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Cocaine Self-Administration in Pigeons[1]

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WINSAUER, P. J. AND D. M. THOMPSON. *Cocaine self-administration in pigeons*. PHARMACOL BIOCHEM BEHAV **40**(1) 41–52, 1991.—Pigeons with chronic indwelling intravenous catheters responded under a multiple schedule of food and cocaine presentation. In one component, responding was maintained by food presentation under a fixed-ratio (FR 50) schedule, whereas in the other component, responding was maintained under the same schedule by IV infusions of cocaine (0.03 or 0.1 mg/kg/injection). A 30-s timeout followed each cocaine infusion. Components alternated after 3 presentations of either food or cocaine, and each session was terminated after 18 cocaine infusions or 2 h, whichever occurred first. In general, under baseline conditions, the response rate was higher in the food component than in the drug component. Under control conditions where saline was substituted for cocaine, the response rate gradually decreased across sessions, while food-maintained responding was generally unaffected. Substituting doses lower or higher than the training dose decreased the rate of cocaine-maintained responding. Food-maintained responding only decreased at higher doses of cocaine. When blackout periods were substituted for the food component (Experiment 2), the response rate in the cocaine component decreased and then stabilized at levels well above zero. Saline substitution on this baseline produced a further decrease in the rate of FR responding. In Experiment 3, the effects of pretreatment with haloperidol (0.056 or 0.1 mg/kg) on both food- and cocaine-maintained responding were examined using a multiple schedule similar to that used in Experiment 1. Each dose was given for a period of 7–10 days. In general, haloperidol dose-dependently decreased both the overall rate of cocaine-maintained responding and the percent of available reinforcers obtained, while having little or no effect on food-maintained responding. This research indicates that cocaine can serve as a reinforcing stimulus for maintaining self-administration behavior in pigeons, and that this behavior is sensitive to antagonism by haloperidol.

Self-administration Cocaine Pigeons Multiple schedule Reinforcement Haloperidol

THE present research examined the question of whether cocaine would be self-administered (intravenously) by pigeons, a species frequently used in research on the behavioral effects of drugs but one apparently overlooked for self-administration studies. In one of the few papers describing procedures for chronic intravenous drug administration in the pigeon, Kosersky and Harris (23) cite part of the reason for this somewhat surprising omission as being the relative inaccessibility and fragility of avian veins. Given the extensive and comparative basis of the literature already existing for the pigeon on the discriminative stimulus properties of cocaine [e.g., (6)], the effects of cocaine on response rate when simple operant schedules of reinforcement are used [e.g., (17)], and the effects of cocaine on rate and accuracy when more complex operant tasks are used [e.g., (25)], it would seem important to know whether or not cocaine has reinforcing properties in the pigeon similar to those in other species. Although the behavioral effects of cocaine in the pigeon have generally been similar to those found in other species such as the rat and monkey, the demonstration of specific differences in the reinforcing properties of cocaine in pigeons and other species may provide some useful insights into the nature of those properties. Cross-species comparisons of specific drug effects have in the past often led investigators to a better understanding of drug actions and the effects of drugs on behavior. A comparison of the discriminative stimulus properties produced by the opioids in pigeons, rats and monkeys, for example, contributed to the characterization of three distinct subtypes of opiate receptor: mu, kappa, and sigma [see review by Herling and Woods (15)]. In addition, these studies (15) indicated that some of the stimulus properties associated with the activation of these receptors were not equivalent across all three species.

Experiment 1 used a multiple schedule with components of either cocaine presentation or food presentation to examine the ability of cocaine to function as a reinforcer and, at the same time, provided a direct comparison with a more traditional reinforcer. Components alternated after three food or cocaine presentations, and responding in both components was maintained under identical fixed-ratio (FR) schedules. To reduce the direct effects of cocaine on response rate (9, 21, 45), a 30-s timeout period was programmed after each cocaine presentation. After responding under baseline conditions stabilized, the control of responding under cocaine injections was assessed by substituting saline for cocaine. Following baseline recovery after saline, varying doses of cocaine were substituted for the training dose. A second experiment using a multiple schedule with components of cocaine presentation and 5-min blackout periods examined the contribution of food-maintained responding in establishing cocaine-maintained responding. The final experiment reintroduced a multiple schedule with both food and cocaine components to examine whether or not the reinforcing properties of cocaine in

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the pigeon were sensitive to antagonism by a prototype dopamine antagonist, haloperidol.

EXPERIMENT 1

METHOD

Subjects

Four adult male White Carneaux pigeons were maintained at approximately 80% of their free-feeding body weights by food presented during the sessions and by postsession supplemental feeding. The 80% values were 470, 465, 455, and 435 g for P-197, P-3799, P-6835, and P-6944, respectively. Water and grit were always available in the home cages. Each subject had an extensive history of responding under FR schedules.

Apparatus

The experimental space was a standard two-key pigeon chamber (BRS/Foringer, Model PH-001) with a test space that measured 49.5 × 36 × 35.5 cm. The translucent response keys, located 17 cm apart on the front wall and 22.5 cm above the wire mesh floor, required a minimum force of 0.18 N for activation. The food aperture (5.7 × 4.5 cm) was centered between the two keys 7 cm above the chamber floor. An in-line projector (BRS/LVE, Model IC 901-696), mounted behind each key, could project colors onto the key. A small bracket mounted on the ceiling of the chamber held the miniature infusion swivel (Spalding Medical Products, Arroyo Grande, CA, model 203). The single-channel swivel was supplied with a 12-inch (30.4-cm)-long feedthrough spring tether which prevented the infusion line from becoming kinked or tangled. Together, the swivel and tether allowed the subject to move freely around the chamber while maintaining an on-line catheter. Outside the chamber, the swivel was connected to a syringe pump (Sage Instruments, Cambridge, MA, model 355). A fan provided ventilation, and white noise was continuously present in the chamber to mask extraneous sounds. The chamber and infusion pump were connected (via a Med Associates interface) to scheduling and recording equipment (an Apple IIe computer, programmed in BASIC, and a cumulative recorder) located in an adjacent room.

Surgical Procedure

The surgical procedures used for catheter placement were adapted with several modifications from methods previously described for use in pigeons (23) and chickens (48). The cannula, however, was adapted from a commercially available intravenous catheter unit (Intracath, Deseret Pharmaceutical Co., Sandy, UT).

The pigeons were anesthetized with an intramuscular injection of ketamine hydrochloride (Ketaset, Bristol Laboratories, Syracuse, NY). A dose of 120 mg/kg was given to each subject to provide approximately 60 min of controlled anesthesia. While the pigeon was under anesthesia, its feathers were removed from an area beginning at the base of the neck and ending just below the interscapular region of the back. In addition, feathers were removed from the ventromedial surface of one of the wings. Next, the 19-gauge needle of the intracath unit was passed through a connective tissue space on the ventromedial surface of the wing to a point just below the skin on the dorsal side of the wing. The needle was then further advanced subcutaneously and medially to exit through the skin in the interscapular region of the animal's back. The entire length of the catheter was then fed into the tip of the needle and back toward the point of entry on the ventromedial surface of the wing. The needle was then withdrawn, leaving the subcutaneous portion of the catheter in place and a short length of catheter protruding from the ventromedial surface.

