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The Acute Effects of Cocaine in Pigeons Performing under a Progressive-Ratio Schedule

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THE ACUTE EFFECTS OF COCAINE IN PIGEONS PERFORMING UNDER A PROGRESSIVE-RATIO SCHEDULE

by

Claudia Ann Jones

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
Degree of Master of Arts
Department of Psychology

Western Michigan University
Kalamazoo, Michigan
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Although the progressive-ratio (PR) schedule has been used frequently to quantify the reinforcing effectiveness of self-administered drugs, it has seldom been used to examine the effects of drugs on food-maintained behavior and has never been used to evaluate the effects of cocaine on such behavior. In the present study, the effects of acute administrations of cocaine were evaluated in pigeons responding under a PR schedule of food delivery. Overall, cocaine produced a dose-dependent effect on food-maintained behavior. In general, acute administrations of cocaine at 0.56 to 3.2 mg/kg increased breaking points, whereas doses above 5.6 mg/kg decreased breaking points. Low doses of cocaine slightly increased the rate of responding in most of the subjects. Higher doses decreased response rates in generally dose-dependent fashion. Although cocaine reduces food intake and subjective hunger for food, the present data indicate that the drug reduces the reinforcing effectiveness of food only at high doses.
ACKNOWLEDGMENTS

I express gratitude to Dr. Alan Poling for his guidance and assistance in the completion of this project and the preparation of this manuscript. I thank Dr. Jack Michael for his support. Recognition goes to Mark LeSage, a graduate student, for his professionalism as laboratory assistant. And I thank Su McAuliffe for her kindness and expertise in editing this manuscript.

I am greatly indebted to my daughter, Tammy Carnes, and my grandson, Billy Carnes, for their love, encouragement, and support during this phase of my life. Above all others, I give honor, praise, and glory to the Holy Spirit, who has been my constant companion during the past three years at Western Michigan University. I dedicate this thesis to Him.

Claudia Ann Jones
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The acute effects of cocaine in pigeons performing under a progressive-ratio schedule

Jones, Claudia Ann, M.A.
Western Michigan University, 1993

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CHAPTER I

INTRODUCTION

Effects of Cocaine

In the past decade, cocaine has emerged as a popular recreational drug, despite its recognized abuse potential (Ray & Ksir, 1992). Hundreds of studies have examined the drug's behavioral and physiological effects in humans and nonhumans, and much is known about its actions (Jaffe, 1990). Prominent among them is the reduction of subjective desire for food in humans, and actual food intake in humans and nonhumans alike (Jaffe, 1990). Although tolerance develops to these anorectic effects when cocaine is administered chronically (e.g., every day), they appear with each exposure when the drug is administered only occasionally (e.g., once a week).

Given that cocaine reduces food intake, one might surmise that the drug would reduce food-maintained responding, regardless of the schedule under which behavior is maintained. But that is not the case. As with other drugs, the effects of cocaine on schedule-controlled responding are complex and are influenced by many variables, including dose, schedule type, rate of responding in the absence of drug, and the consequences of behavior (Poling, 1986). In general, cocaine appears to produce rate-dependent effects, increasing low-rate operants...
(e.g., those maintained under long fixed-interval schedules) at doses that decrease high-rate operants (e.g., those maintained under short fixed-ratio schedules) (Hubner & Moreton, 1991; Kelleher & Morse, 1968; McKearney & Barrett, 1978; Seiden & Dykstra, 1977).

These effects cannot be explained in terms of a motivational analysis alone. Clearly, the effects of cocaine on schedule-controlled responding reflect more than the ability of the drug to act as an establishing operation (Michael, 1993), that is, a variable that reduces the effectiveness of food as a reinforcer and the rate of occurrence of behaviors that historically have produced food.

But the fact that all of the effects of cocaine on schedule-controlled, food-reinforced responding cannot be explained in terms of the drug acting as an establishing operation (EO) does not mean that such an action is absent. It appears that the appropriate schedule for attempting to quantify possible EO effects of cocaine has not previously been used to study the drug, namely the progressive ratio.

