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Effects of Cocaine on Fixed-Ratio Responding of Rats: Modulation by Required Response Force

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EFFECTS OF COCAINE ON FIXED-RATIO RESPONDING OF RATS: MODULATION BY REQUIRED RESPONSE FORCE.

by

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The effects of acute cocaine administrations (5.6 to 32 mg/kg) were determined in rats responding under a multiple fixed-ratio 15 fixed-ratio 15 schedule of food delivery. The minimum response effort required in one schedule component was 25 g, whereas in the other component it was 200 g. Cocaine produced generally dose-dependent decreases in rate of responding and increases in pre-ratio pause times under each component. There was, however, a significant interaction between force and drug dose, and the magnitude of drug effects were larger in the component requiring 200 g for lever operation. Although a number of other parameters have been shown previously to modulate the effects of cocaine on schedule-controlled responding, the present data constitute the first demonstration that minimum response effort does so.

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CHAPTER I

INTRODUCTION

Drug Effects on Schedule-Controlled Responding

Studies of drug effects on schedule-controlled responding have played a significant role in behavioral pharmacology. Schedule control, as defined by McKearney and Barrett (1978),"implies an emerging or ongoing behavior that is modulated and maintained through constant dynamic relations with its setting factors and with its effects on the environment" (p.3). Studies of drug effects on schedule-controlled responding have demonstrated that the schedule of reinforcement under which behavior is maintained powerfully influences the effects of a wide range of drugs, including cocaine (e.g., Kelleher & Morse, 1968; McKearney & Barrett, 1978; Seiden & Dykstra, 1977). Other studies have shown the effects of cocaine on schedule-controlled responding (Woolverton, Kandel, & Schuster, 1978; Branch, 1979; Hughes & Branch, 1991; Nickel, Alling, Kleiner, & Poling, in press; Hoffman & Branch, 1987; Gonzales & Goldberg, 1977; Branch & Dearing, 1982). Acute doses of cocaine have produced dose-dependent decreases in rates and increases in initial pause and pre-ratio pause (Woolverton et al., 1978; Hughes & Branch, 1991). Hughes and Branch (1991) employed a multiple fixed-ratio (FR) 5, fixed-ratio 25, fixed-ratio

rates in each component. Hughes and Branch (1991) also reported decreases in reinforcement rates from 50 to 75% of control rates in the small-ratio component and 1 to 30% of control rates in large-ratio components. These studies have either used different fixed-ratio sizes or different schedules of reinforcement in multiple component schedules. Nickel, Alling, Kleiner and Poling (in press) reported that acute doses of the drug (5.6 to 32 mg/kg) reduced pigeons' response rates under a multiple FR 5 FR 125 FR 250 schedule of reinforcement. In another study, Spealman, Goldberg, Kelleher, Goldberg, and Charlton (1977) trained squirrel monkeys on a multiple component FR 30 FI 600-s schedules of either stimulus-shock termination or food presentation or under a fixed-ratio schedule of food presentation. Their findings were similar to other studies (e.g., Branch & Dearing, 1982; Fowler, 1976; Hoffman & Branch, 1987; Hughes & Branch, 1991; and Woolverton, Kandel, & Schuster, 1978) in that low doses of cocaine produced increases in fixed-interval responding, but high doses largely decreased responding. Cocaine decreased fixed-ratio responding in a dose-related manner.

One schedule aspect that has been essentially ignored as a possible determinant of drug action is the amount of force, or effort, required to emit a response. In the characteristic preparation for examining drug effects on schedule-controlled responding, the operant response (e.g., key-pecking by pigeons, lever-pressing by rats) requires minimal physical effort, and the effort required is not varied. Fowler (1987) argued that response force and duration can be analogous

to response rate and post-reinforcement pause. Fowler pointed out, "Little is known about the effects of behavior-controlling variables on force and duration of operant response" (p.83). Even less is known concerning how the effects of these variables, including drugs, are modulated by required response force. Put simply, response force has been largely ignored as a dependent variable in behavioral pharmacology, and completely ignored as an independent variable. To determine whether required response force modulates drug action, the present study examined the effects of cocaine on rats responding under fixed-ratio (FR 15) schedules of food delivery that differed with respect to the minimum amount of effort required for lever operation (25 versus 200 g). Previous investigations have shown that cocaine produces generally dose-dependent rate reductions under FR schedules. The purpose of the present study is to examine whether this action is affected by response effort.