A skin incision approximately 1.5–2 cm in length was then made on the ventromedial surface of the wing. The incision paralleled the brachial vein and was directed toward the body from the point where the catheter exits. After the incision was made, the overlying connective tissue was separated by blunt dissection and the brachial vein was isolated from other underlying tissues and the brachial plexus. Just before the vessel for insertion of the catheter was punctured, the adapter end of the catheter was connected to a syringe filled with heparinized saline (10 U/ml) and the catheter was flushed. Then, the remaining short length of catheter was trimmed to size (approximately 3.5 cm). Immediately after cutting the vessel, the catheter was inserted into the vessel and advanced inward toward the body until the entire intravascular portion of the catheter was in place. The skin incision was closed with 3 or 4 simple interrupted 3-0 silk sutures.

Following the placement of both the subcutaneous and the intravascular portions of the catheter, the syringe used to flush the catheter was disconnected and replaced with a 7/8-inch injection adapter (Medex Inc., Hilliard, OH). The catheter adapter and injection adapter were then sutured to the pigeon's back just below the midscapular region. This was necessary to prevent the external portion of the catheter from moving freely and possibly pulling the catheter out, both while the pigeon was connected to the catheter arm in the experimental chamber (see Fig. 1) and while the pigeon was moving about in the home cage. To further protect the external portion of the catheter, the pigeon was vested with two layers of lightweight, 3-inch orthopedic stockinette (ABCO, Milwaukee, WI). A lightweight protective collar (Saf-T Shield, Ejay International Inc., Glendora, CA) was also placed on the pigeon for the duration of the experiment. The catheters, when flushed frequently with heparinized saline, remained patent for periods exceeding 8 weeks. If catheter failure occurred due to blockage or leakage during the course of the experiment, the subjects were recatheterized using the other wing.

Behavioral Procedure

Subjects were first required to respond on a single key (right) under a two-component multiple schedule with yellow and green stimuli. Responding in both components was maintained under a fixed-ratio (FR) 50 schedule of food presentation, where each completion of the fixed ratio produced 5-s access to mixed grain. Each food presentation was accompanied by the offset of the keylight and onset of the magazine light. The houselight was illuminated for the entire session. Components changed after 3 reinforcers and alternated six times within each daily session. Each session was terminated after 36 food presentations or 2 h, whichever occurred first.

When the response rate under the multiple schedule of food presentation no longer showed systematic change from component to component or session to session (10–15 sessions), these sessions were terminated. The subjects were then surgically prepared with chronic indwelling venous catheters. Following a 24-h recovery period, the multiple FR 50 FR 50 schedule was changed so that responding in the presence of the yellow stimulus was maintained with food, whereas responding in the presence of the green stimulus produced cocaine, either 0.03 or 0.1 mg/kg/injection. These training doses were selected on the basis of preliminary research with other pigeons. The duration of both

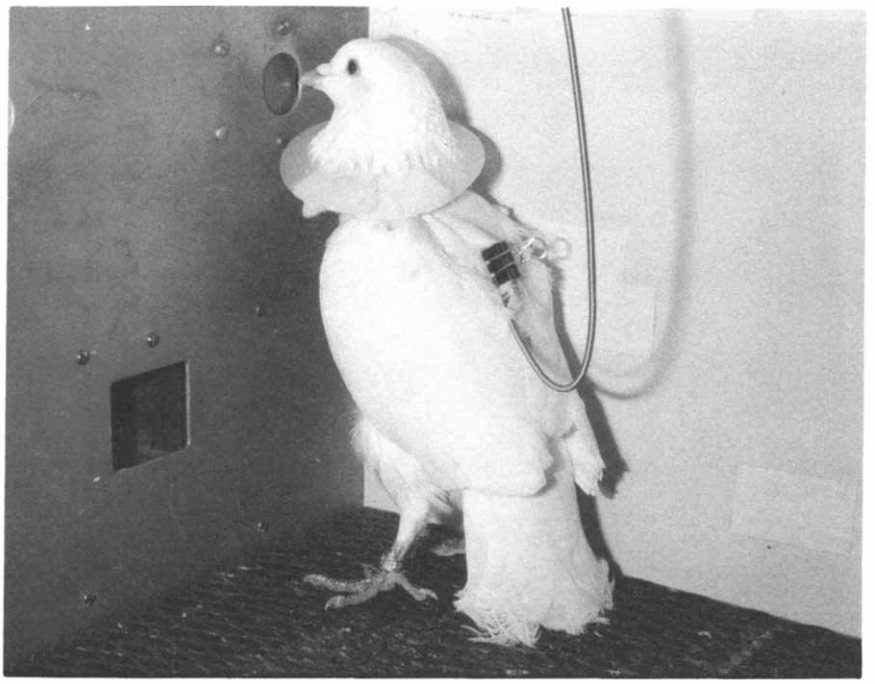

FIG. 1. A photograph of a pigeon responding in the experimental chamber. The distal end of the catheter which exits from the intrascapular region of the pigeon's back was connected, via a spring tether and miniature swivel, to a syringe pump.

the presentations of food and the cocaine infusions was 10 s. The infusion rate for cocaine hydrochloride (Mallinckrodt Inc., St. Louis, MO) was 0.02 ml/s. Solutions of cocaine were prepared every 3 or 4 days in physiological saline, and adjustments for dose were made by changing the concentration (mg/ml). As in the previous multiple schedule, food presentations were accompanied by offset of the keylight and onset of the magazine light. During cocaine infusions, however, offset of the keylight was accompanied by the flashing of the houselight and activation of the syringe pump. A 30-s period in which the key remained off, but the houselight was illuminated, followed each cocaine infusion (timeout). Responses during this period had no programmed consequence. Each session began in a component where responding was maintained by food, and the components alternated after 3 presentations of either food or cocaine. Sessions ended after 18 cocaine infusions or 2 h, whichever occurred first.

Control conditions (saline substitutions) for all subjects were studied immediately following the stabilization of responding under the food-cocaine baseline. This baseline was considered stable when responding within each of the respective components remained relatively constant from session to session (8–16 days). Then, after the response rate under saline (control) conditions appeared stable (usually 4–10 days), cocaine infusions were reinstated to permit baseline recovery. Following baseline recovery after saline, varying doses of cocaine (0.001–1 mg/kg/injection) were substituted for the training dose. The doses were tested in a mixed order, and baseline recovery followed both the initial determination of a dose and the redeterminations. Sessions were conducted twice daily and seven days a week. At least 3 h separated the morning and afternoon sessions for each subject. Lower doses, like saline, were always substituted for a period of more than one day (9). Doses higher than the training dose were substituted for a period of one day (2 sessions) at each determination. For both components, the data were analyzed in terms of overall rate (responses/s). Within-session changes in responding were monitored by a cumulative recorder.