**Progressive-Ratio Schedule**

The progressive-ratio (PR) schedule allows several ratio values to be arranged within each session and permits the actual values of the ratios to be determined by each subject's performance. Specifically, the PR schedule involves increasing the ratio requirement by a specified number of responses after each reinforcer until the subject fails to respond for a specified period, usually 5 to 15 min (e.g., Hodos & Kalman, 1963; Schulze & Paule, 1990, 1991). The subject's failure to
respond ends the session and establishes the final completed ratio, called the breaking point, which is used as a measure of the efficacy of the reinforcer, or response strength (Hodos, 1961). Thus, the primary index of the animal's behavior under the PR is not exclusively dependent on the response rate (Hubner & Moreton, 1991). This may be a useful feature in studying drugs that directly affect response rate, regardless of their possible "motivational" actions.

The PR schedule of reinforcement was initially developed by Hodos in 1961. With rats responding under a PR schedule for sweetened condensed milk reinforcement, Hodos (1961) demonstrated that increased food deprivation resulted in higher breaking points. Likewise, increasing the volume of milk produced higher breaking points, up to a certain volume. Breaking points decreased at the highest volume, a phenomenon likely caused by satiation. Decreasing the concentration of the milk reduced breaking points. Hodos' (1961) study and subsequent extensions (e.g., Hodos & Kalman, 1963; Hodos & Trumbule, 1967) established the PR schedule of reinforcement as an empirical methodology for assessing the relative strength of a reinforcer.

Self-Administration Paradigm

For years, researchers have used the PR schedule to study the relative reinforcing strength of a wide variety of drugs within the self-administration paradigm. That is, the drug itself serves as the reinforcer. For example, Brady, Griffiths, and Winger (1975) evaluated
the reinforcing efficacy of sedative-hypnotics self-administered by baboons responding under a PR schedule of reinforcement. Increases in PR values generally resulted in a decrease of responding and a correlated decrease in the amount of hypnotics self-administered. Morphine maintained the highest breaking point, while methaqualone and secobarbital produced lower breaking points.

In a similar study, Griffiths, Brady, and Snell (1978) compared the behavioral effects of cocaine with the reinforcing effects of three anorectic agents in baboons self-administering drugs under a PR schedule of reinforcement. Across a wide range of drug doses, the maximally effective dose of the different drugs produced different breaking points. Cocaine maintained the highest breaking point, followed by diethylpropion, chlorphentermine, and fenfluramine, respectively.

As a third example of research in this area, Hoffmeister (1979) examined the reinforcing effects of self-administered narcotic drugs in rhesus monkeys responding under a PR schedule of reinforcement. Heroin maintained the highest breaking point, codeine and dextropropoxyphene generated lower breaking points, and pentazocine produced the lowest breaking point. Many other studies employing the PR schedule to evaluate drugs as reinforcers have appeared. They are reviewed elsewhere (Bedford, Bailey, & Wilson, 1978; Griffiths, Bradford, & Brady, 1979; Hubner & Moreton, 1991; Risner & Goldberg, 1983; Risner & Silcox, 1981; Roberts, Loh, & Vickers, 1989).
Food-Maintained Behaviors

Although the PR schedule has been used frequently to quantify the reinforcing effectiveness of self-administered drugs, it has seldom been used to examine drug effects on food-maintained behavior. A noteworthy exception is a series of studies by Schulze and colleagues (Schulze et al., 1988; Schulze & Paule, 1990, 1991; Schulze, Slikker, & Paule, 1989) which employed a complex multiple schedule to examine drug (i.e., THC, diazepam, d-amphetamine, and morphine) effects in rhesus monkeys. The same procedures were used in all of the studies. The PR schedule began with a value of either 1 or 2 lever presses, depending on the individual subject. After each food (190-mg banana-flavored pellet) delivery, the response requirement was increased by the initial PR value. That is, if the initial requirement for food delivery was 2 lever presses, successive requirements were 4 lever presses, 6 lever presses, 8 lever presses, and so on. The PR component continued for only 10 min.

