Pharmacology Biochemistry & Behavior, Vol. 11, pp. 43–49. Printed in the U.S.A.

Effects of Response-Contingent Clock Stimuli on Behavior Maintained by Intravenous Codeine in the Rhesus Monkey[1]

ALICE M. YOUNG,[2] TRAVIS THOMPSON,[3] MARILYN A. JENSEN AND LAURIE R. MUCHOW

Department of Psychology and the Psychiatry Research Unit
University of Minnesota, Minneapolis, MN 55455

Received 29 January 1979

YOUNG, A. M., T. THOMPSON, M. A. JENSEN AND L. R. MUCHOW. *Effects of response-contingent clock stimuli on behavior maintained by intravenous codeine in the rhesus monkey.* PHARMAC. BIOCHEM. BEHAV. 11(1) 43–49, 1979.—Response-contingent brief presentations of clock stimuli differentially correlated with food availability altered rates of codeine-maintained lever pressing. Rhesus monkeys performed under a two lever multiple schedule: Multiple fixed interval clock 5 min variable interval 2 min. Different colored lights were presented during successive 75 sec periods of the fixed-interval clock component. Lever pressing under the FI Clock schedule was maintained by presentation of 1 g Noyes pellets, and lever pressing under the VI schedule by 0.05 mg/kg infusions of codeine PO_4. Characteristic schedule-controlled performance developed in both schedule components. When the clock stimulus from the first or the final period of the FI Clock schedule was presented contingent upon completion of a short fixed ratio of responses during the variable-interval schedule component, the first clock stimulus decreased and the final clock stimulus increased rates of codeine-maintained lever pressing. Neither the first nor the final clock stimulus altered the frequency of codeine injection. The effect of each clock stimulus was accentuated by increasing the duration of stimulus presentation and by decreasing the response requirement for stimulus illumination. These rate-altering effects of the clock stimuli were most pronounced when different reinforcers were presented in the two components of the multiple schedule when either food or intravenous codeine injection was available under both components of the multiple schedule, response-contingent clock stimulus presentation did not alter response rates under the VI schedule.

Clock stimuli Codeine self-administration Rhesus monkey Brief stimuli Multiple schedule FI Clock schedule VI schedule

DRUGS from several pharmacological classes can reinforce responses which lead to their intravenous delivery, e.g., [22, 23]. Performance maintained by drug reinforcers is influenced by pharmacological variables, such as the type and dose of drug, by the history of the subject, and by the environmental contingencies of drug delivery, including the schedule of drug presentation and the current stimulus conditions, e.g., [17, 26]. Recent studies have demonstrated that the contingent presentation of certain environmetal stimuli can markedly alter performance maintained by intravenous drug delivery. Brief presentations of electric shock delivered at the onset of each drug infusion decrease the frequency of lever pressing maintained by continuous reinforcement schedules of intravenous cocaine, amphetamine, or morphine [12, 25]. Brief presentations of stimulus lights intermittently associated with drug injections increase rates of lever pressing maintained by drug infusion and maintain characteristic schedule-controlled performance [8, 16, 21].

The present study examined the effects of contingent presentation of clock stimuli correlated with food availability on performance maintained by intravenous codeine. Clock stimuli are environmental events which change systematically with the passage of time under interval schedules of reinforcement [6]. Depending on the conditions of their presentation, clock stimuli can function as discriminative, reinforcing, or punishing stimuli. When presented independent of responding, clock stimuli exert considerable discriminative control over responding under interval schedules, e.g., [13, 18, 24] and modify the behavioral effects of amphetamine, scopolamine, and pentobarbital, but not of promazine or chlorpromazine [19]. Clock stimuli temporally proximal to a terminal reinforcer (e.g., food) generally serve

[1]This research was supported by National Institute on Drug Abuse Grants DA00884 and DA00332. The authors thank D. Muchow, W. Bloom, and D. Fox for expert technical assistance.

[2]NIDA postdoctoral fellow supported by NIDA Grant DA05271. Present address: Department of Pharmacology, M6322 Medical Science Building 1, The University of Michigan Medical School, Ann Arbor, MI 48109.