CHAPTER II

METHODS

Subjects

Six Long-Evans strain male rats, maintained at 80% of their free feeding weights, served as subjects. Subjects were approximately 270 days old and experimentally naive at the onset of training. They were individually housed with unlimited access to water in a room with controlled lighting (16 hr light 8 hr dark cycle), temperature (22 - 24° C), and humidity (60 - 70%). The study was approved by the Institutional Animal Care and Use Committee of Western Michigan University.

Apparatus

Four aluminum operant conditioning chambers, measuring 20 cm long, 13 cm wide, and 15 cm high, were used. The front (13 x 15 cm) wall of each chamber was equipped with two response levers that were separated by 3.5 cm and centered horizontally 7.5 cm above the floor. Only the left lever was used in this study. A 7-W yellow light was located 6 cm above each lever. A dipper through which 0.1 ml sweetened condensed milk diluted with water (50/50 ratio) could be delivered was centered 3 cm below the levers. When the dipper was

raised, the dipper aperture was illuminated by a 7-W white light. A buzzer (i.e., Sonalert) mounted on the rear wall of the chamber allowed for tone presentation when desired. An exhaust fan supplied masking noise and ventilation.

A rheostatically-controlled electromagnet allowed the minimum force requirement for operation of the left lever to be adjusted from 25 to 200 g. With this arrangement, the lever had to be pressed with a force greater than the specified minimum to initiate movement, which proceeded through a downward arc of approximately 0.2 cm so long as at least 25 g of pressure was applied. At the end of this arc, microswitch operation terminated lever movement and a response was recorded. Control of experimental events and data recording were accomplished through the use of a PDP8/a minicomputer (Supersked) equipped with interfacing and software obtained from State Systems (Kalamazoo, MI).

Behavioral Procedure

During training sessions, which ended after 40 food deliveries, subjects received response-independent deliveries of food (4-s access to sweetened condensed milk) on average every 60 s (i.e., under a random-time 60-s schedule). An FR 1 schedule of food delivery for left-lever presses also was in effect. These conditions engendered lever pressing in all rats. Once each rat lever pressed reliably, the random-time 60-s schedule terminated and the FR value was gradually increased over sessions to 15. Under the FR 15 schedule, fifteenth lever press was immediately followed by a 4-s food delivery. When subjects

completed 10 sessions under the FR 15 schedule, the force requirement for lever pressing was gradually increased over sessions from 25 g to 200 g. The FR 15 schedule with 200 g required response force remained in effect until the rate of responding of each individual rat showed no visually evident trend over 10 consecutive sessions. When this occurred, the experiment proper began. In the experiment proper, a multiple FR 15 FR 15 schedule of food delivery was arranged. The components differed with respect to minimum force requirement. In one FR 15 component, the minimum force requirement was 25 g. In the other FR 15 component, the minimum force requirement was 200 g. For three rats, selected at random, the stimulus lights above the levers were constantly illuminated and the tone remained on throughout the FR 15 component with the 25 g force requirement. For those animals, the lights flashed and the tone came on and went off at 1-s intervals during the FR 15 component with the 200 g force requirement. Relations between stimuli and the two FR 15 components were reversed for the other three subjects. Each FR 15 component was in effect until the programmed ratio was completed five times or until no responding occurred during five consecutive minutes, whichever occurred first. At that time, the other component was arranged. Components continued to alternate until each was arranged on four occasions, after which the session ended.

