedures. During each trial, the *start latency* (i.e., time to leave the start box) and *goal time* (i.e., time required to traverse the runway and enter the goal box once an animal had left the start box) were recorded. In addition, a computer-generated graphic representation of each trial was constructed. These *spatiotemporal records* depicted the location of the animal within the alley at 0.1-s intervals over the course of each trial.

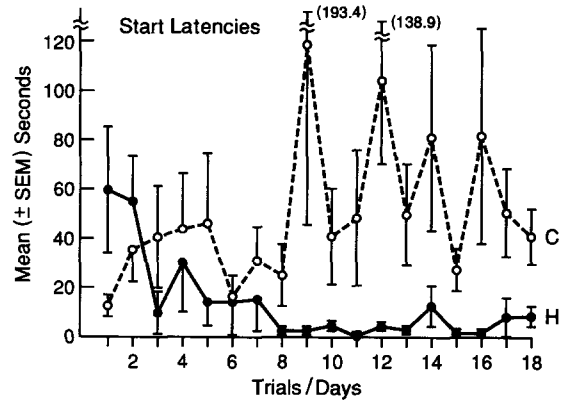

FIG. 1. Mean (±SEM) start latencies (i.e., time to leave the start box once the start box door was opened). Data are expressed as group means for heroin (H) and cocaine (C) subjects during each of 18 consecutive trials. Trials were conducted once each day.

RESULTS

Although all animals learned to traverse the alley for IV drug reinforcement, there were reliable differences in the quantitative and qualitative nature of the operant runway behavior of animals working for cocaine and heroin. Figures 1 and 2 show the mean start latencies and goal times, respectively, for each group over the 18-day course of the experiment. Separate two-factor analyses of variance (ANOVAs) were computed on the start latency and goal time data depicted in the figures. Analysis of start latency revealed a statistically reliable difference in overall group performance, $F(1, 10) = 5.75$, $p = 0.038$, and in the group × trial interaction, $F(17, 170) = 2.20$, $p = 0.006$. As can be seen from Fig. 1, the group effect is clearly a result of the fact that for the

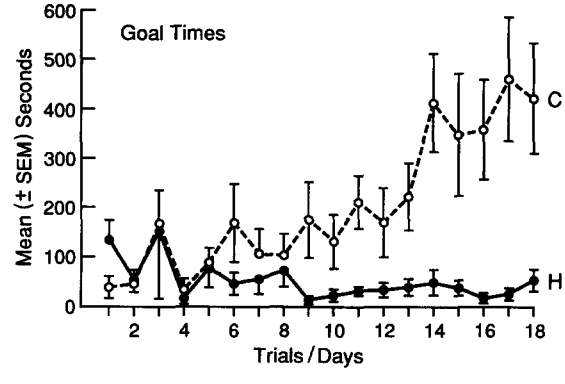

FIG. 2. Mean (±SEM) goal times (i.e., time to enter the goal box once an animal had left the start box). Data are expressed as group means for heroin (H) and cocaine (C) subjects during each of 18 consecutive trials. Trials were conducted once each day.

majority of the experiment heroin animals tended to leave the start box with shorter latencies than animals in the cocaine group. Differences in patterns of responding over trials contributed to the significant interaction effect; thus, while heroin animals tended to leave the start box earlier and earlier over trials cocaine animals did not tend to do so. This was confirmed by computation of additional one-way repeated-measures ANOVAs on each group's start latencies: Heroin animals produced a highly reliable decrease in start latency over trials, $F(17, 85) = 3.41, p = 0.0001$, while cocaine animals produced no reliable change over trials, $F(17, 85) = 1.38$, n.s.

