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Effects of Cocaine, Chlordiazepoxide, and Chlorpromazine on Responding of Squirrel Monkeys Under Second-Order Schedules of IM Cocaine Injection or Food Presentation

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Abstract. Lever pressing by squirrel monkeys was maintained under second-order schedules of either food presentation or IM cocaine injection. Under one second-order schedule, every tenth response produced a brief (1-s) visual stimulus and the first brief stimulus presented after 30 min had elapsed was followed either by ten 300 mg food pellets or by a 3.0 mg IM injection of cocaine. Under another second-order schedule, the first response after 3 min produced the brief stimulus and the tenth brief stimulus was followed either by food or by cocaine. The two types of second-order schedules generated distinctly different patterns of responding. Furthermore, the temporal distribution of responding maintained by food presentation or cocaine injection sometimes differed slightly under the same schedule. Food presentation or cocaine injection occurred only at the end of each daily session, thereby allowing assessment of the effects of presession administration of cocaine, chlorpromazine (CPZ), and chlordiazepoxide (CDP) on responding at times when the direct effects of consequent cocaine injections were minimal or absent. Presession treatment with suitable doses of cocaine increased low rates of food- or cocaine-maintained responding under both types of second-order schedules, whereas CPZ only decreased responding. CDP increased responding in some monkeys, whereas in other monkeys it had little or no effect. Individual differences in the effects of CDP were not related to the schedule of reinforcement, the maintaining event, or the control rate of responding. Thus, the behavioral effects of cocaine, CDP, and CPZ were largely independent of whether responding was maintained by food or by cocaine.

Key words: Cocaine – Chlordiazepoxide – Chlorpromazine – Drug self-administration – Drugs and schedule-controlled behavior – Drug effects on behaviors maintained by different reinforcing events

In studying the effects of drugs on schedule-controlled behavior it is often important to assess the potential interactions between the drug effect and the type of event that maintains responding. Such interactions may be especially important when the event maintaining responding is also a drug, since it has been suggested that changes in drug-reinforced responding following pretreatment with another drug may be interpreted as an antagonism of the reinforcing effect of the consequent drug injection (Gill et al. 1978; Johanson et al. 1976; Wilson and Schuster 1972, 1973). In addition to antagonism of the consequent drug's reinforcing effects, however, several other factors may influence behavior under these circumstances. For example, the pretreatment drug may modify behavior without interacting with effects of the consequent drug. Furthermore, when interactions between the pretreatment drug and the reinforcing drug do occur, they may not necessarily involve antagonism of the consequent drug's reinforcing effect. Under most procedures in which responding is maintained by drug injections, the injections occur repeatedly within experimental sessions. In addition to reinforcing effects, these injections can have other effects which alter subsequent ongoing rates and patterns of responding (e.g., Spealman and Kelleher 1979).

The influence of recurring injections of the consequent drug within sessions can be eliminated by scheduling these injections to occur only at the end of the session and by separating sessions with sufficient time so that the effects of the drug administered at the end of one session have dissipated by the next session (e.g., Goldberg and Tang 1977). Through the use of second-order schedules, it is possible to maintain extended sequences of responding with a single injection of a drug occurring at the end of the session (Goldberg et al. 1975, 1976; Katz 1979, 1980). Under second-order schedules, responding that is maintained under one schedule requirement (the unit schedule) is treated as though it is a unitary response that is reinforced according to a second schedule (Kelleher 1966). Often under second-order schedules an environmental stimulus is briefly presented upon completion of each unit schedule requirement. For example, in a study with rhesus monkeys, the completion of each ten-response fixed-ratio (FR-10) unit produced a 2-s red light and the first FR-10 unit completed after a 60-min fixed interval (FI) produced the red light and an IM injection of cocaine (Goldberg et al. 1976). This schedule can be designated as FI-60 min (FR-10:S).

Previous studies have shown that performances maintained under second-order schedules of cocaine injection can be similar to performances maintained under comparable schedules of food presentation (Kelleher 1975 for review).

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Additionally, these similar performances are affected in a like manner by changes in dose of drug or amount of food delivered as a consequence of responding (Goldberg 1973; Katz 1980), as well as by other changes in the schedules (Goldberg and Tang 1977; Kelleher and Goldberg 1977; Katz 1979). Thus, performances under second-order schedules are well suited for studying the effects of drugs on responding maintained by drug injections.