RESULTS

In general, responding in both components of the multiple schedule was stable and remained consistent from session to session. Although the response rate was lower in the components of cocaine presentation than in the components of food presentation, cocaine presentation reliably maintained responding, and characteristic patterns of fixed-ratio responding were evident in both components (i.e., pauses occurred after reinforcement followed by a relatively high and constant rate of responding). The difference in overall rate and the effects produced following saline substitutions are clearly illustrated by the daily session data for P-197 in Fig. 2. As shown, under baseline conditions, stable rates of responding were obtained in both components during both sessions conducted on each day. After substituting saline for cocaine, however, there was a selective decrease in responding in the schedule component previously associated with cocaine presentation and a small increase in food-maintained responding. Note that when cocaine was reinstated after several days of minimal responding for saline, there was rapid recovery of baseline levels of responding.

Some of the within-session effects obtained with subject P-197 after saline substitutions are shown in the cumulative records in Fig. 3. The top record shows a typical baseline session before saline substitution where components of food-maintained responding alternated with components of cocaine-maintained responding. As can be seen, the overall response rate in the food components was greater than that in the cocaine components, with longer preratio pauses generally accounting for the difference. The consistent pattern of cocaine presentations

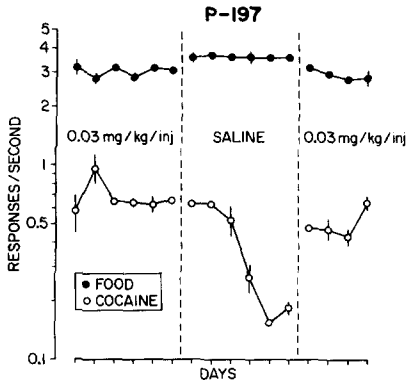

FIG. 2. The effects on overall rate in both components of the multiple schedule when saline infusions replaced cocaine infusions for 6 days in Subject P-197. The points and vertical lines indicate the mean and range for the two sessions (morning and afternoon) conducted on each day. Points without vertical lines indicate instances in which the range is encompassed by the point. A constant (0.1) was added to each response rate to facilitate the plotting of the data on a logarithmic scale.

throughout the session is indicated by the event pen. The middle record shows the response pattern that occurred after 4 days under saline (control) conditions. The pattern indicates increasing disruption of responding after saline presentation with each additional cycle of the multiple schedule. In contrast, the high rate and consistent pattern of responding in the components of food-maintained responding remained intact. The bottom record shows a similar pattern of disruption on day 6 of saline substitution

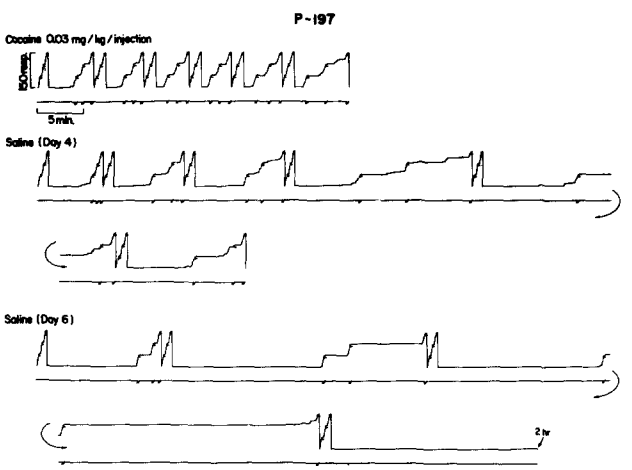

FIG. 3. Cumulative records for Subject P-197 showing the within-session effects of saline substitution (days 4 and 6) on responding under a multiple schedule with alternating components of either food or cocaine. The top record shows a baseline session in which the injection dose of cocaine was 0.03 mg/kg. In both components, the response pen stepped upward with each response and was deflected downward with each presentation of either food or drug. The event pen was deflected downward only during cocaine injections. A 30-s timeout in which the recorder did not advance followed each injection. Sessions began in a component where responding was maintained by food presentation. Components of the multiple schedule changed after 3 reinforcements, and each change in components reset the stepping pen. Sessions ended after 18 cocaine presentations or 2 h, whichever occurred first.

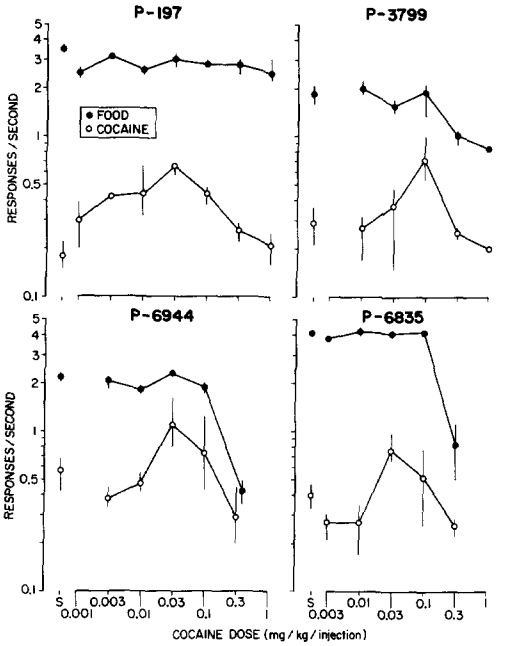

FIG. 4. Effects of varying injection doses of cocaine on overall response rate in both components of the multiple schedule for each subject. Three of the four subjects (i.e., P-197, P-6944 and P-6835) were trained with an injection dose of 0.03 mg/kg/injection, whereas the fourth (P-3799) was trained with an injection dose of 0.1 mg/kg/injection. The points and vertical lines at S indicate the means and ranges for the final 5 or 6 saline (control) sessions. The points with vertical lines in the dose-effect data indicate the mean and range for 2–6 determinations. The points without vertical lines indicate either a single session or an instance in which the range is encompassed by the point. A constant (0.1) was added to each response rate to facilitate the plotting of the data on a logarithmic scale.

where the pauses both at the start of each component and after each reinforcement were longer for each cycle of the multiple schedule.

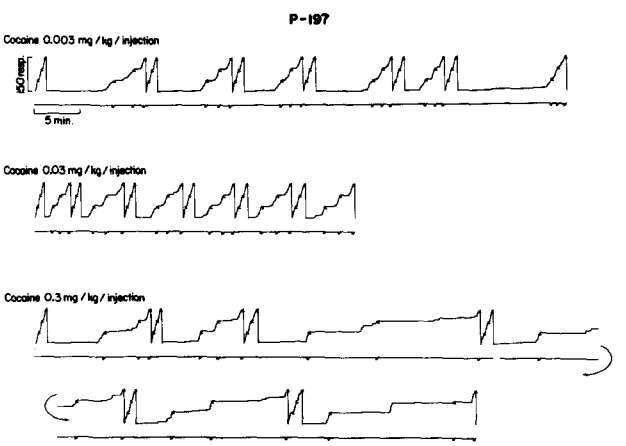

FIG. 5. Cumulative records for Subject P-197 showing the within-session effects of varying injection doses of cocaine on responding under a multiple schedule with alternating food and cocaine components. For other details, see caption for Fig. 3.