The goal times (Fig. 2) of heroin and cocaine animals were also different. Once again, heroin-reinforced animals tended to maintain a relatively fast running speed (i.e., brief goal times), while cocaine animals took progressively longer to enter the goal box over trials. The two-factor ANOVA computed on the data depicted in Fig. 2 confirmed the statistical reliability of these observations. There was a significant main effect for group, $F(1, 10) = 9.03, p = 0.013$, trials, $F(17, 170) = 3.33, p < 0.0001$, and group × trial interaction, $F(17, 170) = 4.76, p < 0.0001$. All three of these effects are clearly attributable to the large and progressive increases in the goal times of the cocaine group compared to the fast and relatively stable goal times of the heroin group (see Fig. 2).

The apparently atypical responding of the cocaine animals is in fact consistent with our own previously reported results (15). In that study, the progressive increase in goal times was not a result of slow running speed but rather an unusual stop-and-retreat behavior that increased in frequency over trials. This behavior was characterized by a cessation in forward locomotion prior to entering the goal box, followed by a retreat all the way back into the start box. Time-place records were therefore analyzed in the present study to determine the occurrence and frequency of retreat behavior. The results of that analysis are presented as Fig. 3, which depicts the total number of retreats made by each group over each trial. The figure clearly confirms the progressive increase in the frequency with which cocaine-reinforced animals stop short of the goal box and return toward the start box. In contrast,

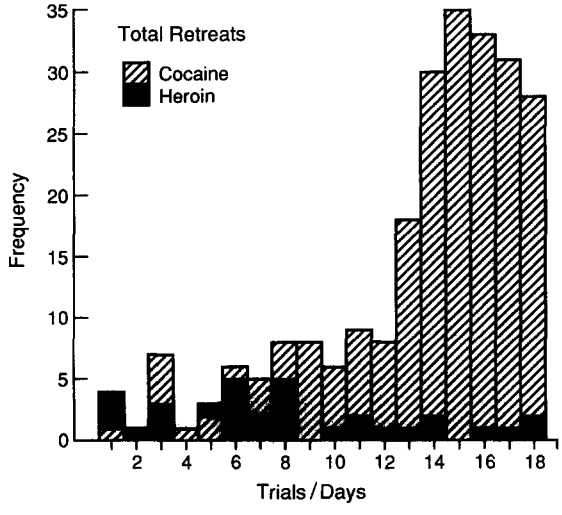

FIG. 3. Total frequency of retreat behavior (see the text for explanation) exhibited by each group during each of the 18 test trials.

heroin-reinforced animals demonstrate little of such behavior. On average, cocaine animals emitted a total of 39.5 retreats (SEM = ±13.8) over the 18 days/trials of the experiment, while heroin animals averaged 5.3 (±2.2) [two-tailed t-test for independent samples, $t(10) = 2.43, p = 0.035$].

The group differences in retreat performance are clearly illustrated in Fig. 4, which provides sample spatiotemporal records of a representative animal from each group. The x-axis of these records indicates total session length (determined by the time required for the animal to enter the goal box) and the y-axis represents the location of the animal (at 0.1-s intervals) within the alley. The number "1" on the ordinate corresponds to a photocell at the threshold between the start box and the alley while the number "10" corresponds to a photocell located just outside the entry to the goal box. Obviously, the very nature of this coordinate system provides for a form of cumulative record of an animal's precise location as a function of time during each individual trial. In addition, like a standard cumulative record the slope of the line provides an index of response strength (i.e., running speed) with steep slopes indicative of fast running and shallow slopes indicative of slow running. Figure 4 shows the progressive increase in retreat behavior (from Trials 5 to 10 to 15) of the cocaine animal and the noticeable lack of such behavior in a representative heroin animal. Note that although the cocaine animal is taking progressively longer to enter the goal box this is occurring as a consequence of the increased frequency of retreat behavior and not a reduction in running speed.