[3]Address reprint requests to: Dr. Travis Thompson, Department of Psychology, Elliott Hall, University of Minnesota, 75 East River Road, Minneapolis, MN 55455.

as positive reinforcers, while clock stimuli distant from the terminal reinforcer may act as punishers [13, 18, 24].

In the present study, lever pressing by rhesus monkeys was maintained under a two-ply multiple schedule. In the first phase of the experiment, one component of the schedule was a fixed-interval clock (FI Clock) schedule of food presentation, and the second component was a variable-interval (VI) schedule of intravenous codeine presentation, chosen because it would allow response rate to vary fairly independently of the frequency of drug delivery. After lever pressing performance was established, the clock stimuli from the first or final segments of the FI Clock component were presented contingent on codeine-maintained lever pressing in the VI component. Presentation of the clock stimuli temporally distant from food contingent on responses in the VI component decreased the rate of codeine-maintained responding, whereas contingent presentation of clock stimuli proximal to food increased the rate of codeine-maintained lever pressing. In the second phase, the effects of the clock stimuli were examined under multiple schedules in which one reinforcer, food or intravenous codeine, was presented in both the FI Clock and the VI components.

METHOD

Animals

Four adult male rhesus monkeys weighing 6.9 to 9.6 kg served as experimental subjects. Monkeys No. 3 and 5 were experimentally naive. Monkeys No. 4 and 9 had performed under concurrent VI schedules of food or codeine availability: Monkey No. 9 also had received oral and parenteral chlorpromazine and tetrahydrocannabinol administration while performing under various schedules of food presentation. The most recent exposure to chlorpromazine and tetrahydrocannabinol had occurred approximately two years before the start of the present experiment. Throughout the experiment, the monkeys were fed approximately 100 g of Purina Monkey Chow, one piece of fruit, and a chewable vitamin pill each day. Drinking water was available at all times except during the experimental sessions.

Each monkey was fitted with a leather vest connected to a stainless steel restraining arm [20] and prepared with an intravenous polyvinylchloride catheter under phencyclidine anesthesia. The catheter was implanted in a jugular or femoral vein, and the proximal end terminated near the right atrium.

Apparatus

The monkeys were individually housed in stainless steel or wooden cages, on the rear wall of which were mounted stainless steel panels containing two response levers (Gerbrands No. 6312) centered 15.2 cm apart and 20.3 cm above the floor of the chamber, a food hopper, and stimulus lamps. The hopper opening was centered 2.5 cm above the floor of the cage and was equipped with a white light. Five stimulus lamps, each 2.5 cm in diameter, were mounted in a vertical column 11.4 cm above each lever. The color of each lamp could be changed by changing the colored lens cap. A white stimulus lamp, 2.5 cm in diameter, was centered 40.6 cm above the floor of the chamber, midway between the vertical lamps. All stimulus lights were illuminated by 2.8 W light bulbs. Each chamber was equipped with a pellet dispenser (Foringer No. 1282) and a motor-driven syringe pump. White noise was present in the experimental room during sessions. Programming and recording functions were performed by standard electromechanical equipment located in an adjacent room.

Procedure

Each monkey was initially trained under a two lever multiple schedule of food delivery: Multiple fixed interval clock variable interval. Following acquisition of the lever pressing response on both levers, the interval values under both schedule components were gradually increased over several weeks to the terminal values: Mult FI Clock 5 min VI 2 min. An experimental session began with five FI Clock 5 min components programmed on the left lever. During each FI Clock component, the color and position of the illuminated stimulus lamp above the left lever changed every 75 sec. Each monkey was assigned a unique stimulus light color associated with each lamp position. Presentation of successive clock stimuli did not depend on the occurrence of a lever press. The first left lever press emitted after the termination of the 5 min interval extinguished the final stimulus lamp and produced a 1 g Noyes banana-flavored pellet accompanied by an 11 sec illumination of a white hopper light. If a subject did not respond within 10 sec of the termination of an interval, food availability was terminated (limited hold contingency) and all stimulus lights were extinguished for 11 sec. During FI Clock components, presses of the right (VI) lever withheld reinforcer availability for five sec. Following the fifth food presentation or limited hold, a 10 min timeout (TO) was in effect, during which all chamber lights were extinguished and responses on either lever had no programmed consequences. Then, a VI 2 min schedule of food availability was in effect for 20 min on the right lever, accompanied by the simultaneous illumination of the four stimulus lights above the right lever. Each monkey was assigned a unique stimulus light color. Under the VI 2 min schedule, food was presented contingent on the first right lever press after an interval varying from four to 446 sec had elapsed since termination of the previous reinforcer delivery. During food delivery, the stimulus lamps above the right lever were extinguished and the hopper was illuminated for 11 sec. Presses of the left (FI Clock) lever during the VI component withheld reinforcer availability for 5 sec. At the end of 20 min, a TO period was in effect for 10 min. The schedule components were then each presented a second time. Experimental sessions were conducted seven days per week.