Pharmacological Procedure

Drug injection began after mean response rates amd pre-ratio (or post-

reinforcement) pause times for an individual rat showed no visually-evident trend over 10 consecutive sessions. During the drug regimen, each subject received four doses (5.6, 10, 17.8, and 32 mg/kg) of cocaine hydrochloride (Sigma, St. Louis) dissolved in isotonic saline solution and prepared at an injection volume of 1 ml/kg. Drug injections were given according to a BBCD design, where B represents baseline (no injections), C represents vehicle, and D represents drug sessions. Drug and vehicle injections were administered intraperitoneally 10 min prior to behavioral testing. All doses were administered twice, in two ascending series.

CHAPTER III

RESULTS

During each session, mean response rates and mean pre-ratio pause times (total pause time/total trials) under the two different FR 15 components were recorded for each animal. The former measure was calculated by dividing total responses by total time in the appropriate component. The latter measure was calculated by determining the time elapsed from the offset of each food delivery to the first subsequent response (an individual pre-ratio pause), then calculating the mean of these values. The effects of acute doses of cocaine on response rate are shown in Figure 1. Data shown are the mean response rates of vehicle and each dose of cocaine (5.6, 10.0, 17.8, and 32.0 mg/kg) for each rat. During vehicle control sessions, the mean response rate for the six rats during the FR 15 component with the lower (25 g) required effort was 2.07 responses per second; the range across individual animals was 1.62 to 2.52 responses per second. For the FR 15 component with the higher (200 g) required effort, the mean group rate was 0.83 responses per second and the range across rats was 0.40 to 1.32 responses per second. Regardless of whether the minimum force requirement in the FR 15 component was 25 g or 200 g,cocaine produced dose-dependent rate reductions.