DISCUSSION

The present study employed behavioral testing procedures that incorporated aspects of both self-administration and CPP methodologies. Animals were trained to emit an operant response (alley running) to enter a distinctive environment (the goal box) where IV drug injections were experimenter applied. A comparison of cocaine- and heroin-reinforced behaviors in this paradigm revealed substantial differences in both qualitative (response patterns) and quantitative (start latencies and goal times) indices of operant performance. Over trials, the heroin group left the start box with shorter and shorter latencies and entered the goal box with progressively faster goal times. This pattern was representative of all six subjects in the group and the resulting within-group variability was extremely small (see the error bars in Figs. 1 and 2). In contrast, cocaine animals exhibited no reliable change in start latency over trials (although they were reliably slower at leaving the start box than heroin animals) and their goal times increased fivefold over the course of the experiment. Further, as was the case with heroin animals, the behavior of the cocaine group was consistent across animals with all six rats demonstrating the same pattern of runway performance. Finally, as already indicated, the elevated cocaine goal times were not a result of slow running. Examination of the graphic *spatiotemporal records* indicates no difference in running speeds between the heroin and cocaine groups (see slopes of the lines in Fig. 4). Cocaine animals, however, were far more likely to stop in the alley (prior to entering the goal box) and then turn and retreat back into the start box and it was the incidence of this retreat behavior that elevated cocaine goal times.

It should be noted that only a single dose of cocaine and heroin were tested in the present study (0.75 mg/kg/injection for cocaine and 0.06 mg/kg/injection for heroin). However, these doses were specifically selected to ensure comparability with those employed in the IV self-administration literature,

