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# Effects of Cocaine and Fenfluramine on Progressive-Ratio Performance[1]

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THOMPSON, D. M. *Effects of cocaine and fenfluramine on progressive-ratio performance.* PHARMAC. BIOCHEM. BEHAV. 7(6) 555–558, 1977. – Pigeons obtained food on a progressive-ratio schedule that required 8 additional responses for each successive reinforcement. The number of responses in the final completed ratio of the session was defined as the breaking point. When cocaine was administered (IM, 5 min presession), the breaking point increased and then decreased as a function of increasing doses (0.3–10 mg/kg). In contrast, across the same range of doses of fenfluramine, the breaking point only decreased. At doses of each drug that decreased the breaking point, the high running rate of responding was interrupted by pauses. At doses of cocaine that increased the breaking point, the running rate was also disrupted, but the disruption was characterized by lower, irregular rates rather than pausing. The increases in breaking point observed at 3 mg/kg of cocaine were no longer seen when fenfluramine was administered at the same time.

Progressive ratio  Performance  Food reinforcement  Perseveration  Cocaine  Fenfluramine

A PREVIOUS study from this laboratory [17] assessed the acute effects of varying doses of d-amphetamine on progressive-ratio performance in pigeons. The progressive-ratio schedule required an increasing number of responses for each successive food reinforcement: 8, 16, 24, 32, etc. When the pigeon failed to complete the next ratio in the sequence within 60 min, the session terminated. The number of responses in the final completed ratio was defined as the breaking point (cf. [8]). When d-amphetamine was administered (IM, 30 min presession), the breaking point increased as the dose increased from 0.5 to 2 mg/kg and then decreased to below control values at the largest dose (4 mg/kg).

The inverted-U dose-effect curve found with d-amphetamine in pigeons [17] has also been obtained in other studies using progressive-ratio schedules, e.g., with d-amphetamine [16] and scopolamine [13] in rats and chlordiazepoxide and phenobarbital in pigeons [18]. The question of whether similar dose-effect curves would be found with cocaine and fenfluramine in pigeons on a progressive-ratio schedule was the main focus of the present research.

Previous studies using fixed-ratio schedules of food reinforcement have generally found that both cocaine and fenfluramine produce dose-related decreases in the rate of responding [5, 9, 11, 12, 14, 15, 21, 23]. The breaking point in the progressive-ratio schedule, however, is a behavioral measure that can vary independently of response rate. On the basis of drug self-administration research (e.g., [2, 3, 6, 7, 15, 23, 24, 25]), it was expected that cocaine, but not fenfluramine, would resemble amphetamine in terms of increasing the breaking point at some doses. Due to the fact that such differential drug effects were obtained, and because previous research had shown that fenfluramine can antagonize amphetamine-induced stimulation [1], an attempt was then made to block the cocaine-induced increase in breaking point by administering fenfluramine at the same time.

## METHOD

### *Animals*

Two adult male White Carneaux pigeons, with a history of fixed-ratio reinforcement, were used. The pigeons were maintained within 10 g of 80% of their free-feeding weights throughout the research by food presented during the sessions and by postsession supplemental feeding. The 80 percent values were 535 g and 550 g for No. 2214 and No. 5143, respectively. Water and grit were always available in the home cages.

### *Apparatus*

The experimental chamber was a single-key box designed

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to provide a food reinforcer. A 30 X 30 X 30 cm aluminum enclosure with a Plexiglas door was housed in a commercial ice chest, which was fitted with an exhaust fan and a one-way observation window. The translucent response key (Gerbrands Model B) was centered on the front wall, 20 cm above the wire-mesh floor. The key could be illuminated from behind by two green 7.5-W bulbs. A white 7.5-W houselight was mounted on the back wall near the ceiling. A minimum force of 15 g was required to operate the response key. Located 10 cm below the key was a 5 X 5 cm opening through which a solenoid-operated hopper containing mixed grain was made available as the reinforcer. The scheduling of events was accomplished by means of timers, steppers and associated relay circuitry; the recording was by counters and a cumulative recorder. White noise was continuously present in the chamber to mask extraneous sounds.

*Procedure*

Throughout the following procedures the reinforcer was 5-sec access to grain. Presentation of the food magazine was accompanied by the offset of the keylight and houselight, and the onset of the magazine light. A blackout (all lights off) of variable duration preceded and followed each session. With few exceptions, there were seven daily sessions a week.

*Baseline conditions.* The baseline performance was maintained by an arithmetic progressive-ratio schedule. The ratio increment was 8 responses; i.e., at the start of each session, 8 responses were required for the first reinforcement, 16 responses for the second, 24 for the third, etc. The criterion for the breaking point was reached when the pigeon failed to complete the next ratio in the sequence within 60 min, at which time the session was terminated.