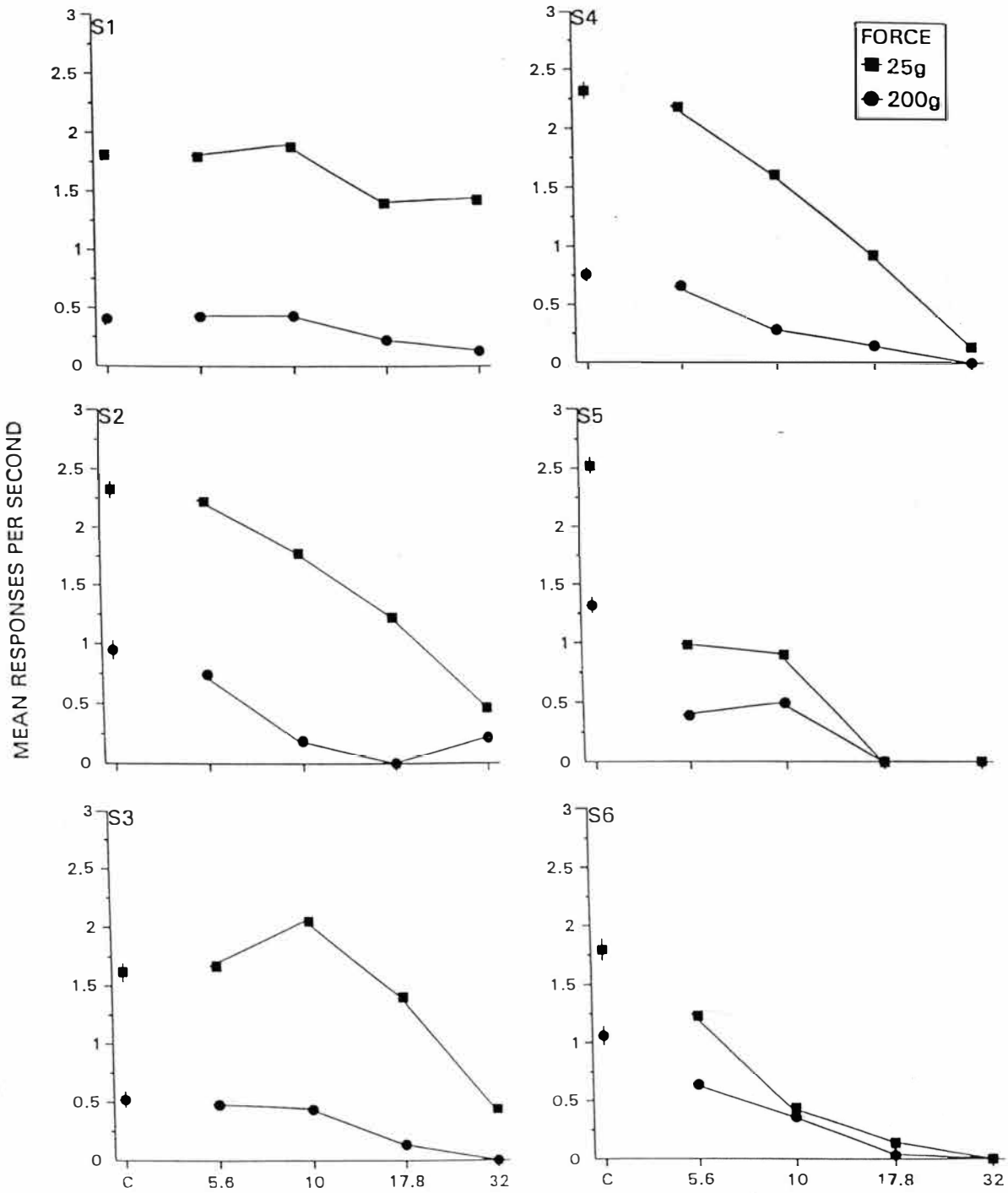

Figure 1. Effects of Single Injections on Response Rates in the Sessions for Rats Responding on a Concurrent Schedule of Food Delivery.

Statistical analysis (2-factor repeated measures analysis of variance) revealed a significant difference between 25 g and 200 g minimum force requirements ($F = 28.08$, $p < .01$). Also, there was a significant difference in response rates at the doses administered ($F = 17.13$, $p < .01$). For S1, cocaine's effects, across doses, were the weakest, whereas for S5 and S6, cocaine produced rate-decreasing effects at the lowest dose (5.6 mg/kg).

The effects of cocaine on pre-ratio pause are shown in Figure 2. Data shown are the mean pre-ratio pause times during tests with vehicle and acute doses of cocaine (5.6, 10.0, 17.8, and 32.0) for each rat. During vehicle control sessions, the mean pre-ratio pause time for the six rats during the FR 15 component with the lower (25 g) required effort was 2.32 seconds; the range across individual animals was 1.03 to 3.63 seconds. For the FR 15 component with the higher (200 g) required effort, the mean pause time was 6.69 seconds and the range across rats was 4.19 to 12.82 seconds.

Statistical analysis (2-factor repeated measures analysis of variance) releaved a significant difference between 25 g and 200 g minimum force requirements ($F = 48.62$, $p < .01$). This effect is evident in Figure 2, which shows the effects of cocaine on pre-ratio pause under the two FR 15 components. Cocaine produced generally dose-dependent increases in pause time in both FR components, although the magnitude of this effect was usually greater in the component with the higher force requirement. The very large increases in mean pause time at high doses (i.e., 17.8 and 32 mg/kg) under both components reflect,