The present study compared the effects of cocaine, chlordiazepoxide (CDP), and chlorpromazine (CPZ) on responding maintained by either food presentation or cocaine injection under second-order schedules. Cocaine was of interest because previous studies indicate that treatment with this drug can alter responding maintained by cocaine in a manner similar to responding maintained by other consequent events, such as food or electric shock (Herling et al. 1979; Spealman and Kelleher 1979). CDP was studied because its effects can depend on the particular event maintaining responding under a variety of conditions, including those in which the presentation of the consequent events occur only at the end of the session (Barrett and Katz 1981; Barrett et al. 1981). Finally, CPZ was studied because it has been suggested that its effects on cocaine-maintained responding may differ from its effects on behavior maintained by other reinforcers, such as food (Gill et al. 1978; Johanson et al. 1976; Wilson and Schuster 1972). Furthermore, the effects of CPZ on cocaine-maintained responding may involve interactions between the two drugs that are a direct result of recurring injections of cocaine during the experimental session (Herling and Woods 1980). It was of interest, therefore, to compare the effects of CPZ on food- and cocaine-maintained responding under conditions in which the rate-modifying effects of cocaine were minimal or absent.

Materials and Methods

Seven adult male squirrel monkeys (*Saimiri sciureus*) weighing 650–900 g were studied. The monkeys were housed individually and had unrestricted access to food and water in the home cage. All subjects had previous experience under various schedules of food or shock presentation and had received drugs. Some of the subjects (MS-1, MS-2, MS-6, MS-10, MS-19, MS-23) had experience under second-order schedules of IM cocaine injection or food presentation (Katz 1979, 1980).

Apparatus. During experimental sessions, the monkeys sat in a clear Plexiglas chair similar to the one described by Hake and Azrin (1963). Three pairs of 7.5 W colored lamps were mounted at eye level behind the front panel of the chair and served as visual stimuli. A response lever (BRS/LVE lever 121-05, Beltsville, MD) was mounted on the front panel approximately 8 cm above waist level. A downward force on the lever exceeding 20 g (0.19 N) produced an audible click of a relay mounted behind the chair's front panel and counted as a response. Banana-flavored 300 mg food pellets (Noyes, Lancaster, NH) could be delivered into a recessed receptacle, also mounted on the front panel. Movement of the monkey's tail was restricted by a small stock located below the waist plate of the chair to prevent interference with IM injections. The chair was enclosed within a ventilated sound-attenuating chamber supplied with white noise to mask extraneous sounds.

Procedure. Monkeys were trained under second-order schedules of either IM cocaine injection or food presentation. Details of the training procedure have been presented elsewhere (Katz 1979). Under one second-order schedule, the first response after a 3-min FI had elapsed produced a 1-s change in illumination from a white to an amber light (brief stimulus). Completion of the tenth FI unit produced a 5-min change from the white to the amber light during which either cocaine was injected (MS-10, MS-23) or food was presented (MS-1, MS-2). This schedule is designated as FR-10 (FI-3 min:S). Under the other schedule, each tenth response produced a 1-s change from a white to an amber light. Completion of the first FR-10 unit after 30 min had elapsed produced a 3-min change from the white to the amber light during which either cocaine was injected (MS-6, MS-19, MS-32) or food was presented (MS-6, MS-26). This schedule is designated as FI-30 min (FR-10:S).

For those monkeys receiving cocaine injections at the end of the session, the chamber door was opened during the final amber-stimulus period and 3.0 mg cocaine HCl in 0.5 ml saline was injected into the calf muscle. The chamber door was then closed for the remainder of the stimulus period. The total duration of the injection procedure lasted approximately 10 s. This dose of cocaine was chosen because it has been found to reliably maintain responding under second-order schedules with squirrel monkeys (Katz 1979). For those monkeys receiving food, ten 30 mg food pellets were automatically delivered at 1-s intervals during the final amber-stimulus period.

Sessions were conducted daily (Monday–Friday). Given that responding was stable, drugs were administered before the session on Tuesdays and Fridays, with Thursdays serving as noninjection control sessions. The drugs were studied in the order CDP, CPZ, and cocaine. Each drug was administered in a mixed-dose series and at least two determinations were made at each dose.

Monkey MS-19 died following the series of CDP doses and was replaced by MS-6. After the dose-effect curves under the FI-3 min (FR-10:S) schedule of food presentation were completed, MS-6 was trained under the corresponding schedule of cocaine injection. When responding stabilized under the schedule of cocaine injection, dose-effect curves again were determined for CDP, CPZ, and cocaine.

Drugs. CDP HCl, CPZ HCl, and cocaine HCl were dissolved in 0.9% sodium chloride solution and were injected in a volume of 1.0 ml/kg into the calf muscle. Doses refer to the total salt of each drug. Cocaine and CPZ were administered immediately before the start of the session, and CDP was given 60 min prior to the start of the session.