Following development of stable lever pressing performance with food as the consequent event in both components of the multiple schedule, codeine PO_4 (0.1 mg/kg/infusion) was introduced as the consequent event under the VI 2 min component for Monkeys No. 4 and 9. Codeine phosphate (Merck, Inc.) was dissolved in physiological saline so that all doses, expressed as the salt, were delivered in a 0.5 ml volume over 11 sec. During drug delivery, the stimulus lamps over the right lever were extinguished and the large white stimulus light in the center of the work panel was illuminated.

In order to select a unit dose of codeine which maintained a steady rate of lever pressing over both VI components and did not disrupt performance under the FI Clock schedule of food delivery, the effects of a short range of unit doses of codeine (0.025 to 0.10 mg/kg/infusion) were initially determined. Each codeine dose was made available for at least 20 consecutive sessions in an unsystematic order.

Then, the clock stimuli from the first or final 75 sec

TABLE 1

BASELINE PERFORMANCE UNDER THE MULTIPLE FI CLOCK 5 MIN VI 2 MIN SCHEDULE OF REINFORCEMENT

	FI Clock 5 min component			VI 2 min component	
	Response rate* R/min	Quarter Life*†	Reinforcers delivered*‡	Response rate* R/min	Reinforcers* delivered
Consequent Stimulus:		Food		Codeine, 0.05 mg/kg/infusion	
Monkey No. 4	18.1 (±1.6)	0.81 (±0.00)	9.8 (±0.5)	31.5 (±1.4)	19.2 (±2.5)
Monkey No. 9	2.6 (±0.9)	0.74 (±0.05)	9.0 (±1.2)	2.5 (±0.4)	17.2 (±0.8)
Consequent Stimulus:		Food		Food	
Monkey No. 4	26.3 (±3.7)	0.73 (±0.04)	9.8 (±0.5)	79.0 (±2.2)	18.4 (±2.1)
Consequent Stimulus:		Codeine, 0.05 mg/kg/infusion		Codeine, 0.05 mg/kg/infusion	
Monkey No. 3	1.7 (±1.1)	0.79 (±0.01)	6.6 (±1.7)	15.5 (±2.1)	17.8 (±1.3)
Monkey No. 5	4.7 (±0.7)	0.71 (±0.05)	7.8 (±1.1)	14.4 (±2.4)	15.6 (±1.3)

*Each value represents the mean ± 1 SD over five consecutive sessions.

†Quarter life is expressed as a percentage of the interval. The maximum possible quarter life, which indicates all responses fell in the final 75 sec of the interval, is 0.81.

‡Ten reinforcer presentations were possible during the FI Clock components.

periods of the FI Clock schedule were presented contingent on lever pressing under the VI schedule of codeine injection. During the VI component, the first or final clock stimulus was presented above the left lever following completion of a short fixed ratio (FR) of lever presses on the right lever. Availability of drug was withheld while a clock stimulus was illuminated. During clock stimulus presentation sessions, the FI Clock schedule of food presentation continued as before. The ratio value for clock stimulus presentation was initially held constant at FR 20 for Monkey No. 4 and FR 10 for Monkey No. 9, and the duration of the clock stimulus illumination was varied from 0.5 to 3.0 sec. The duration of clock stimulus illumination was then held constant at 1.5 sec, and the fixed-ratio value for clock stimulus presentation was systematically decreased: FR 20, 10, 5, 2 for Monkey 4 and FR 10, 5, 2, 1 for Monkey 9. Each clock stimulus was presented during at least three sessions at each parameter value. At least two control sessions separated all clock stimulus presentation sessions.