In the first study (Schulze et al., 1988), THC doses ranging from 0.003 to 0.3 mg/kg were examined. THC (0.1 and 0.3 mg/kg) slightly decreased breaking points. Overall response rates were not affected. Doses of diazepam from 0.25 to 4.00 mg/kg were evaluated in the second study (Schulze et al., 1989). Diazepam had no effect on overall breaking points or response rates. In the third study (Schulze & Paule, 1990), d-amphetamine doses ranged from 0.01 to 1.0 mg/kg. The higher doses of d-amphetamine (0.3 and 1.0 mg/kg) decreased breaking points and response rates. No increases were observed at lower doses. In the last
study (Schulze & Paule, 1991), acute administrations of morphine ranged from 0.1 to 5.6 mg/kg. With the highest doses of morphine (1.0, 3.0, and 5.6 mg/kg), substantial dose-dependent reductions in PR breaking points and response rates were evident. With the lowest dose (0.1 mg/kg) of morphine, the PR breaking point increased slightly. In all of the studies by Schulze and his colleagues, the PR component was arranged within a multiple schedule that also involved 10-min components in which temporal response differentiation, delayed matching-to-sample, incremental repeated acquisition, and conditioned position responding were assessed.

Although those procedures yielded a wide range of behavioral data in a brief (i.e., 50-min) session, it is questionable whether 10 min provides an adequate assessment of PR responding.

**Purpose of the Present Study**

The purpose of the present study was to examine behavioral effects of acute administrations of cocaine in pigeons responding under a PR 5 schedule of food delivery that continued for 1 hr or until responding ceased for 5 consecutive min, whichever occurred first. Despite the fact that the PR schedule appears to be well suited to quantifying EO effects of cocaine, and such effects have been suggested outside the behavioral pharmacology literature, that schedule appears to never have been used to examine the effects of cocaine on food-maintained behaviors. For example, reviews of stimulant effects (Demellweek & Goudie, 1983; Seiden & Dykstra, 1977; Wolgin, 1989)
make no reference to such studies, although many studies using the PR schedule to quantify cocaine's reinforcing effects have appeared (e.g., Bedford et al., 1978; Griffiths, Findley, Brady, Dolan-Gutcher, & Robinson, 1975; Griffiths et al., 1978; Griffiths et al., 1979; Hubner & Moreton, 1991; Risner & Goldberg, 1983; & Roberts et al., 1989).
CHAPTER II

METHODS

Subjects

Six White Carneau pigeons, maintained at 80% of their free-feeding weights, served as subjects. Three birds were drug naive; three had histories of acute exposure to hallucinogenic drugs. The nonnaive pigeons were drug-free for at least 6 months prior to the start of the present study. Each bird was individually housed with unlimited access to grit and water in a colony area with controlled lighting (16 hrs light, 8 hrs dark each day), temperature (22-24 degrees C), and humidity (60%-70%). The research project was approved by the Institutional Animal Care and Use Committee of Western Michigan University before implementation.

Apparatus

Subjects were trained and tested in four operant conditioning chambers (Lehigh Valley Electronics, BRS/LVE, Lehigh Valley, PA), measuring 32 cm long, 36 cm high, and 35 cm wide. In each chamber, three response keys 2.5 cm in diameter were located 23 cm from the bottom of the front wall, approximately 5.5 cm apart. Only the center key, illuminated in white, was operative in the present study. The key
was operated by a minimum of 0.2 g of pressure. An aperture horizontally centered in the front wall 7.5 cm above the floor allowed access to a grain feeder. When raised, the feeder was illuminated by a 7-W bulb and was filled with Purina Pigeon Grain (Ralston-Purina, St. Louis, MO). A 7-W white bulb (houselight) centrally located 30 cm above the chamber floor on the intelligent panel provided ambient illumination. An exhaust fan mounted on the back wall of the chamber supplied continuous masking noise and ventilation. Additional masking noise was provided by a white noise generator through a speaker mounted on the lower right corner of the intelligent panel. An ALR Flyer 32DT microcomputer and MED-PC software (Med Associates, East Fairfield, VT) was used for controlling experimental events and recording data.