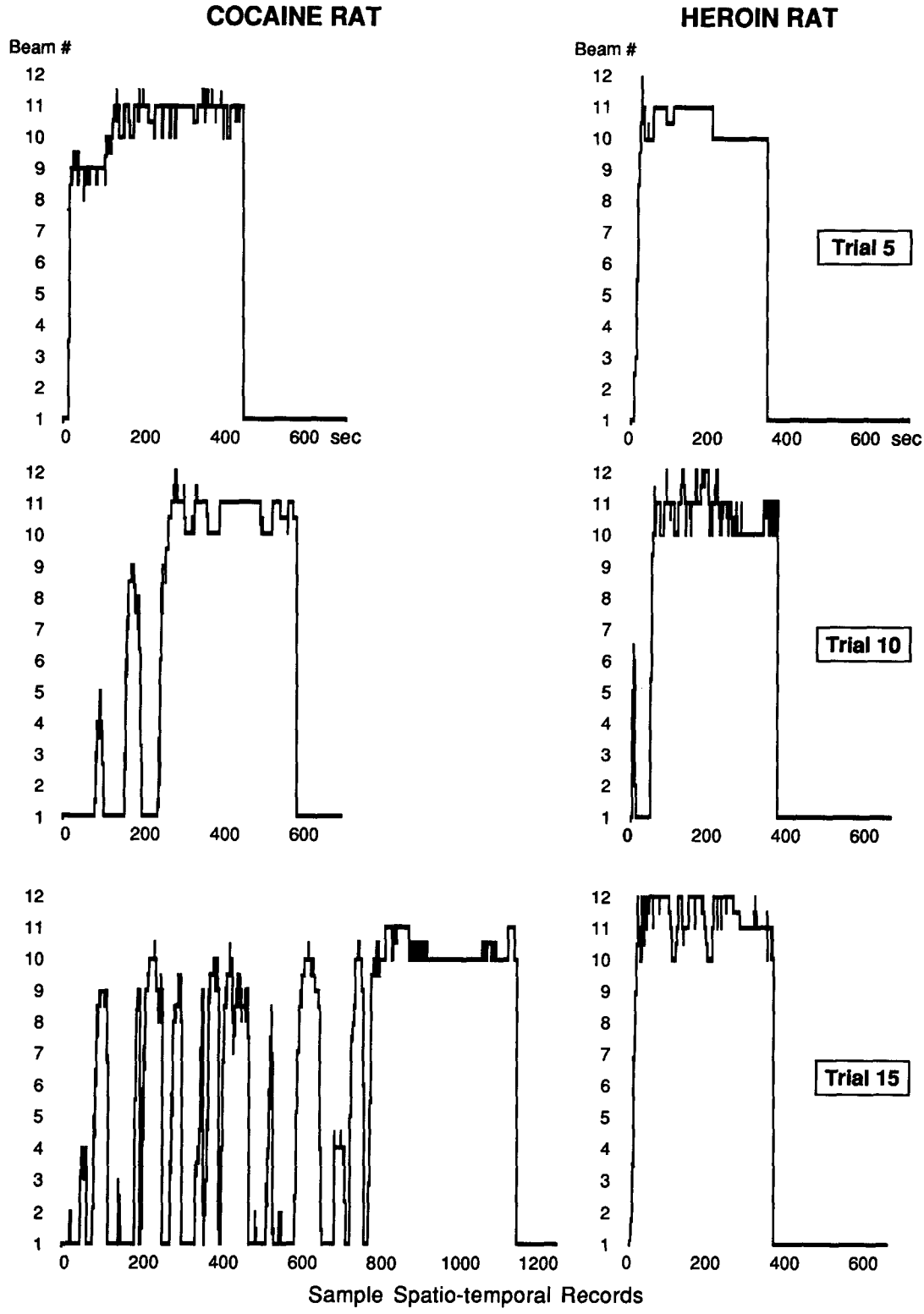

FIG. 4. Representation spatiotemporal records from a single cocaine rat (left) and a single heroin rat (right). The top two, middle two, and bottom two panels represent performance on days/trials 5, 10, and 15, respectively. These graphs each depict the location of an individual animal in the runway during the course of a single trial. The *x*-axis represents session length (determined by how long it took the animal to enter the goal box) and the *y*-axis codes for location within the runway ("1" corresponds to a photobeam at the threshold between the start box and the alley while "10" corresponds to a point just outside the entry to the goal box). Although both animals ran quickly on each trial (as indicated by the steep slopes of the curves), the cocaine rat exhibited a progressive increase in retreat behavior not observed in the heroin animal. Note that the location at which the cocaine rat stopped its forward progress on each approach to the goal box (Trial 15) tended to be in close proximity to the goal box entrance.

where often changes in the responses generated by a single reinforcing dose of cocaine or heroin are examined following some experimental manipulation (10,12,17,27,35,39,53,55). It is therefore reasonable to conclude that at doses typically used to maintain lever-press self-administration in rats cocaine and heroin produce qualitatively and quantitatively different patterns of predrug operant behavior. Of course, it remains to be determined whether such differences are characteristic of the entire reinforcing portion of the dose–response curves for cocaine and heroin and not idiosyncratic aspects of the single doses employed here. A thorough analysis of this possibility is currently in progress in our laboratory.

The behavior of cocaine animals in the present study confirms our own previously reported observations (15). Because cocaine effects in humans are reported to include both euphoric and anxiogenic qualities (1,30,42,48), in the laboratory one might predict that such dual actions would be observable in behavioral test paradigms that examine the subject's approach to stimuli associated with cocaine administration. In this view, retreat behavior might be reflective of a conflict resulting from concurrent positive and negative associations with the goal box. Consistent with this hypothesis was the observation that retreat behaviors did not occur randomly in the alley (as they do in nonreinforced animals) but rather reliably increased in likelihood as a function of animals' proximity to the entryway of the goal box [(15); see also Fig. 4]. In addition, like other forms of conflict (8,9) the retreat behavior observed in the present paradigm was found to be highly responsive to treatment with the anxiolytic agent, diazepam (15). Of course, for conflict to occur one needs to demonstrate concurrent positive as well as negative properties. Again, in our original work we demonstrated that animals that exhibited retreat behavior comparable to that observed in the present study still developed conditioned preferences for a novel place paired with four IV cocaine injections (15).