Analysis of Results. Response rates under each schedule were determined by dividing the total number of responses in the presence of the white-stimulus light by the total time that the white light was on. Thus, response rates are those exclusive of rates during brief-stimulus presentations and during the stimulus accompanying cocaine injections or food presentation. The effect of presession administration of a drug on response rate was considered significant when the range of response rates following drug administration did not overlap with the range of response rates during nondrug control sessions.

For analysis of FI patterns of responding under the FR-10 (FI-3 min: S) schedule, an index of curvature was calculated

Table 1. Average rates of responding (responses/s) and indices of curvature during control sessions. Figures represent the average of at least three noninjection control sessions. Numbers in parentheses under the FR-10 (FI-3 min:S) schedule are indices of curvature

	FI-30 min: (FR-10:S)					FR-10 (FI-3 min:S)			
	Food		Cocaine			Food		Cocaine	
Subject	MS-6	MS-26	MS-6	MS-19	MS-32	MS-1	MS-2	MS-10	MS-23
Cocaine	0.51	0.43	0.84	–	0.45	0.34 (0.27)	0.26 (0.23)	0.35 (0.10)	0.47 (0.06)
Chlordiazepoxide	0.42	0.35	0.46	0.74	–	0.39 (0.23)	0.35 (0.22)	0.34 (0.10)	0.43 (0.05)
Chlorpromazine	0.45	0.34	0.69	–	0.50	0.28 (0.28)	0.27 (0.24)	0.32 (0.11)	0.34 (0.08)

using the method of Fry et al. (1960). The number of responses were recorded during each 45-s segment of the FI units. These values were then cumulated over an entire session.

Results

Control Performance. Under the FI-30 min (FR-10:S) schedule, responding within the session was positively accelerated. There was an initial pause early in the interval, followed by an increase in responding to a higher rate that was maintained until food was delivered or cocaine was injected. Each brief-stimulus presentation was followed by a short pause and, except during the early portion of the interval, a subsequent abrupt transition to a high rate of responding that was maintained until the next brief stimulus was produced. Response rates generally were higher when responding was maintained by cocaine than when it was maintained by food (Table 1).

Under the FR-10 (FI-3 min:S) schedule of food presentation, responding generally showed a gradual acceleration within each FI unit. That is, rates were lower early in each interval and increased as the interval progressed. In addition, response rates increased over successive FI units within the session. Under the FR-10 (FI-3 min:S) schedule of cocaine injection, there was a less striking pause early in each FI unit and responding occurred at a more constant rate throughout each unit. Table 1 shows rates of responding and indices of curvature during control sessions under the FR-10 (FI-3 min:S) schedule with both maintaining events. An index of curvature of zero indicates a constant rate of responding throughout the FI units. A maximum value of 0.75 indicates that all responding occurred during the last 45 s of the FI units. Cocaine often maintained a more constant rate of responding throughout the FI units than did food presentation, as shown by the lower index of curvature values for cocaine.

Effects of Drugs. Figure 1 shows changes in control rates of responding maintained by food or cocaine as a function of each drug treatment under the FI-30 min (FR-10:S) and FR-10 (FI-3 min:S) schedules. Suitable doses of cocaine (0.01 – 1.0 mg/kg) produced significant incrases in rates of responding under both second-order schedules of food presentation or cocaine injection in all monkeys except MS-23. Under the FI-30 min (FR-10:S) schedule, cocaine produced a decrease in the initial pause and high steady rates of responding occurred throughout the remainder of the session. Under the FR-10 (FI-3 min:S) schedule, cocaine produced greater increases when responding was maintained by food than when responding was maintained by cocaine. During the schedule of food presentation, both the lower rates occurring during the early portion of the session and lower rates during the early portion of each FI unit usually were increased by suitable doses of cocaine. High doses of cocaine typically decreased responding below control levels under both second-order schedules of food presentation or cocaine injection.

CDP produced substantial increases in responding in only monkey MS-1 under the FR-10 (FI-3 min:S) schedule of food presentation. In all other monkeys, low to intermediate doses of CDP either did not increase responding (MS-2, MS-23, MS-6, MS-26) or produced an increase in responding that only marginally exceeded the upper range of control rates (MS-10, MS-19). When overall increases did occur with CDP, there was a decrease in the initial pause under the FI-30 min (FR-10:S) schedule and an increase in low control rates of responding during early portions of the session. Under the FR-10 (FI-3 min:S) schedule, increases were confined to the initial portions of each FI unit. Higher doses of CDP produced rates of responding near or below control levels.