Behavioral Procedures

After preliminary keypeck training, each bird was exposed to fixed-ratio (FR) schedules that were gradually increased to FR 50. Once keypecking was reliable under the FR 50 schedule, a PR 5 schedule of food delivery was implemented for each pigeon. The PR schedule began with a ratio value of 5 at the beginning of each session and was increased by an additional value of 5 each time the subject earned a reinforcer. Thus, the requirement for food delivery across the course of each session was 5, 10, 15, 20, 25, 30, 35, 40, 45, 50. . . . Completion of a ratio requirement was reinforced with 3-s access to grain. The white center key and the chamber light remained on during
The session continued for 1 hr or until the bird ceased to respond for 5 consecutive min, whichever occurred first, at which time the key light and chamber light were turned off. The breaking point was defined as the value of the final ratio completed during each session and was recorded. Sessions were conducted 7 days per week at about the same time each day.

Pharmacological Procedures

After data for breaking points were stable (i.e., showed no visible trend across 10 consecutive sessions), the experiment proper began. Prior to drug injections, each pigeon was injected intramuscularly with a vehicle of isotonic saline for two days consecutively to desensitize the subject to injection. Each subject was then returned to baseline for four days, after which the dose-response determination began. During this determination, each bird was exposed to two ascending series of acute cocaine administrations. Cocaine hydrochloride (Sigma Chemical Co., St Louis, MO) was dissolved in isotonic saline solution prepared at an injection volume of 1 ml/kg. Injections were made into the pectoral muscle 5 min prior to selected sessions. To minimize bruising, the injections were alternated between left and right pectoral muscles. The regimen began with 0.56 mg/kg of cocaine, a dose so low that no detectable behavioral effect was observed. This dosage was selected on the basis of prior studies (e.g., Hoffman, Branch, & Sizemore, 1987). The dose was increased progressively until it was sufficiently high to suppress rates of responding under all schedules to
below 10% of the control level. Increases were in a sequence of quarter-log units to 5.6 mg/kg (i.e., 0.56, 1, 1.8, 3.2, and 5.6 mg/kg, expressed as the salt), and above 5.6 mg/kg in eight-log units (i.e., 7.5, 10, 13.3, 17.8, and 23.7 mg/kg). For each pigeon, doses were given according to a BBBBCD design, where B represents baseline sessions (no injection), C vehicle control sessions (saline injection), and D drug sessions (cocaine injection).
CHAPTER III

RESULTS

Figure 1 shows the average breaking points (plus and minus 1 standard error) for all subjects as a group during drug and vehicle control conditions. In general, at low doses of cocaine (e.g., 0.56 to 3.2 mg/kg),

Each point in the dose-response curve is the mean performance of six pigeons. The points at C indicate the mean for control (saline) sessions. Vertical lines indicate standard errors of the mean. Points without vertical lines indicate an instance in which the standard error is encompassed by the point.

Figure 1. Mean Breaking Point Across Two Acute Determinations at Each Unit Dose of Cocaine Averaged Across All Subjects.

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breaking points were higher than during vehicle control sessions. At doses above 3.2 mg/kg, the mean breaking point decreased with dose. The highest doses produced relatively low (or zero) breaking points in all subjects.

Figures 2, 3, and 4 show breaking points for individual subjects. In general, the data for individual pigeons are similar to group mean data. That is, most of the subjects had increased breaking points at low doses of cocaine and decreased breaking points at high doses. However, the dose-effect curves show that the dose of cocaine required to decrease the breaking point below the control level differed somewhat across subjects.

The average overall rate of responding (plus and minus 1 standard error) for all pigeons as a group are presented in Figure 5. Overall, the lower doses of cocaine slightly increased response rates above the control level. In general, rates decreased in dose-dependent fashion at doses above 5.6 mg/kg. Very low response rates occurred at doses of 13.3 mg/kg and above.