Finally, the multiple schedule contingencies were changed so that the same reinforcer was presented during both the FI Clock and the VI schedule components. For Monkey No. 4, a 1 gm Noyes banana-flavored pellet was presented contingent upon lever presses in both schedule components. For two new monkeys, No. 3 and No. 5, a 0.05 mg/kg injection of codeine was presented contingent on lever presses under both components of the multiple schedule. Monkeys No. 3 and 5 initially performed under the mult FI Clock 5 min VI 2 min schedule of food presentation. When lever pressing rates stabilized, codeine PO_4 (0.1 mg/kg/infusion) replaced food as the consequent event under the VI schedule. When drug-maintained performance developed, the unit codeine dose was decreased to 0.05 mg/kg. Finally, 0.05 mg/kg codeine infusions were introduced as the consequent stimuli under the FI Clock schedule.

For all three monkeys, the clock stimuli from the first and final periods of the FI Clock were presented for 1.5 sec contingent upon completion of a FR 20 of lever presses during the VI component. The FR value was then decreased: FR 10, 5, 2. Each clock stimulus was presented during at least three sessions at each ratio value. All clock stimulus presentation sessions were separated by at least two control sessions.

Data Analysis

Mean rates of lever pressing in the FI Clock and VI components over an entire session were calculated from digital counters and elapsed time meters. Responses emitted and time elapsed during clock stimulus presentation were not included in VI component response rate calculations. In order to calculate the quarter life value [9] for the FI Clock component, the interval was divided in four equal 75 sec bins. Lever presses in corresponding segments of each interval were summed on counters over an entire session, and an average quarter life value was calculated over both FI Clock components. Data from clock stimulus presentation sessions were expressed as percent change from control rates, since baseline response rates were markedly different among the monkeys. Monkeys No. 4 and 9 responded differently to clock stimulus presentation: their data were presented separately. Monkeys No. 3 and 5 responded similarly to clock stimulus presentation: therefore, their data were averaged.

RESULTS

Different Consequent Stimuli Presented During the Schedule Components

Characteristic schedule-controlled performance was maintained under the mult FI Clock 5 min:*food* VI 2 min:*codeine* schedule (Table 1). During the FI Clock component, animals usually paused during the first three clock stimuli, as indicated by the high quarter life values, then lever pressed at a steady rate in the presence of the fourth (final) clock stimulus until food delivery. Monkey No. 4 responsed at a sustained high rate throughout the final clock stimulus, while Monkey No. 9 lever pressed at a much lower rate. Steady rates of lever pressing were maintained throughout each 20 min presentation of the VI 2 min component by delivery of 0.05 mg/kg unit doses of codeine. Monkey No. 4 lever pressed at a much higher rate than did Monkey No. 9; the number of infusions, however, was similar for both animals.

Performance under both schedule components changed as a function of the unit dose of codeine available under the VI schedule (Fig. 1). For both subjects, lever pressing rate during the FI Clock component decreased as a function of