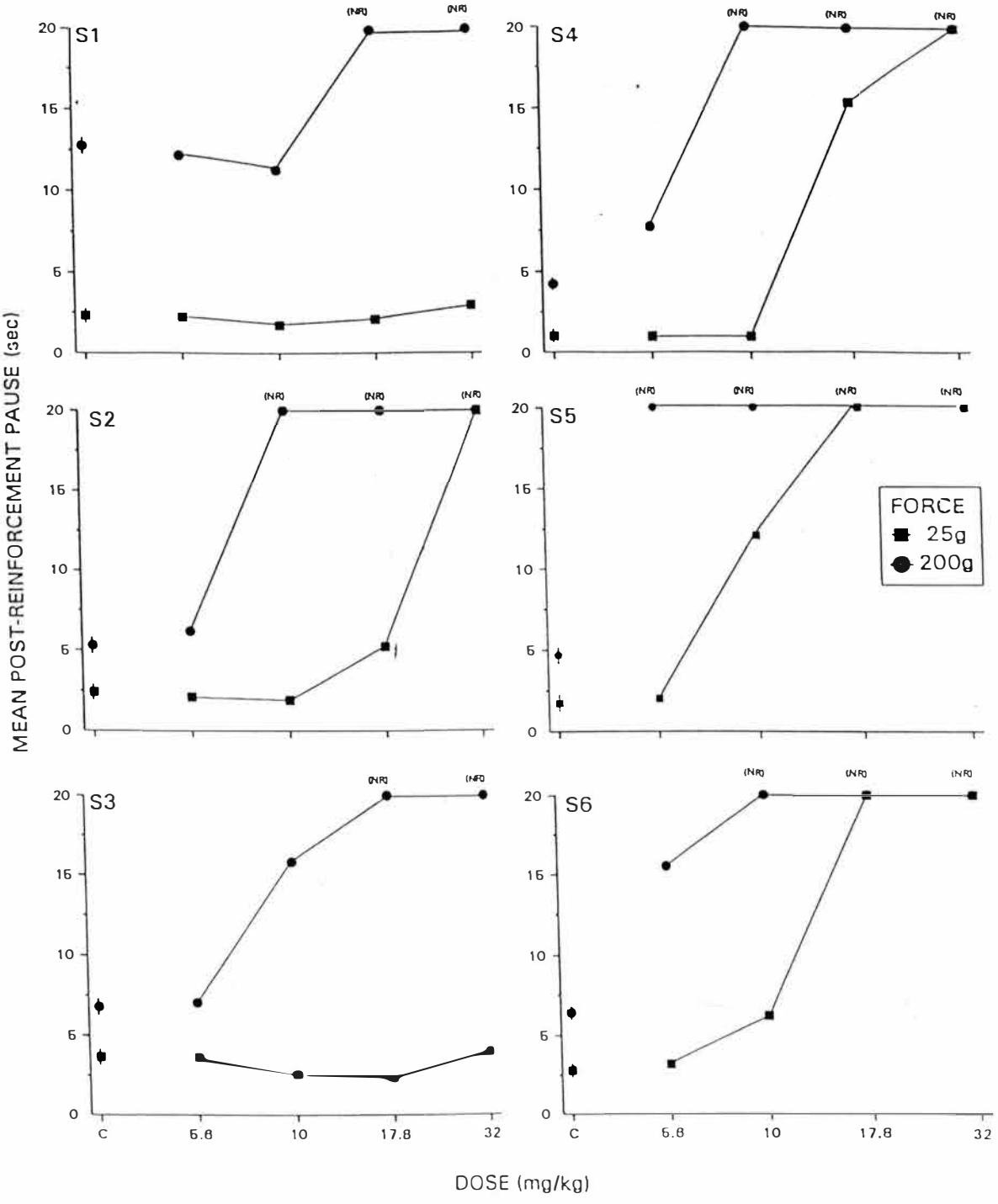

Figure 2. Effects of Single Injections on Post-Reinforcement Pause in the Sessions for Rats Responding on a Concurrent FR 15 FR 15 Schedule of Food Delivery.

in part, the occurrence of sessions in which animals failed to complete a single ratio. Although failures to complete a single ratio were observed under both components, they occurred more often under the component with the higher force requirement.

The effects of cocaine on response rate are expressed as a percentage of vehicle control data in Figure 3. Under the 25 g component, mean response rates were 81, 70, 41, and 20% of control at cocaine doses of 5.6, 10, 17.8, and 32 mg/kg, respectively. Under the 200 g component, mean response rates were 66, 43, 11, and 7% of control at these same doses.