Figures 6, 7, and 8 depict the overall rate of responding for individual subjects across all experimental conditions. In general, rate data for each individual subject are similar to the group mean data. Most of the birds evidenced increased rates of responding with lower doses of cocaine (e.g., 0.56 and 1.0 mg/kg). Response rates decreased somewhat at intermediate determinations (e.g., 1.8 to 5.6 mg/kg) and drastically decreased at doses above 5.6 mg/kg. However, considerable intersubject variability is evident.
Each graph represents data from a single bird. The points at C indicate the mean for control (saline) sessions. Vertical lines indicate standard errors of the mean. Points without vertical lines indicate an instance in which the standard error is encompassed by the point.

Figure 2. Mean Breaking Point Across Two Acute Determinations at Each Unit Dose of Cocaine for Subjects 2 and 8.
Each graph represents data from a single bird. The points at C indicate the mean for control (saline) sessions. Vertical lines indicate standard errors of the mean. Points without vertical lines indicate an instance in which the standard error is encompassed by the point.

Figure 3. Mean Breaking Point Across Two Acute Determinations at Each Unit Dose of Cocaine for Subjects 5 and 7.
Each graph represents data from a single bird. The points at C indicate the mean for control (saline) sessions. Vertical lines indicate standard errors of the mean. Points without vertical lines indicate an instance in which the standard error is encompassed by the point.

Figure 4. Mean Breaking Point Across Two Acute Determinations at Each Unit Dose of Cocaine for Subjects 3 and 4.
Each point in the dose-response curve is the mean performance of six pigeons. The points at C indicate the mean for control (saline) sessions. Vertical lines indicate standard errors of the mean. Points without vertical lines indicate an instance in which the standard error is encompassed by the point.

Figure 5. Mean Responses per Second Across Two Acute Determinations at Each Unit Dose of Cocaine Averaged across All Subjects.
Each graph represents data from a single bird. The points at C indicate the mean for control (saline) sessions. Vertical lines indicate standard errors of the mean. Points without vertical lines indicate an instance in which the standard error is encompassed by the point.

Figure 6. Mean Responses per Second Across Two Acute Determinations at Each Unit Dose of Cocaine for Subjects 2 and 8.
Each graph represents data from a single bird. The points at C indicate the mean for control (saline) sessions. Vertical lines indicate standard errors of the mean. Points without vertical lines indicate an instance in which the standard error is encompassed by the point.

Figure 7. Mean Responses per Second Across Two Acute Determinations at Each Unit Dose of Cocaine for Subjects 5 and 7.
Each graph represents data from a single bird. The points at C indicate the mean for control (saline) sessions. Vertical lines indicate standard errors of the mean. Points without vertical lines indicate an instance in which the standard error is encompassed by the point.

Figure 8. Mean Responses per Second Across Two Acute Determinations at Each Unit Dose of Cocaine for Subjects 3 and 4.
CHAPTER IV

DISCUSSION

The breaking point of pigeons performing under the PR schedule was increased substantially with acute administrations of certain doses of cocaine in the present study. In general, doses below 5.6 mg/kg increased breaking points, whereas higher doses decreased them relative to control ratios. If breaking points under the PR schedule are assumed to provide an index of the reinforcing effectiveness of the scheduled event (i.e., food delivery), as many authors claim them to be (Hodos, 1961; Hodos & Kalman, 1963; Hodos & Trumbule, 1967), the present data suggest that cocaine does not simply act as an EO (Michael, 1993) that reduces the reinforcing effectiveness of food. Applying an EO analysis to the present data would lead to the conclusion that cocaine increased the reinforcing effectiveness of food at low doses, but decreased it at high doses. Although possible, such an analysis is inconsistent with the effects of cocaine on food intake in nonhumans and on subjective hunger for food and food intake in humans (Jaffe, 1990).