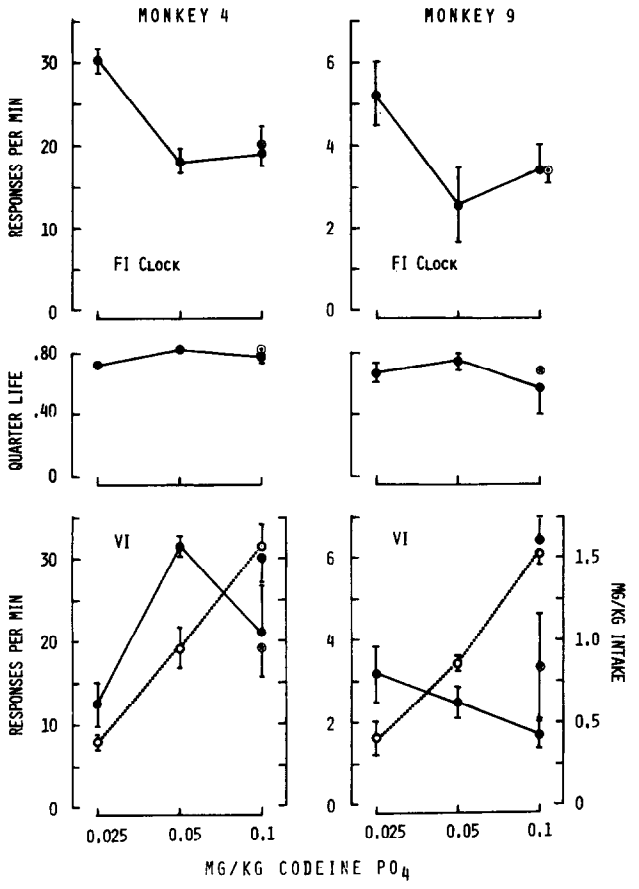

FIG. 1. Effects of codeine unit dose on lever pressing rate and quarter life value under the FI Clock component and on lever pressing rate (closed circles) and total drug intake (open circles) under the VI schedule of a multiple FI Clock 5 min: *food* VI 2 min: *codeine* schedule. Each point represents the mean ± SD over the final five sessions at each unit codeine dose for each monkey. The unconnected points at 0.10 mg/kg represent a second determination at this dose. Note that the ordinate response rate scales are different for each monkey.

the dose of codeine used to maintain responding under the VI schedule. These rate decreases were not accompanied by systematic changes in quarter life values. For Monkey No. 4, a unit dose of 0.05 mg/kg maintained the highest response rate under the VI 2 min schedule of codeine injection. Increasing the unit codeine dose to 0.1 mg/kg or decreasing it to 0.025 mg/kg decreased lever pressing rate. Monkey No. 9's low rates of lever pressing for codeine injection only decreased slightly as the unit dose was increased from 0.025 to 0.1 mg/kg. For both monkeys, total codeine intake increased as a function of unit dose. A unit dose of 0.05 mg/kg maintained steady response rates over both VI schedule components and was selected for further study in both monkeys.

The response contingent presentation of the clock stimuli associated with food availability altered the rate of codeine-maintained behavior. The direction of the change in response rate was controlled by the temporal location of a clock stimulus within the fixed-interval component (Table 2 and Fig. 2). The clock stimulus from the first 75 sec period of the FI decreased codeine-maintained lever pressing rates, whereas the clock stimulus from the final 75 sec of the interval increased rates of codeine-maintained lever pressing. The magnitude of these effects depended on the duration of clock stimulus presentation (Table 2). Increasing the duration of illumination of the first clock stimulus decreased lever pressing rates for both monkeys. In contrast, lengthening the final clock stimulus accentuated its rate-increasing effects in Monkey No. 9, with 3 sec presentations of the final clock stimulus doubling response rate under the VI schedule component. For Monkey No. 4, increasing the duration of the final clock stimulus did not systematically enhance its rate-increasing effects. These changes in lever pressing rate under the VI schedule were not accompanied by equivalent changes in the number of codeine injections delivered. During clock stimulus presentation sessions, performance under the FI Clock schedule did not change, and the frequency of left lever (i.e., FI Clock—appropriate) responses during the VI schedule component did not increase. A clock stimulus duration of 1.5 sec was used for the remainder of the study.

TABLE 2

EFFECTS OF DURATION OF CLOCK STIMULUS ILLUMINATION ON PERFORMANCE UNDER THE VI 2 MIN SCHEDULE OF 0.05 MG/KG CODEINE INFUSION

	Monkey No. 4		Monkey No. 9	
	Response rate* R/min	Infusions delivered*	Response rate* R/min	Infusions delivered*
First Clock Stimulus Duration				
0.5 sec	105.0	92.1	119.6	88.0
1.5 sec	68.6	104.5	90.4	90.5
3.0 sec	77.5	85.1	80.3	109.2
Final Clock Stimulus Duration				
0.5 sec	130.8	100.5	158.6	103.3
1.5 sec	110.0	97.1	184.1	91.7
3.0 sec	121.0	89.3	200.9	87.9

*Values are expressed as a percentage of the mean control value, which was calculated from the session immediately preceding each clock stimulus presentation session.