CPZ produced dose-related decreases in response rate. Under both second-order schedules, decreases in responding were comparable for both food- and cocaine-maintained responding. CPZ shortened the initial pause and markedly disrupted patterning under the FI-3 min (FR-10:S) schedule.

Discussion

In the present study, although rates and patterns of responding under second-order schedules were qualitatively similar, they differed slightly quantitatively, depending on whether the maintaining event was food delivery or IM cocaine injection. Responding maintained by cocaine injection generally occurred at a higher rate with fewer pauses during the early portion of the session and during the initial segments of the individual FI units under the FR-10 (FI-3 min:S) schedule. As in previous studies, single IM injections of cocaine occurring at the end of the session consistently maintained responding throughout the session (Goldberg et al. 1976; Katz 1979). Because the duration of action of IM cocaine is relatively short (3 – 4 h) (Gonzalez and Goldberg 1977; Spealman et al. 1977), and the once-daily cocaine injections were confined to the end of the session, any pharmacological interactions between the treatment drug and the maintaining event which could influence responding during the session were precluded.

Several studies have shown that the effects of cocaine depend more on the schedule-controlled rates and patterns of

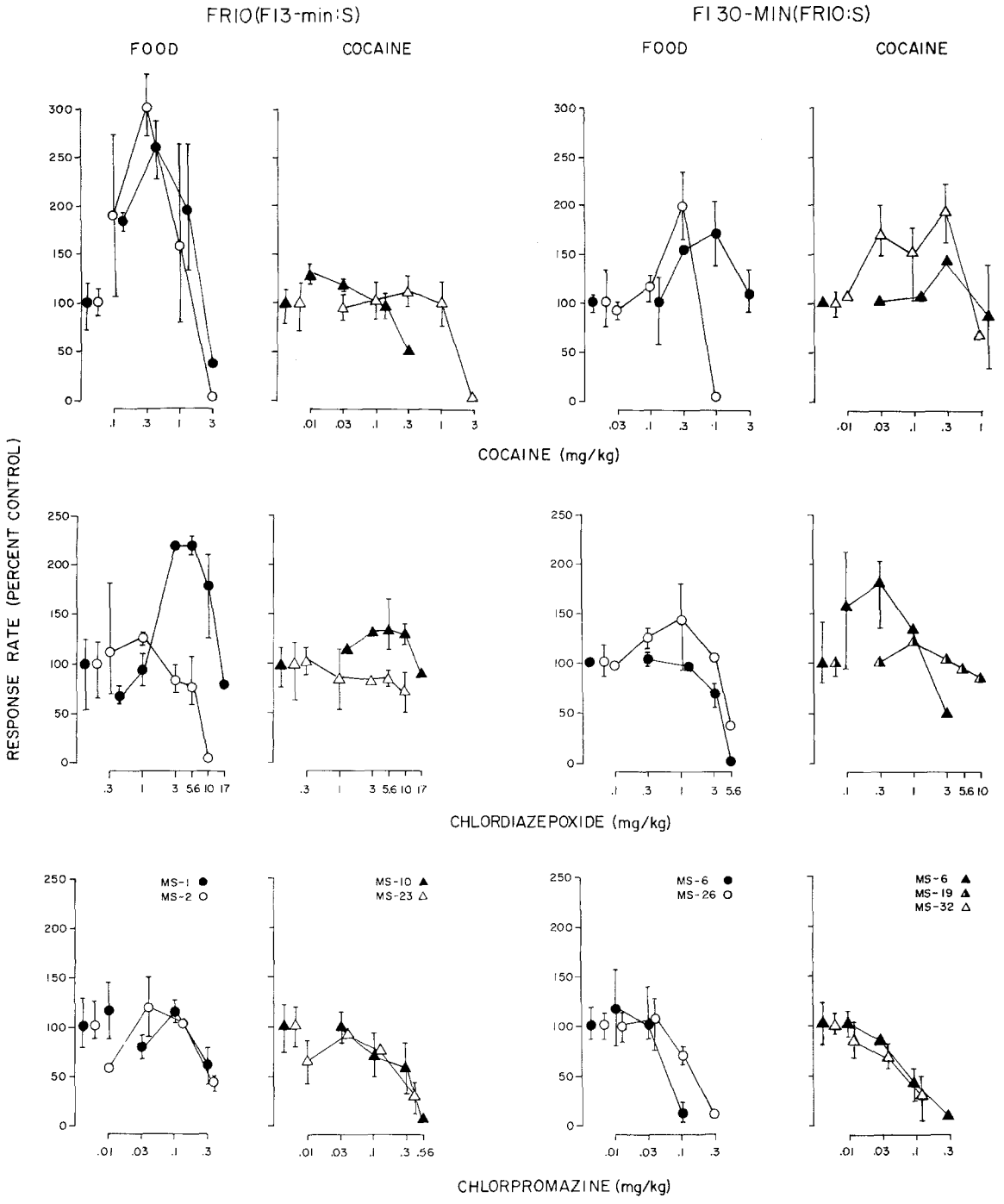

Fig. 1. Dose-response curves of effects of cocaine, chlordiazepoxide, and chlorpromazine on responding maintained by either food presentation or cocaine injection under both second-order schedules. Vertical lines show the range of effects