The increase in breaking points produced by low doses of cocaine in the present study differs from results shown in a recent study (Schulze & Paule, 1990) using another stimulant, d-amphetamine, with monkeys responding under a PR schedule. In that study, no increase in
the breaking point was observed at low doses. However, a stimulant-induced increase in breaking points occurred at higher doses of d-amphetamine (0.3 & 1.0 mg/kg). Although the compounds used in the two studies are different, it is also possible that procedural differences played a role in the somewhat dissimilar results. Schulze and Paule (1990) indicated that their PR ratios (e.g., 2 lever presses, 4 lever presses, 6 lever presses, and so on) were chosen because the breaking point (final completed ratio) was reached within each 10-min session. Procedures used in the present study allowed food delivery for 1 hr or until responding ceased for 5 consecutive min, whichever occurred first. Usually, the subjects continued to respond for 30 min to 1 hr. Perhaps the extended time period or more rapid incrementing of ratios in the present study contributed to the difference in obtained drug effects.

Although reviews of stimulant effects (Demellweek & Goudie, 1983; Seiden & Dykstra, 1977; Wolgin, 1989) indicate that the PR schedule has not been used to examine the effects of cocaine on food-maintained behaviors, the FR schedule has been employed for this purpose. For example, Hoffman et al. (1987) investigated the acute effects of cocaine in pigeons responding under FR schedules of food delivery. They used a three-component multiple schedule comprising an FR 5, FR 25, and FR 125. Acute administrations of cocaine (1 to 10 mg/kg) produced dose-dependent rate reductions under each of the FR components. Similar results have been reported in other studies that
employed FR schedules (Kelleher & Morse, 1968; McKeary & Barrett, 1978; Seiden & Dykstra, 1977).

It is not clear why cocaine at low doses decreased response rates under FR schedules in prior investigations, but increased rates and breaking points under the PR schedule in the present study. Like other stimulants, cocaine has rate-dependent effects. Low doses generally decrease high-rate operants and increase low-rate operants, whereas high doses reduce all operant behavior (McKim, 1981; McKeary, 1981). Although overall rates under the PR schedule were relatively high, it is possible that rates toward the end of the session (when ratios were high) were relatively low, hence increased by the drug. Data relevant to this possibility were not collected in the present study and appear to merit attention in subsequent investigations.
Appendix A

Institutional Animal Care and Use Committee
WESTERN MICHIGAN UNIVERSITY
INSTITUTIONAL ANIMAL CARE
AND USE COMMITTEE (IACUC)

Application to use Vertebrate Animals for Research or Teaching

The use of any vertebrate animals in research and/or teaching without prior approval of the Institutional Animal Care and Use Committee (IACUC) is a violation of Western Michigan University policies and procedures. This Committee is charged with the institutional responsibility for assuring the appropriate care and treatment of vertebrate animals.

Mail the signed original and five (5) copies of the typed application and any supplements to Research and Sponsored Programs, Room A-221 Ellsworth Hall, (616) 387-3670.

Any application that includes use of hazardous materials, chemicals, radioisotopes or biohazards must be accompanied with SUPPLEMENT A.

Any application that includes survival surgery must be accompanied with SUPPLEMENT B.

Claudia Ann Jones
Psychology (Experimental) 616-387-4503

Principal Investigator/Instructor
Department
Campus Phone

Signature Date

Dr. Alan Poling
Psychology (Experimental) 616-387-4483

Responsible Faculty Member (if PI is not faculty member)
Department
Campus Phone

Signature Date

Title of Project Course Acute and Chronic Effects of Cocaine Under a Progressive Ratio Schedule

CheckOne: Teaching Research X Other

I. ANIMAL USE CATEGORIES (check ONLY one category)

A. X Projects that involve little or no discomfort (including injections).

B. Projects that may result in some discomfort or pain, but of short duration. Anesthetics, analgesics or tranquilizers will be used.

C. Projects that may result in significant discomfort or pain. Anesthetics, analgesics, or tranquilizers will not be used.
BIBLIOGRAPHY


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