*Drug testing.* Before the drug testing began, the baseline performance was stabilized. The performance was considered stable when the breaking points no longer showed systematic change from session to session. After baseline stabilization (30–40 sessions), dose-effect curves for cocaine and fenfluramine were obtained. Five doses of each drug were tested and two determinations for each dose were taken with each pigeon. The drug testing followed the design CFFC, where C and F represent the blocks of five doses of cocaine and fenfluramine; within each block, the doses were tested in a mixed order. A dose of cocaine HCl or fenfluramine HCl was dissolved in saline and injected IM 5 min presession. Drug sessions were separated by at least 4 days, during which time there were baseline sessions and a control session (saline alone injected IM 5 min presession). The volume of each injection was 0.1 ml/100 g body weight.

After the dose-effect curves had been obtained for each drug, an attempt was made to block the effects of the 3 mg/kg dose of cocaine by administering 1 mg/kg of fenfluramine at the same time. Both drugs were injected IM (one on the right side, the other on the left) 5 min presession. About a week later, the effect of 3 mg/kg of cocaine alone was then redetermined.

## RESULTS

Figure 1 shows the dose-effect curves obtained with cocaine and fenfluramine for both pigeons. A drug was considered to have an effect on the breaking point to the extent that the dose data fell outside of the control range.

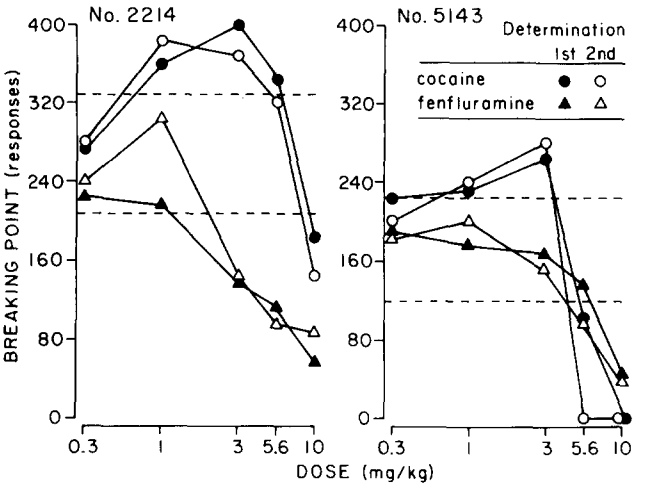


FIG. 1. Effects of varying doses of cocaine and fenfluramine on the breaking point (the number of responses in the last completed ratio of a session) of two pigeons' progressive-ratio performance. The two dashed horizontal lines for each pigeon indicate the range of the control data (20 saline sessions).

As can be seen, the dose-effect curves for cocaine and fenfluramine are clearly different. As the dose of cocaine was increased from 0.3 to 10 mg/kg, the breaking point increased and then decreased. In contrast, with increasing doses of fenfluramine, the breaking point only decreased. There were no systematic differences between the first and second determinations of the dose-effect curves for either drug.

Figure 2 shows the cumulative response records of No. 2214 for a representative saline session and selected drug sessions (first determinations). Similar results were obtained with No. 5143. The control performance (saline) was characterized by a break-run pattern of responding; i.e., after each reinforcement, there was a pause (break), which tended to increase in duration as the ratio increased, and then a high rate of responding (run), which generally continued uninterrupted until the next reinforcement. This biphasic response pattern was affected by both drugs. At the higher doses of fenfluramine (e.g., 3 mg/kg in Fig. 2), there were clear instances of the running rate being interrupted by pauses. A similar effect was obtained with doses of cocaine that decreased the breaking point (not shown). At doses of cocaine that increased the breaking point (e.g., 3 mg/kg), the running rate was also disrupted, but the disruption was characterized by lower, irregular rates rather than pausing. The effects of 3 mg/kg of cocaine were not seen when 1 mg/kg of fenfluramine was administered at the same time (bottom record). It should be noted that this dose of fenfluramine, when administered alone, had no effect on the breaking point (Fig. 1) and the biphasic response pattern generally remained intact (Fig. 2). The effects of 3 mg/kg of cocaine were again seen when this dose was subsequently administered alone (not shown).

## DISCUSSION

When cocaine was administered to pigeons performing on a progressive-ratio schedule, the number of responses in the last completed ratio of a session (breaking point)