The dose-effect data for all four subjects are shown in Fig. 4. Across a wide range of doses, cocaine generally produced only dose-dependent rate-decreasing effects in the component where responding was maintained by food presentation. In contrast, in the component where responding was maintained by cocaine presentation, doses both lower and higher than the training dose generally produced similar rate-decreasing effects. More specifically, in three of four subjects (P-3799, P-6944 and P-6835), the data points for both the lowest and the highest injection doses of cocaine fell within or below the range determined for saline (control) responding. Although the rate-decreasing effects obtained for doses other than the training dose in P-197 were not as large, an inverted U-shaped curve for overall response rate in the cocaine component was still evident.

The cumulative records in Fig. 5 show the within-session effects of varying injection doses of cocaine in subject P-197. The middle record represents the pattern of responding that occurred during a session in which the training dose of cocaine (i.e., 0.03 mg/kg/injection) was presented in one component of the two-component multiple schedule. The top and bottom records represent the patterns of responding that occurred when lower and higher (10-fold) injection doses were available, respectively. Unlike the record for the training dose (middle), the top record shows long pauses occurring before the initiation of responding in every component where cocaine was presented. Once responding began in that component, however, the rate and pattern of responding is similar to that seen for the training dose. The change in pattern of cocaine presentations is reflected by the event pen (i.e., increased time between triads of cocaine presentations over the 2-h session). Throughout the session, the rate and pattern of responding for food remained relatively constant. The record for the higher dose (bottom) shows a pattern of cocaine-maintained responding completely different from either the session involving the training dose or the lower dose of cocaine. In the record for this session, for example, most of the pausing occurred after the initiation of responding. This pattern of responding during the cocaine component also produced a different overall pattern of cocaine presentations. As indicated by the event pen, both the time between each cocaine presentation and the time necessary to obtain the total number of injections was longer. As in the other two records, this dose had little or no effect on the rate and pattern of responding in the food component.

DISCUSSION

As in previous self-administration studies involving other species such as rats [e.g., (8,27)] and monkeys [e.g., (12, 36, 45)], the substitution of saline for cocaine produced marked decreases in self-administration behavior. In addition, the selective decreases obtained after saline substitution were similar to those seen in several other studies using a multiple schedule to compare food and self-administered drug in monkeys (1, 13, 43). In the more relevant study by Woolverton and Virus (43) where food and cocaine were directly compared, the investigators found that saline selectively decreased responding previously maintained by cocaine from levels in the range of 1–2 responses/s to levels less than 0.25 responses/s. Interestingly, in that study as well as the present study, the decreases in responding in this extinction procedure occurred over the course of 4–10 sessions.

When the dose of cocaine was manipulated in the present experiment, doses both lower and higher than the training dose produced rates of responding slightly above or near control (saline) levels. This inverted U-shaped function is the typical curve observed in drug self-administration procedures involving fixed-ratio schedules of reinforcement where timeouts have been programmed after each reinforcer [see Winger (40)]. In most of the studies in which similar effects have been obtained [e.g., (9, 18, 39, 46)], the descending limb of the function appeared to be due to the direct rate-decreasing effects of the drug, whereas the ascending limb was thought to reflect the reinforcing properties of the drug. Given the different patterns of responding which developed in the present study after low and high doses of cocaine were substituted for the training dose (see Fig. 4), the biphasic function could have similar meaning in the pigeon. The increasingly disrupted rate and pattern of responding occurring after the presentation of high doses of cocaine suggest that the rate-decreasing effects were also due to drug accumulation. In addition, at these higher doses, the rates of cocaine presentation seemed to indicate a direct relation between interinjection interval and the dose of cocaine presented, a relationship clearly exhibited with this drug in other species (19).

The completely different pattern which occurred when lower doses of cocaine were self-administered (i.e., long pauses at the beginning of each component of cocaine presentation with little disruption of responding after initiation) did not appear to be the result of the direct effects of cocaine, but rather a decrease in the reinforcing properties of cocaine. In other words, the pattern of responding after lower doses more closely resembled the pattern that emerged after saline than did the higher doses.

The dose-dependent rate-decreasing effects obtained in the food component when high doses of cocaine were self-administered were similar to those reported in other studies involving either simple FR schedules of food presentation (17,37) or a multiple schedule where responding in one of the components was maintained under an FR schedule (33). Smith (33), for example, found that cocaine dose-dependently decreased the FR response rate of pigeons under a multiple FI FR schedule of food presentation.

In general, the differential effects obtained in both components of the multiple schedule were similar to those seen in other species. Again, Woolverton and Virus (43) found that in components where cocaine was available, FR rates first increased to a maximum and then decreased as the dose was increased. In that study, it was argued that increasing the dose of cocaine increased its reinforcing efficacy. Given the similar effects in the present study, it would not be unreasonable to assume that this might also be the case for the pigeon. Furthermore, it is possible that the descending portion of the dose-effect function could reflect decreases in the reinforcing efficacy of cocaine and not the direct effects of cocaine on the rate. This might have happened at those doses in each subject which decreased the rate of cocaine-maintained responding, but had no effect on food-maintained responding.

Taken together, the data in this experiment would indicate that cocaine has reinforcing properties in the pigeon similar to those seen in many other species. Despite using a ratio schedule where the direct effects of cocaine are known to complicate the analysis of reinforcing efficacy, characteristic patterns of cocaine self-administration developed and were comparable to those observed in several other species. Furthermore, the selective decrease in cocaine-maintained responding after saline substitution indicated the pharmacological and behavioral specificity of cocaine as a reinforcer in the pigeon.

EXPERIMENT 2

The environmental context in which a drug influences behavior has often been shown to be important. Depending on the experimental situation, for example, a drug may serve as an

effective reinforcer or punisher [e.g., see (45) or (47)]. It seemed necessary, therefore, to examine the reinforcing properties of cocaine in a situation where food was not available to influence cocaine-maintained responding within the multiple schedule. Early studies on multiple schedules and conditioned reinforcement have demonstrated that substantial behavior can be maintained in a multiple-schedule component even when no primary reinforcement is provided in that component [e.g., see Thomas (38)]. Therefore, to rule out the possibility that cocaine-maintained responding in the first experiment was somehow chained to and maintained by the production of the FR component of food presentation, the multiple schedule was changed so that food was no longer available during the session. In this experiment, a multiple schedule with alternating FR components and blackout periods served as a baseline to assess the reinforcing properties of cocaine in the pigeon. When responding stabilized, saline was substituted for cocaine.

METHOD

Subjects

Three of the four subjects used in Experiment 1 had viable catheters at the end of that experiment and served in this experiment (i.e., P-3799, P-6835 and P-6944).

Apparatus

The apparatus was the same as that used in Experiment 1.

Behavioral Procedure

In Experiment 2, the multiple schedule with alternating components of food and cocaine presentation was changed such that food was no longer available during the session. Instead, the food component was replaced with a 5-min blackout (i.e., a timeout arranged by turning out all the lights in the experimental chamber). During the blackout, both the keylight and houselight were dark, and responding had no programmed consequence. Each session began in a blackout, which then alternated with FR components (FR 50) of cocaine presentation. The stimulus conditions in the FR components were identical to those used in the multiple schedule in Experiment 1 (i.e., a green keylight with the houselight illuminated). Moreover, each cocaine presentation was accompanied by a flashing houselight and followed by a 30-s timeout, and FR components ended after 3 cocaine presentations. In all three subjects, the injection dose of cocaine which reliably maintained stable fixed-ratio responding (after initiation) was 0.3 mg/kg/injection. In two of three subjects (P-6944 and P-3799), stable session-to-session responding was facilitated by the administration of noncontingent injections ("priming") immediately before the start of each session. For both of those subjects, the priming dose of cocaine was increased over the course of baseline stabilization from 0.3 mg/kg to 1 mg/kg.