The effects of cocaine on pre-ratio pause are expressed as a percentage of vehicle control in Figure 4. Under the 25 g component, mean pause times were 100, 183, 922, and 1,971% of control at cocaine doses of 5.6, 10, 17.8, and 32 mg/kg, respectively. In contrast, mean pause times under the other component were 200, 4,000, 15,980, and 18,154% of control at these same doses. The very high percentages of vehicle control rates reflect the occurrence of sessions in which the animals failed to complete a single ratio, thereby producing a very large pause time.

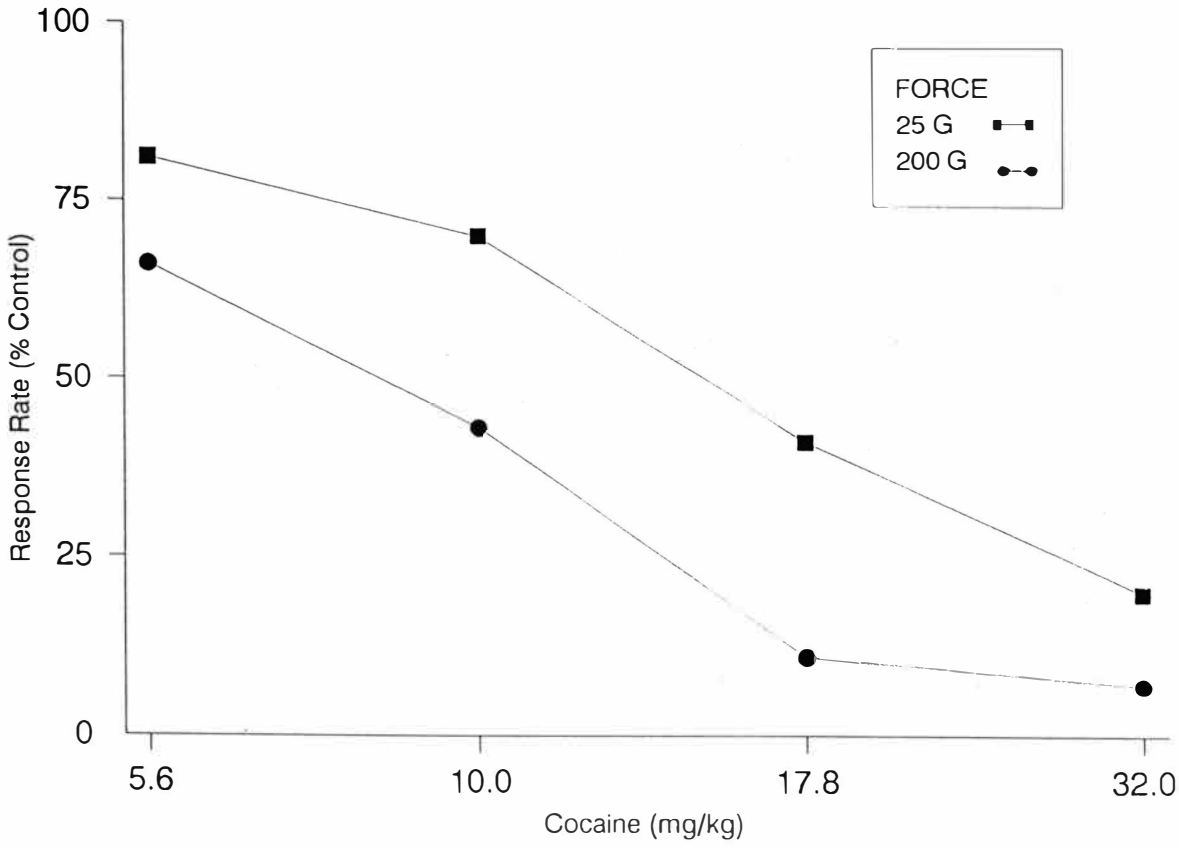

Figure 3. The Effects of Cocaine on the Rate of Responding of Rats Exposed to a Multiple FR 15 FR 15 Schedule of Food Delivery in Which the Minimum Force Requirements for a Lever Press was 25 g in One Component and 200 g in the Other Component.