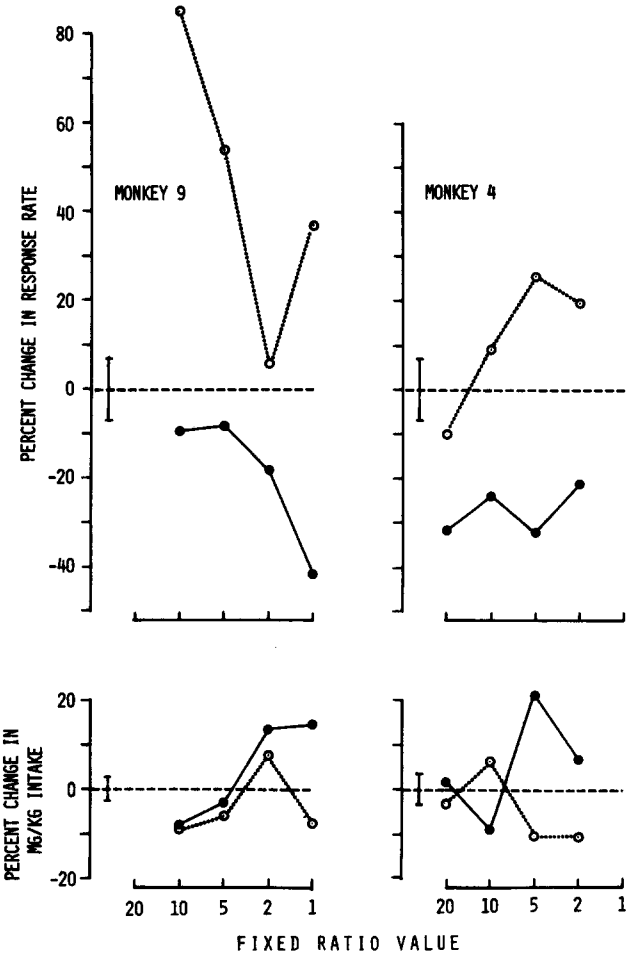

FIG. 2. Effects of decreasing the response requirement for clock stimulus presentation on lever pressing rate and total drug intake during the VI component of a multiple FI Clock 5 min: *food* VI 2 min: *0.05 mg/kg/injection codeine* schedule. Clock stimuli were presented for 1.5 sec upon completion of a fixed ratio (FR) of responses on the VI schedule lever. Open circles and dotted lines represent percent change from the preceding control session value during sessions in which the final clock stimulus was presented; closed circles and solid lines represent percent change when the first clock stimulus was presented upon completion of the FR. Each point represents the mean over the last two clock stimulus sessions. In both conditions, codeine availability was withheld during clock stimulus illumination. Brackets represent ± 1 SEM of the control values.

The rate-altering actions of the first and final clock stimuli also depended on their schedule of presentation (Fig. 2), but these effects differed between subjects. For Monkey No. 9, decreasing the number of lever presses required to illuminate the clock stimulus from the first period of the FI progressively decreased the rate of codeine-maintained responding. Lever pressing rate decreased 40% when every response, except those which produced codeine injections, produced a 1.5 sec flash of the first clock light. For Monkey No. 4, decreases in FR size did not accentuate the rate-decreasing effects of the first clock stimulus. When the clock stimulus from the final period of the FI was presented to Monkey No. 4, decreasing the ratio of responses required to illuminate the stimulus lamp increased the rate of lever pressing during the VI schedule component. Changes in ratio value generally attenuated the rate-increasing effects of the final clock stimulus for Monkey No. 9. Cumulative records of lever pressing under the VI schedule suggested that the rate decreases accompanying presentation of the first clock stimulus were the result of increased pausing and did not reflect a decrease in the running rate of lever pressing. The final clock stimulus appeared to increase local response rates in both VI schedule components. In general, changes in overall and local response rates were not accompanied by systematic changes in the frequency of codeine injection. The number of infusions made available during each 20 min VI 2 min schedule component varied during baseline sessions, allowing changes of ± 20% between successive sessions. The increases and decreases in the frequency of codeine injection during clock stimulus presentation sessions represent changes within the usual range of control session values.