responding than on the type of event maintaining responding (Barrett 1976; Spealman et al. 1977). In the present experiment, cocaine generally increased overall response rates regardless of whether the maintaining event was food or cocaine under both second-order schedules. The greatest increases in responding with cocaine occurred during early portions of the session or during the initial portion of each FI unit where control rates of responding were lowest. Only one monkey (MS-23) did not show increases in responding with cocaine. However, this monkey also had the highest control rates of responding and the lowest index of curvature under the FR-10 (FI-30 min:S) schedule (Table 1). Since previous research has shown that cocaine can have rate-dependent effects under FI schedules (Spealman et al. 1977), the lack of increases observed with MS-23 may have been related to the absence of relatively low rates of responding early in each FI unit.

In general, the present results with cocaine are consistent with the findings of Gonzalez and Goldberg (1977), who reported that cocaine increased responding of squirrel monkeys under second-order schedules maintained by food, and those of Herling et al. (1979), who compared the effects of

presession administration of cocaine on responding under FI-5 min (FR-10:S) second-order schedules of either food presentation or IV cocaine injection. Although substantial increases in overall responding were not obtained by Herling et al. (1979), cocaine affected responding maintained by food or IV cocaine delivery similarly. Thus, the results of the present study and those of previous studies are consistent with the suggestion of Spealman and Kelleher (1979), that the administration of cocaine alters subsequent responding maintained by cocaine in a manner similar to the way in which it alters responding maintained by other reinforcers.

Previous research has shown that CDP can increase responding maintained by food presentation under a variety of schedule conditions including second-order schedules similar to those used here (Barrett et al. 1981). In the present experiment, CDP produced substantial increases in responding in only one monkey (MS-1), while rates of responding of all other monkeys were incresed only marginally (MS-10, MS-19) or not at all. The different effects of CDP in different monkeys did not seem to depend on either the schedule of reinforcement or the maintaining event, since disparate effects of the drug occurred under the same schedule with the same maintaining event; for example, compare monkeys MS-1 and MS-2 under the FR-10 (FI-3 min:S) schedule. Furthermore, response rate did not appear to be a primary factor in determining the different effects of CDP since the drug produced different effects in monkeys whose control rates of responding were nearly comparable (e.g., monkeys MS-1 and MS-2).

The behavioral effects of CPZ and other phenothiazines have been found to be relatively independent of the type of event maintaining responding (Barrett and Katz 1981; Kelleher and Morse 1968; McKearney and Barrett 1978 for reviews). Typically, these drugs only decrease food-maintained responding in monkeys (Dews 1976). In contrast, some phenothiazines have been reported to increase responding maintained by cocaine injection, leading to the suggestion that these drugs have specific effects on responding maintained by cocaine (Gill et al. 1978; Johanson et al. 1976; Wilson and Schuster 1972). In the present and a previous study (Katz 1980), CPZ or promazine only decreased responding maintained by cocaine injection, and these decreases were similar to those produced by the drugs on food-maintained responding. Since consequent cocaine injections occurred at the end of the session in these studies, it appears that increases in cocaine-maintained responding following treatment with CPZ are not specific to cocaine as a reinforcer, but rather to recurring within-session cocaine injections. Additionally, phenothiazine-induced increases in cocaine-maintained responding typically are obtained at relatively high doses of cocaine per injection which, considering their frequency, would be expected to decrease subsequent cocaine-maintained responding (cf. Spealman and Kelleher 1979; Wilson et al. 1971). Indeed, when the effects of CPZ on responding maintained by different doses of cocaine were compared, responding maintained by suitably low doses of cocaine was affected in a manner similar to food-maintained responding. Only at higher doses of cocaine, which maintained responding at levels below maximum, did CPZ increase response rate (Herling and Woods 1980). Together with the present results, these findings indicate that phenothiazines can affect responding maintained by cocaine and food in a similar manner and that when phenothiazine-induced increases in cocaine-maintained responding occur, they are likely to be the result of an antagonism of the response-rate decreasing effects of self-administered cocaine.

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