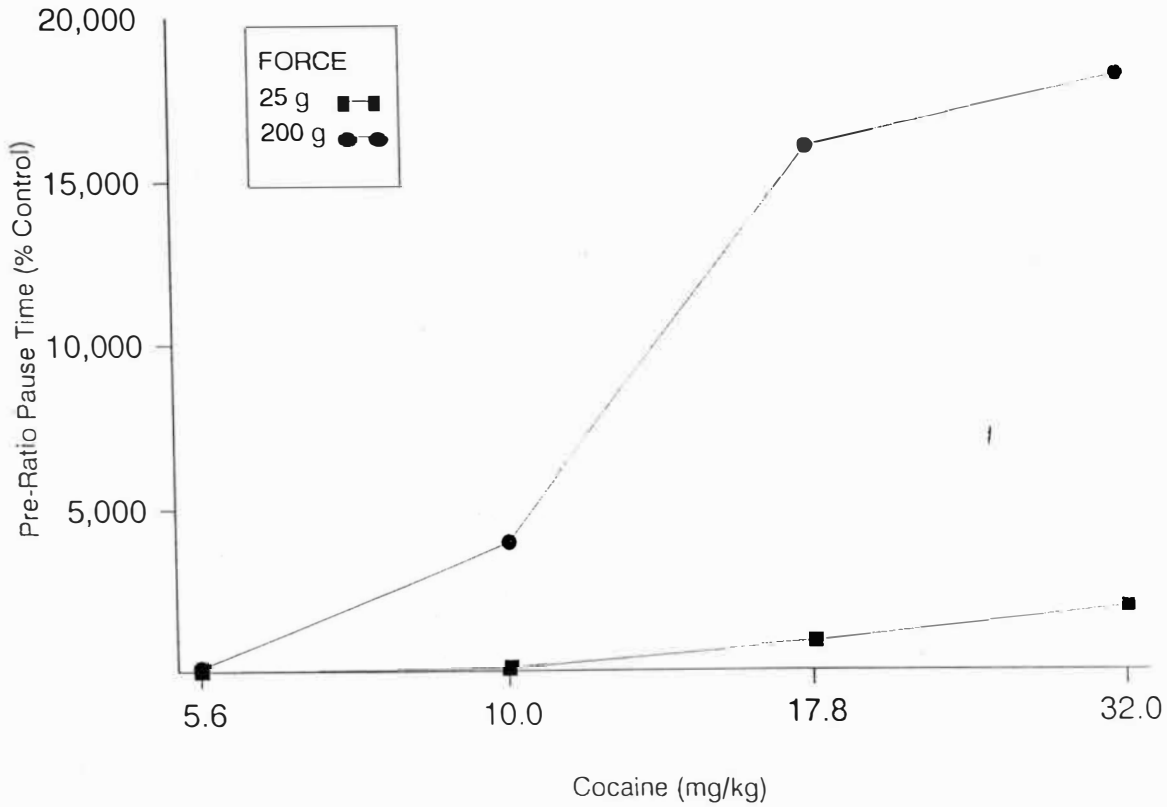

Figure 4. The Effects of Cocaine on Pre-Ratio Pause in Rats Exposed to a Multiple FR 15 FR 15 Schedule of Food Delivery in Which the Minimum Force Requirement for a Lever Press was 25 g in One Component and 200 g in the Other Component.

CHAPTER IV

DISCUSSION

As in previous investigations (Armus, 1986; Chung, 1965; Alling, 1993), increasing required response effort decreased response rate and increased pre-ratio pause time in the present study.

Also consistent with the results of earlier studies (Branch & Dearing, 1982; Gonzales & Goldberg, 1977; Hoffman, Branch, & Sizemore, 1987; Hughes & Branch, 1991;and Woolverton et al., 1978), cocaine produced generally dose-dependent rate reductions under both FR components. At high doses, the effects of the drug on both dependent measures were pronounced. Moreover, higher doses of cocaine produced greater effects at the 200 g minimum force requirement than at the 25 g force requirement. This may suggest that higher doses given acutely may affect greater response effort.