The multiple schedule baseline was considered stable when responding in the FR components remained relatively constant from component to component and session to session (10–15 sessions). When stable, saline infusions replaced cocaine infusions for a period of 6 or 7 days (12–14 sessions). During this period of saline substitution, subjects P-6944 and P-3799 were administered the same priming dose that they received prior to baseline sessions. After this period in which only saline was available during the session, cocaine infusions were reintroduced to permit baseline recovery. Sessions ended after 18 cocaine infusions or 2 h, whichever occurred first. As in Experiment 1, subjects were generally tested twice daily and seven days a week. Occasionally, subjects were only tested once a day in order to maintain relatively constant levels of body weight and postfeeding. The infusion rate for cocaine was held constant from the first experiment at 0.02 ml/s. The data analysis was similar to that used in Experiment 1.

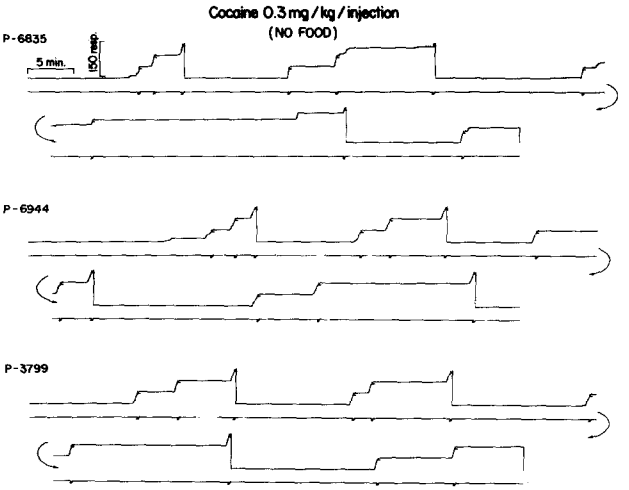

FIG. 6. Within-session effects for all three subjects responding under a multiple schedule with alternating FR components of cocaine presentation and periods of blackout. Blackouts (not shown) were 5 min in duration and followed the completion of each FR component. The injection dose for all three subjects was 0.3 mg/kg/injection. In the FR components, the response pen stepped upward with each response and was deflected downward with each presentation of cocaine. The event pen was also deflected downward during the 10-s cocaine presentations. A 30-s timeout in which the recorder did not advance followed each injection. Sessions began in a blackout. Components of fixed-ratio responding changed after 3 reinforcements, and each change reset the stepping pen. Complete sessions for all three subjects are shown. Sessions ended after 18 cocaine presentations or 2 h, whichever occurred first.

RESULTS

In general, all three subjects showed consistent overall rates and patterns of responding under the multiple schedule of FR

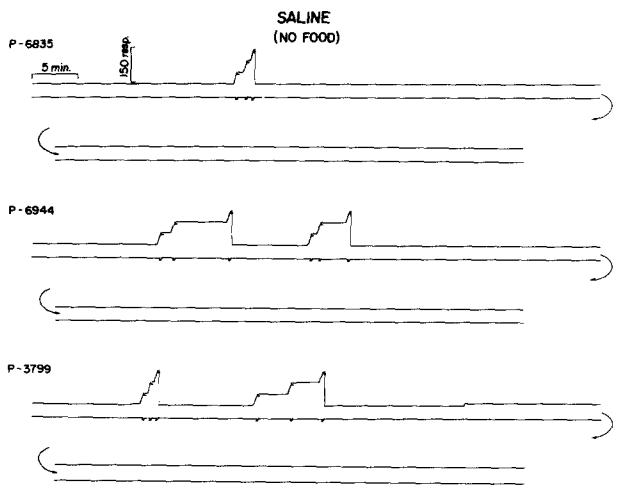

FIG. 7. Cumulative records for all three subjects showing the within-session effects of saline substitution on responding under the multiple schedule. Complete sessions are shown. For other details, see caption for Fig. 6.

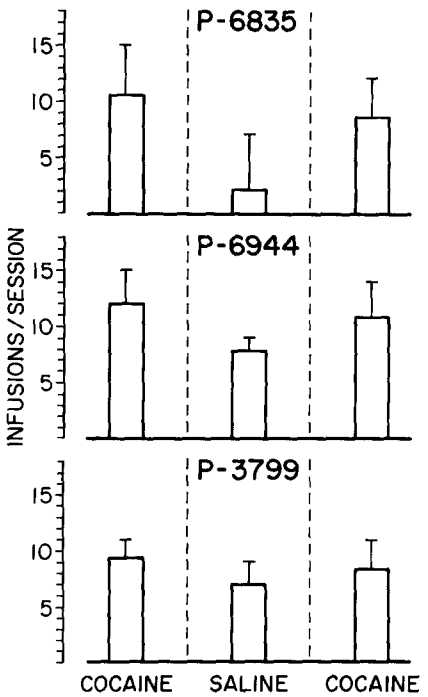

FIG. 8. Mean number of infusions per session for each bird for the 5 sessions prior to saline substitution, the last 5 sessions of saline substitution, and the 5 sessions immediately following saline substitution. The vertical lines above the bars represent the upper range for each group of 5 sessions. The injection dose of cocaine for all subjects was 0.3 mg/kg/injection. Both cocaine and saline infusions were delivered at a constant rate of 0.02 ml/s.

components (maintained by cocaine presentation) and blackout periods. However, sessions usually ended with the 2-h session limit, and overall response rates during the session tended to be low (0.06–0.16 responses/second). In addition, only rarely did subjects obtain more than 11 or 12 cocaine presentations per session. These effects can be seen in the cumulative records shown in Fig. 6. As shown, the records for all three subjects indicate a consistent pattern of cocaine-maintained responding. Cocaine presentations were obtained throughout the 2-h session (event pen), and the total number of infusions obtained was similar. In all three subjects, however, infusions were obtained somewhat more rapidly during the initial 60 min of the session.

A completely different pattern of responding under the multiple schedule occurred when saline infusions replaced cocaine infusions. This pattern is shown in the representative cumulative records for each subject in Fig. 7. Here, as shown, responding in the initial cycles of the multiple schedule was characterized by a high steady rate, while responding after that was characterized by long periods of little or no responding. In general, the long pauses after the initial cycles resulted in lower overall response rates (0–0.08 responses/s), while the completion of only 1 or 2 cycles of the multiple schedule resulted in fewer infusions per session. Therefore, overall measures of saline-maintained responding tended to be lower than those for cocaine-maintained responding despite the high response rates early in the session. Figure 8, for example, shows the overall effect of substituting saline for cocaine on the mean number of infusions obtained during the session. As can be seen, all three subjects obtained fewer infusions under saline conditions than during either baseline conditions or the recovery period immediately following the reintroduction of cocaine.