While sensitive to either positive or negative attributes of a drug's actions, the CPP test (as typically described in the literature) may not be particularly well suited for identifying the putative conflict behavior exhibited here. In the runway test, animals experienced cocaine infusions daily for 21 days (including training). In contrast, the CPP test in general includes but 6–8 conditioning days, only half of which involve drug–place pairings (6). Because the initial reaction to cocaine in humans is reported to be euphoric (19,42,43), it is this effect that is most contiguous with the conditioning environment and hence most likely to be associated with that environment. The anxiogenic actions of cocaine, typically reported to emerge after the euphoria subsides (1,30,48), would therefore be expected to take longer to condition and hence might be expected to influence the chronic runway test and not the relatively acute CPP. In support of this notion is the observation both in the present study and in our previous work (15) that retreat behavior increased over the course of the experiment. While this might reflect a progressive increase in the negative properties of cocaine, it can also be accounted for by a learning function related to the gradual conditioning of the drug's negative properties with the goal box.

Lever-press models of self-administration may also be inappropriate for assessing cocaine-induced states of conflict. Once again, because the *initial* reaction to the drug appears to be predominantly positive in nature animals need only emit another lever press each time the positive effects of the drug subside or the negative effects begin to take precedence. In the present paradigm, only one operant response is emitted each day, thereby providing an index of the animal's motivation to enter the goal box (where the drug reinforcer is administered). Therefore, while traditional lever-press procedures provide a useful index of the animal's motivation to *maintain* drug self-administration they do not assess the animal's motivation to *initiate* drug self-administration in the first place. In fact, the typical self-administration study includes a noncontingent "prime" at the onset of the test session, thereby ensuring that even the first operant response is influenced by the pharmacological actions of the drug reinforcer. While the study of factors that maintain drug self-administration is certainly important, it is nevertheless equally important to investigate subjects' motivation to initiate or reinstate self-administration behavior (10,11,14). In studies of human drug abuse, for example, a great deal of attention is paid to the state of the individual *prior to* the onset of drug intake because it is during this nondrugged state that the motivational factors resulting in remission or reinstatement of drug abuse behavior are present. In the present runway test, the behavior of nondrugged animals is examined immediately prior to the subject's entry into the goal box. This paradigm is, therefore, ideal for investigating the motivational states of animals prior to delivery of the drug reinforcer.

An alternative explanation for the observed retreat behavior in cocaine-treated animals views such behavior as a form of *conditioned stereotypy*. Indeed, it has been well established that administration of dopamine agonist drugs induces a potent hyperactivity and/or stereotypy that can be classically conditioned (3,24,37,41). With respect to the current experiment, the application of cocaine might be expected to induce an unconditioned stereotyped behavior pattern (i.e., pacing back and forth) that comes to be associated with the goal box over trials. The observed retreat behavior could therefore be explained as a form of conditioned stereotypy comparable to that observed following place–amphetamine pairings in other studies (3,24). However, while this is most certainly a reasonable explanation for the current results there are three pieces of information that favor the authors' interpretation of the data. First, in each of the studies in which conditioned stereotypy has been reported animals exhibit such behavior when placed directly into the environment previously paired with the unconditioned effects of the drug. In the current situation, animals exhibit retreat behavior while in the runway and not the goal box, where the drug is delivered. Second, the cocaine-induced retreat behavior, like other behavioral expressions of conflict, is dose dependently reversed by benzodiazepine pretreatment (15). Finally, in our most recent work (22) we observed an identical pattern of retreat behavior in animals approaching a goal box associated with concurrent application of food and mild foot-shock. While none of these items directly challenge the viability of the conditioned stereotypy hypothesis, together they lend credence to the authors' interpretation of retreats as a reflection of conflict behavior.

There has been a great deal of speculation about whether the reinforcing properties of opiate and psychomotor stimulant drugs are mediated through separate or common neural substrates (26,51). Such work necessarily involves an investigation of the neural *consequences* of opiate and stimulant drug delivery. In contrast, the present study examined the behavior of animals prior to drug delivery as a means of assessing nondrugged animals' motivation to seek and obtain the drug reinforcer. In this situation, heroin animals exhibited prototypical operant runway behavior in which both start latency and goal times decreased gradually over the course of

the experiment. Cocaine animals, however, demonstrated an increasing hesitation to enter the goal box over trials. Such results suggest that the motivational state underlying drug-seeking behavior is qualitatively different for heroin- and cocaine-reinforced animals.

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