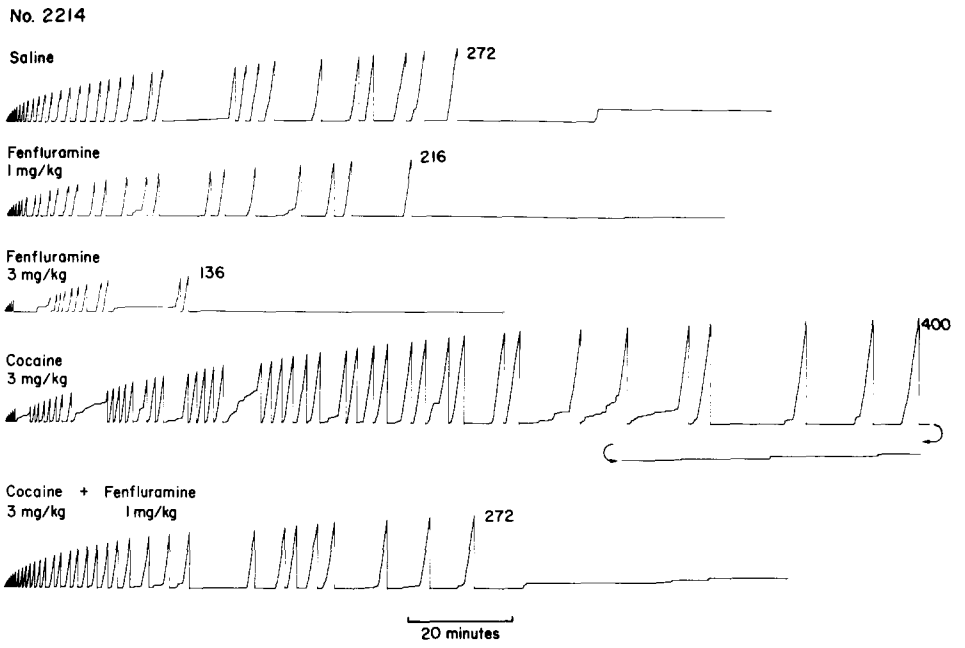


FIG. 2. Cumulative records of one pigeon's progressive-ratio performance during saline and drug sessions. The response pen reset after each reinforcement. At the start of each session, 8 responses were required for the first reinforcement, 16 responses for the second, 24 for the third, etc. The number of responses in the last completed ratio (breaking point) is indicated for each session.

increased and then decreased as a function of increasing doses (0.3–10 mg/kg). The inverted-U dose-effect curve for cocaine resembles the dose-effect curves found previously in progressive-ratio studies with d-amphetamine (0.5–4 mg/kg) in pigeons [17], d-amphetamine (0.25–6 mg/kg) in rats [16], scopolamine (0.05–2 mg/kg) in rats [13], and chlordiazepoxide (5–40 mg/kg) and phenobarbital (10–80 mg/kg) in pigeons [18]. In contrast, an inverted-U dose-effect curve was not obtained with fenfluramine in the present study; the breaking point only decreased with increasing doses (0.3–10 mg/kg).

The finding that cocaine and fenfluramine had different dose-effect curves (with the breaking-point measure) could not have been predicted on the basis of previous research involving these drugs and food-reinforced fixed-ratio performance [5, 9, 11, 12, 14, 15, 21, 23]. That research has shown that both cocaine and fenfluramine produce dose-related decreases in the rate of responding. The present results (cumulative records) are consistent with this finding; e.g., at the higher doses of fenfluramine (or cocaine), there were instances of the running rate being interrupted by pauses. Although such pausing may be related to the possible anorectic effect of these drugs in pigeons (the amount of grain consumed was not measured), this seems unlikely, at least for cocaine. For example, Smith [12] used a multiple fixed-ratio fixed-interval schedule of food reinforcement with pigeons and found that the rate of fixed-ratio responding was decreased at doses of cocaine that increased the overall rate of fixed-interval responding. It would be unreasonable to argue that cocaine had an anorectic effect during the fixed-ratio component but did not have this effect a few seconds later during the fixed-interval component (cf. [10]).

The finding that d-amphetamine and cocaine, but not fenfluramine, increased the breaking point at some doses would seem to suggest a baseline selectivity for abused vs. non-abused anorectic agents. It is well established that d-amphetamine and cocaine can serve as reinforcers to maintain self-administration behavior in monkeys, whereas fenfluramine is ineffective in this animal model of drug abuse [7, 15, 23]. In the present research, although 3 mg/kg of cocaine disrupted the running rate (a depressant effect), it also stimulated performance in the sense of increasing the work output (breaking point); i.e., there was an increase in the amount of repetitive responding or perseveration (cf. [13]). Such perseveration is consistent with previous reports of cocaine-induced stereotyped behavior [20,22]. It should be pointed out, however, that in another behavioral situation, where pigeons obtained food by making four responses on three keys in a specified sequence, cocaine-induced perseveration (repetitive responding on one key) resulted in impaired performance [19].

The present results demonstrated that the effects of 3 mg/kg of cocaine on progressive-ratio performance were blocked by fenfluramine. This finding complements a previous report [1] that fenfluramine can antagonize amphetamine-induced stimulation (hyperactivity, decreased pentobarbital sleeping time, and stereotyped behavior in mice and rats). The possibility that fenfluramine might be a useful blocking agent in the treatment of cocaine abuse remains to be investigated (cf.[4]).

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