DISCUSSION

The results from the second experiment support and extend the finding that cocaine has reinforcing properties in the pigeon. In this experiment, cocaine-maintained responding occurred in the absence of food-maintained responding, suggesting the presentation of cocaine alone served as the maintaining event for FR responding in this experiment. Although a higher dose was required to maintain responding in all three subjects, presentation of cocaine alone produced stable FR responding from session to session. As in the first experiment, saline substitution produced decreases in the overall rate of responding in all three subjects. Interestingly, after several sessions in which saline was substituted for cocaine, responding for all the subjects was characterized by a burst of responding early in the session followed by a complete cessation of responding. This extinction pattern with saline substitutions was reported for monkeys responding under a similar multiple FR FR schedule [e.g., (13,43)].

Clearly, some of the differences between Experiment 1 and Experiment 2 (i.e., a higher dose was required to maintain stable responding) were due to interactions of the different components of the multiple schedule. The context in which behavior occurs, particularly multiple-schedule interactions, is known to be an important variable in drug studies. In a study by McKearney and Barrett (24), for example, amphetamine was found to have different effects on punished responding in the squirrel monkey depending on whether an extinction component or shock postponement schedule (avoidance) alternated with the punishment component. Barrett and Stanley (2) have shown that the effects of ethanol on responding maintained under a fixed-interval schedule (FI 3 min) can be modified by changing the fixed-ratio value in a multiple FI FR schedule. The multiple schedule used in Experiment 1 provided a baseline in which cocaine self-administration could be initiated and maintained for an extended period of time and which provided a substantial amount of behavior to examine. This is in contrast to the many studies with rats where ratio values are comparatively low [e.g., (8, 26, 27, 34)]. More importantly, this experiment showed that even in the absence of one of the contextual sources of control (i.e., the food component of the multiple schedule), behavior could be maintained under an FR 50 schedule of cocaine presentation.

It could be argued that the two subjects which were regularly "primed" to facilitate stable responding from session to session make a case for the weakness or lack of reinforcing properties of cocaine in the pigeon. However, periods of drug abstinence are not uncommon and have frequently been reported in rats self-administering stimulants (8,26). Pickens and Harris (26), for example, reported drug abstinence periods after d-amphetamine lasting 12–48 hours, during which time the subjects typically slept and ate. As reported by these investigators, the lengths of the self-administration periods did not appear to be related to length of preceding self-administration period or time of day. Drug abstinence periods could easily be terminated with noncontingent drug infusions. Given that the subjects in the present study were run twice a day and received a dose which decreased the overall rate of responding, it is not surprising that, without these priming injections, there would have been a high degree of variability in responding across sessions. This, however, is not an indication that cocaine has little or no reinforcing efficacy in the pigeon.

Several studies involving other species (i.e., the rat and squirrel monkey) have examined the mechanisms underlying re-

instatement. In fact, work done in the squirrel monkey by Stretch and Gerber (36) with amphetamine first indicated that priming only reestablished responding to the extent that it reestablished the stimulus conditions that are present during drug self-administration. Slikker et al. (32) extended the generality of this finding to cocaine in rhesus monkeys. Stewart (34) and Stewart and de Wit (35), for example, have shown in the rat that the mechanisms involved in reinstating responding with cocaine are the same ones involved in maintaining responding. In addition, these investigators have also shown that reinstatement of responding is not the indirect result of cocaine's stimulant or excitatory effect on the subject. The similarity of both the baseline data and the saline substitution data across all the subjects would also tend to rule out the possibility that the observed effects were somehow the result of a nonspecific excitatory property of cocaine. If the noncontingent injections administered before the session were simply increasing low levels of behavior, then the long periods of pausing following the initial burst of responding early in the session would be unexpected for the two subjects receiving the noncontingent injections. Of interest, however, is the possibility that these injections could be responsible for the additional FR responding which occurred after the initial component during saline substitution. In general, the present results with cocaine in pigeons complement previous findings with cocaine and d-amphetamine in monkeys and rats showing that priming injections of a drug can reinstate the self-administration of that drug.

EXPERIMENT 3

Having established in Experiments 1 and 2 that cocaine can serve as a positive reinforcer in pigeons, an attempt was made in Experiment 3 to antagonize the reinforcing effects of cocaine with the dopamine antagonist haloperidol. The involvement of central dopaminergic mechanisms in the reinforcing properties of cocaine is well established for both nonhuman primates [e.g., (42,44)] and rodents [e.g., (8, 11, 30, 31)]. The evidence for this has largely come from pharmacological data which indicate that the primary mode of action of cocaine here is to block reuptake of dopamine [e.g., (28)], and behavioral data which indicate that patterns of cocaine self-administration change in both species if this increase in synaptic dopamine is rendered ineffectual either by lesioning the dopamine neurons in question [e.g., (30,31)] or blocking the postsynaptic receptors [e.g., (11,41)]. These data have also indicated that D_2 receptors play an essential role in the reinforcing properties of cocaine. For example, Woolverton et al. (44) have shown that several D_2 receptor agonists, but not a D_1 receptor agonist, are self-administered by monkeys.

In the present study, haloperidol (a D_2 receptor antagonist) was given as a pretreatment to examine whether or not dopaminergic mechanisms influencing cocaine self-administration in monkeys and rats also influence cocaine self-administration in pigeons. As in the first experiment, this experiment used a multiple schedule with components of either cocaine presentation or food presentation. Components alternated during each session, and responding in both components was maintained under identical fixed-ratio (FR) schedules. Pretreatments with haloperidol were given before the start of a session, and continued for a period of 7–10 days. This time period was chosen because a comparable time period was required in Experiment 1 to see substantial changes in cocaine-maintained responding following saline substitution.

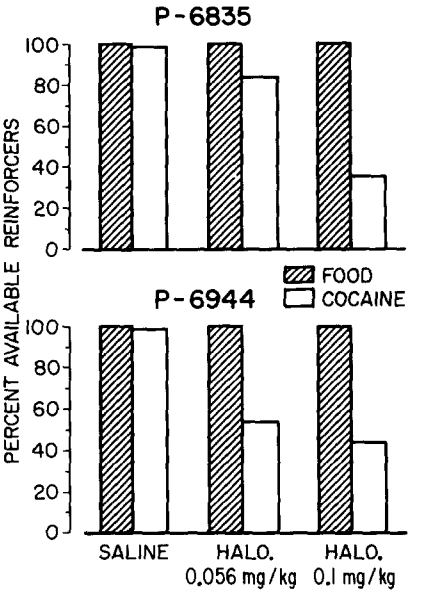

FIG. 9. Percent available reinforcers (food or cocaine) obtained by P-6835 and P-6944 following pretreatment with either saline or two doses of haloperidol. Both saline and haloperidol (0.056 or 0.1 mg/kg) were given IM 30 min before the start of the session and for a period of 7–10 days each. The percent available reinforcers was calculated as follows: (total reinforcers obtained/total reinforcers available) × 100. Since sessions frequently ended at varying times after the initiation of a component, only data from completed components were used in these calculations.