In previous studies evaluating the schedule-controlled effects of drugs,it has been shown that many drugs have an inverted U-shaped dose response curve (Seiden & Dykstra, 1977), in that low doses usually have a rate-increasing effect and high doses have a rate-decreasing effect. Woolverton et al., (1978) found an inverted U-shaped curve in response rate with doses of cocaine ranging from 4.0 to 32.0 mg/kg in rats exposed to an FR schedule. In the present study, this effect was not evident

(with the exception of subject S3), and only in the 25 g minimum force requirement. Dose-dependent rate decreases under FR schedules have been reported in other studies (e.g., Nickel et al., in press; Branch & Sizemore, 1987; Hughes & Branch, 1991), thus the inverted U-shaped function reported by Woolverton et al. (1978) appears to be an anomaly.

Although the qualitative effects of cocaine did not depend on the minimum force requirement, this variable significantly affected the quantitative effects of the drug. At all doses and with both dependent variables, the relative effects of cocaine were greater under the FR 15 component that required more force. To our knowledge, the present data represent the first demonstration of an effect of this kind. Previous studies have, however, shown that required response effort in another sense, namely FR size, can modulate the acute effects of cocaine (e.g., Hoffman et al., 1987; Hughes & Branch, 1991; and Nickel et al., in press). In those investigations, the magnitude of the rate reduction produced by a given dose of cocaine was directly related to the size of the FR schedule of food delivery in effect. For example, Hughes and Branch (1991) found that cocaine doses of 0.3 and 1.0 mg/kg reduced the response rates of squirrel monkeys to 40 to 57% of control rates under the smallest FR to which they were exposed (FR 5 for all four animals), whereas the same doses reduced rates to 8 to 12% of control rates under larger FRs (i.e., those ranging from 17 to 125 across components and animals).

Previous studies have shown that pre-ratio pause size is directly related to FR size (Felton & Lyon, 1966; Ferster & Skinner, 1968; and Powell, 1968), and

a similar relation was observed with the minimum force requirement in the present study. Although FR size and minimum response effort appear to produce similar behavioral effect and to modulate the rate-reducing effects of cocaine in comparable fashion, it is unclear whether these variables actually are symmetrical to their actions, how they interact, and the neuropharmacological mechanisms through which they modulate the behavioral effects of cocaine.

Interestingly, tolerance develops more readily to the effects of cocaine under relatively short FR schedules than under longer schedules (Hoffman et al., 1987; Hughes & Branch, 1991; Nickel et al., in press), although why this occurs remains to be determined. No one has ascertained whether a similar relation obtains when effort is manipulated in terms of the actual physical force required to emit each response under same-sized FRs, but this could be easily accomplished using the procedures employed in the present investigation coupled with a chronic drug regimen.

In conclusion, cocaine exerts rate-decreasing and pause time increases effects, and more so when required response effort increased. This is the first demonstration that minimum required response effort modulates the effects of cocaine on fixed-ratio responding.

Appendix A

Institutional Animal Care and Use Committee
Protocol Approval

INVESTIGATOR CERTIFICATION

Title of Project: The effects of cocaine on response rate and response force in rats

If any of the above procedures are changed, I will submit a new protocol.

I understand that any failure to comply with the *Animal Welfare Act*, the provisions of the *DPHS Guide for the Care and Use of Laboratory Animals* and requirements set down by the IACUC may result in the suspension of my animal studies.

Malath Makhay — *Signature: Principal Investigator*

Psychology — *Department*

10-10-91 — *Date*

REVIEW BY THE INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE

_____ Disapproved ✓ Approved _____ Approved with the provisions listed below

Provisions
or
Explanation:

Richard Gurney — *IACUC Chairperson*

10-17-91 — *Date*

Researcher's Acceptance of Provisions:

Signature: Principal Investigator *Date*

IACUC Chairperson Final Approval *Date*

Approved IACUC Number 91-10-02

Revised February 12, 1991

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