METHOD

Subjects

P-6835 and P-6944 from the previous two experiments continued to have viable catheters, and subsequently served in this experiment.

Apparatus

The apparatus described in earlier experiments was used for Experiment 3.

Procedure

A two-component multiple schedule similar to the one used in Experiment 1 was reintroduced immediately following the completion of Experiment 2. As in Experiment 1, yellow and green stimuli were present during alternating components of food and cocaine presentations, respectively, and responding in both components was maintained under an FR 50 schedule. Unlike Experiment 1, however, components changed after 3 reinforcers or 30 min, whichever occurred first. The addition of the time contingency allowed for a component change even in the absence of responding. Sessions ended after 18 cocaine infusions or 2 h, whichever occurred first. For both subjects, the infusion dose of cocaine, which reliably maintained the highest rate of baseline responding, was 0.1 mg/kg/injection. The infusion rate remained the same over the course of all three experiments (i.e., 0.02 ml/s).

TABLE 1

EFFECTS OF HALOPERIDOL PRETREATMENT ON RESPONSE RATE (RESPONSES/SECOND) UNDER A MULTIPLE SCHEDULE MAINTAINED BY FOOD OR COCAINE

Subject	Days of Pretreatment 1	2	3	4	5	6	7	8	9	10
P-6835										
Saline	2.96*	2.87	3.30	3.49	3.13	3.23	3.23			
	0.16†	0.20	0.30	0.28	0.11	0.20	0.32			
Haloperidol	3.28	3.52	3.44	3.11	2.08	2.07	2.60	3.04	2.87	2.89
0.056 mg/kg	0.16	0.23	0.13	0.04	0.02	0.08	0.21	0.24	0.32	0.14
Haloperidol	3.38	2.86	2.72	0.73	2.29	0.86	0.71			
0.1 mg/kg	0.06	0.01	0.02	0.00	0.10	0.03	0.01			
P-6944										
Saline	1.23	1.28	1.28	1.51	1.10	1.26	1.19	1.13		
	0.59	0.54	0.34	0.60	0.27	0.19	0.25	0.15		
Haloperidol	1.19	1.15	1.02	1.09	1.11	0.91	1.00	0.26	0.83	0.82
0.056 mg/kg	0.39	0.16	0.22	0.00	0.00	0.00	0.16	0.00	0.04	0.00
Haloperidol	1.33	1.31	0.97	0.94	1.04	1.32	1.12	1.26	0.91	1.00
0.1 mg/kg	0.78	0.00	0.13	0.13	0.00	0.08	0.01	0.02	0.00	0.00

*Food component.
†Cocaine component.

As in the previous experiments, the baseline was considered stable when FR responding remained relatively constant from component to component and across sessions. After baseline stabilization (7 days for P-6835 and 9 days for P-6944), testing with saline and two doses of haloperidol began. Either saline or haloperidol (McNeil Laboratories, Inc., Fort Washington, PA) was given IM 30 minutes before the start of each session for a period of 7–10 days. At least 3 days of baseline recovery with no presession injections followed each group of sessions involving a pretreatment. Periods in which either saline or the two doses of haloperidol were administered occurred in a mixed order both within and across subjects. The volume for all pretreatment injections was 0.1 ml/100 g body weight. Because afternoon sessions were occasionally not conducted, only data from the morning session are presented. The data analysis was similar to that used in Experiments 1 and 2, except for the additional analysis of percent available reinforcers (see Fig. 9).

RESULTS

Figure 9 shows the overall effects of either 0.056 mg/kg or 0.1 mg/kg of haloperidol on the mean percentage of reinforcers obtained during all the days in which a pretreatment was given. As shown, under control conditions (i.e., saline pretreatment), both subjects generally obtained all the available reinforcers in both components of the multiple schedule during the 2-h session. In contrast, pretreatment with haloperidol generally produced a selective and dose-dependent decrease in the percent available cocaine reinforcers while having no effect on the percent available food reinforcers. Although the decrease in the percent available cocaine reinforcers was somewhat larger for P-6944 at the 0.056-mg/kg dose, the dose-dependent selective effects were clearly evident in both subjects.

The overall rates of responding for both components of the multiple schedule on all the pretreatment days are shown in Table 1. Note that, under each of the pretreatment conditions, the response rates for the food component were always higher than the rates for the cocaine component. In general, when a saline pretreatment was given, the rates of responding for both subjects were relatively consistent across days, although the response rates for subject P-6944 in the cocaine component did show a downward trend during the last four days. When haloperidol was administered, however, selective and dose-dependent decreases in response rates in the cocaine component were evident on the first day in P-6835, and on the second day in P-6944. Moreover, substantial decreases in cocaine-maintained responding were apparent for both subjects for at least five days. Note the response rate data for P-6835 on days 7–10 at the 0.056-mg/kg haloperidol dose, where the response rates in the

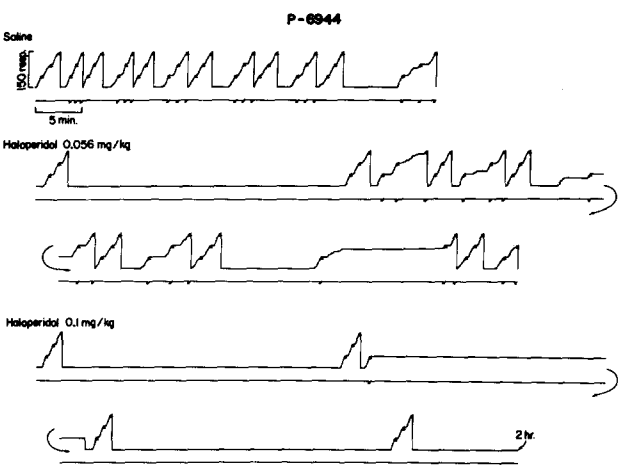

FIG. 10. Cumulative records for Subject P-6944 showing the within-session effects of haloperidol pretreatment (0.056 or 0.1 mg/kg) on responding under a multiple schedule with alternating components of either food or cocaine. The injection dose of cocaine was 0.1 mg/kg/injection. For other details, see caption for Fig. 3.

cocaine component returned to levels observed under saline pretreatment conditions after being near zero on days 4 and 5. This same upward trend did not occur in subject P-6944 when pretreatments of haloperidol were also given for 10 days.

The within-session effects on both response rate and reinforcement pattern can be seen in the cumulative records in Fig. 10. The top record shows a control session where the start of the multiple-schedule baseline was preceded by a saline injection. As can be seen, control responding in both components was relatively stable except for an extended pause which occurred at the beginning of the last cocaine component. After 0.056 mg/kg of haloperidol (middle record), however, the overall pattern of responding changed. Long pauses and disrupted ratio responding occurred throughout the session in the cocaine component, whereas responding during the food component remained relatively unaffected. The substantial disruption of cocaine-maintained responding can also be seen by examining the pattern of cocaine presentations as indicated by the event pen. Both the time to the first cocaine presentation and the time between cocaine presentations are longer after haloperidol pretreatment than after saline pretreatment. When 0.1 mg/kg of haloperidol was given before the session, little or no responding in the cocaine components occurred. In fact, only one cocaine presentation occurred during the entire session. This effect, like the effect found at the 0.056-mg/kg dose of haloperidol, was also selective since responding during food components remained unchanged from saline pretreatment conditions.

DISCUSSION

As in the first experiment, responding under the multiple schedule of food and cocaine presentation stabilized quickly. Although the overall response rates for the two components were different, the response rates in each component were consistent from day to day. In addition, both subjects generally obtained all the available reinforcers over the 2-h session even though responding was not required for a component change, as in Experiment 1. Pretreatment with haloperidol generally produced dose-dependent decreases in cocaine-maintained behavior while having little or no effect on food-maintained behavior. Such changes in cocaine-maintained behavior have been reported in both rodents and nonhuman primates following pretreatments with other D_2 antagonists [e.g., (8, 11, 43)]. In two experiments where cocaine was the only reinforcer available, both pimozide and sulpiride were found to decrease cocaine self-administration in rats (8,11). In a closely related study that used a multiple schedule of food and cocaine presentation, Woolverton and Virus (43) found that pimozide also decreased cocaine-maintained responding in rhesus monkeys. Unlike the present study, however, pimozide decreased food-maintained responding as well. In another experiment involving rhesus monkeys and only a single reinforcer, Herling and Woods (14) reported that chlorpromazine produced dose-related decreases in responding maintained by cocaine.

Many studies have shown that pretreatments with a variety of compounds affecting the dopamine system can differentially affect cocaine-maintained responding. In fact, the present results with haloperidol in pigeons, and the data with pimozide and sulpiride in monkeys and rats (8, 11, 14, 43), directly contrast with data from other cocaine self-administration studies where dopaminergic blockers were used. In these studies, pretreatment with the same or similar dopaminergic compounds produced an increase in cocaine self-administration. More specifically, both haloperidol and pimozide were reported to increase cocaine self-administration in rats (30,31), while both haloperidol and perphenazine were found to increase fixed-ratio responding maintained by cocaine in rhesus monkeys (5,20).

Interpreting changes in cocaine-maintained responding following pretreatment with various dopaminergic antagonists is at best difficult, given the inverted U-shaped dose-response function generally found for cocaine under typical FR schedules of reinforcement (40). Certainly, evidence in this experiment and others (20,43) demonstrates that pretreatment with various dopamine blockers does not produce patterns of cocaine self-administration comparable to saline substitution (i.e., extinction) and suggests that mutual antagonism of response rate effects may explain the type of responding seen following haloperidol. However, haloperidol's highly selective effect on response rate in the present study makes it difficult to ignore interpretations supporting some change in the reinforcing properties of cocaine following dopaminergic blockade. Support for the idea that there is some change in the stimulus properties of cocaine also comes from lesion studies where selective decreases in cocaine self-administration have often indicated decreases in reinforcing efficacy [see (10,22)]. In addition, there is some support from drug discrimination studies which indicate that dopaminergic blockade (particularly blockade of D_2 receptors) affects the discriminative properties of cocaine [see (4,42)]. Colpaert et al. (4), for example, found that haloperidol decreased overall responding on the cocaine lever without exerting a significant effect on the rate of responding to the first reinforcer. As these investigators noted, this suggests antagonism not only of the discriminative control of cocaine but also antagonism of its reinforcing properties.

In all likelihood, cocaine self-administration in the pigeon is a function of many factors. As Dworkin and Smith (10) suggest for other species, cocaine self-administration is a function of the reinforcing, rate-modulating, and discriminative stimulus effects of the drug. Thus the degree to which any one of these factors is affected by dopamine antagonists can only be answered with further research. This is especially true for the pigeon, since there is little, if any, existing self-administration data. Clearly, the contributions of behavioral factors alone have not been completely researched in the pigeon or other species. In the present research, for example, it is possible that the availability of two reinforcers in the behavioral baseline helped to determine whether or not rate-decreasing or rate-increasing effects are seen in cocaine self-administration following pretreatment with haloperidol. Changes in the efficacy of the reinforcer could simply be more critical when only one reinforcer is available to the subject. In any case, the present data in pigeons and the data in other species continue to demonstrate the complex nature of the reinforcing properties of cocaine.

GENERAL DISCUSSION

Experiments 1 and 2 demonstrated that pigeons will self-administer cocaine. The data support the view that cocaine has reinforcing properties in the pigeon at least similar to those produced in other species. Although the schedule in Experiment 1 required the pigeons to respond in the cocaine component to advance the schedule to the food component, this contingency cannot account for the data obtained when saline was substituted for cocaine. Moreover, this contingency was not present in Experiments 2 and 3, which also indicated that cocaine was an effective reinforcer. There is a considerable amount of research that still needs

to be done, however, before it can be said with certainty that cocaine is as robust a reinforcer in pigeons as it is in other species. The present data indicate pigeons can be reliable subjects for such studies and will maintain drug-reinforced responding for long periods of time given the appropriate baseline and drug access conditions.

Along with other research examining the behavioral determinants of drug reinforcement [see (47)], the present findings with pigeons seem to indicate that the environmental conditions under which an individual is introduced to a drug and under which such contact is sustained can modulate the likelihood that the drug will function as a reinforcer. It is possible that the presence of a food component in the multiple schedule, for example, contributed to the initiation of drug-reinforced responding. In fact, Carrol et al. (3) and others [e.g., (7)] have shown that food deprivation alone can produce increases in cocaine self-administration. However, in both Experiments 1 and 2, these factors did not appear to be important in the maintenance of responding. As Young and Herling (47) point out, "The factors controlling a behavioral repertoire prior to the establishment of a contingent relationship between behavior and drug delivery may be more important to the initiation than to the maintenance of drug-reinforced responding" (p. 15). That is, once contingent drug delivery gained control of a behavioral repertoire in the pigeon, the development and maintenance of drug-taking behavior appeared to be controlled primarily by prevailing drug access conditions rather than by the conditions important in initially establishing the drug as a reinforcer. The control (saline) data from both experiments, which demonstrate a substantial decrease in responding previously maintained by cocaine, and the dose-effect data from the first experiment, are strong evidence for the behaviorally and pharmacologically specific control established by cocaine despite deprivation level and possible multiple-schedule interactions.

The present findings with haloperidol in Experiment 3 support the idea that central dopaminergic mechanisms play a distinct role in the reinforcing properties of cocaine in the pigeon. Similar to their effects in other species (e.g., monkeys and rats), D_2 antagonists altered responding maintained by cocaine presentation (20,29). Moreover, the changes in cocaine-maintained responding occurred at dosages of haloperidol that had little or no effect on food-maintained responding. Although no strong conclusions can be drawn from either the direction of change (i.e., increases or decreases) or the degree of selectivity, the present data in the pigeon seem to indicate that some change in reinforcing efficacy is occurring, and that an explanation based on mutual antagonism is not completely sufficient. The partial responding occurring after pretreatment with various dopaminergic antagonists fails to indicate a distinct change in any single property of cocaine. Interestingly, the cocaine self-administration data in all the species tested, including the pigeon, seem to highlight a complex interaction between behavioral and pharmacological processes.

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