Same Consequent Event Presented During Both Schedule Components

Schedule-controlled performance was maintained under the FI Clock 5 min and the VI 2 min schedules when either food or codeine was presented during both schedule components (Table 1). When food was available during both components, Monkey No. 4 lever pressed at a high sustained rate under the VI schedule. Under the FI Clock schedule, Monkey No. 4 paused throughout the first two clock stimuli, then abruptly changed to a high rate during the third or fourth clock stimulus. The animals exposed to codeine in both schedule components, Monkeys No. 3 and 5, made few responses during the first three stimuli of the FI Clock, as indicated by the high quarter life values, then lever pressed at a low rate during the fourth stimulus until codeine delivery. However, they occasionally did not initiate responding during the fourth stimulus light or, more frequently, paused for more than 10 sec at the end of an interval and missed the scheduled codeine injection. Both monkeys lever pressed at moderate rates under the VI schedule of codeine injection.

The clock stimuli had relatively little effect on lever pressing rates under the VI schedule when the same consequent event was presented during both the FI Clock and the VI schedule components (Fig. 3). When food was the consequent stimulus in both schedule components, illumination of either the first or the final clock stimulus upon completion of 2 to 20 lever presses during the VI schedule component did not markedly alter either response rate or the number of food pellets delivered. When codeine was presented in both schedule components, brief presentations of the clock stimulus from the final 75 sec period of the FI did not systematically change response rates under the VI schedule. The effects of the first clock stimulus depended on its schedule of presentation. Decreasing the ratio of lever presses required to illuminate the first clock light slightly increased and then decreased lever pressing rate under the VI schedule of codeine injection.

DISCUSSION

Contingent presentation of certain environmental stimuli can produce marked changes in behavior maintained by drug reinforcers. Electric shocks [12, 15, 25], stimuli paired with drug injection [8, 16, 21], and stimuli associated with periods

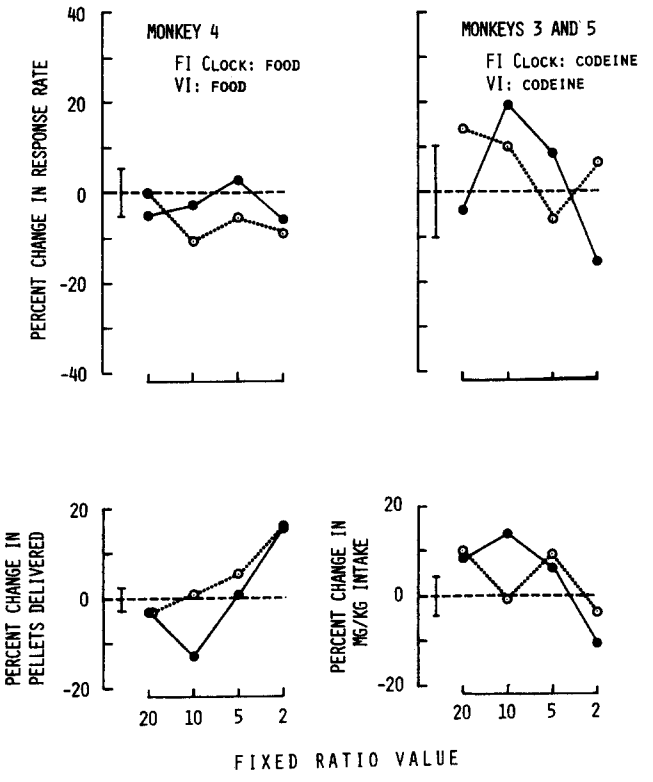

FIG. 3. Effects of decreasing the response requirement for clock stimulus presentation on lever pressing rate and total reinforcer presentations during the VI schedule component of a multiple FI Clock 5 min VI 2 min schedule. Monkey No. 4 received a 1 gm Noyes banana-flavored pellet as the consequent event in both schedule components: Monkeys No. 3 and No. 5 received 0.05 mg/kg/infusion injections of codeine in both components. Open circles and dotted lines represent percent change from the preceding control session value during sessions in which the final clock stimulus was presented: closed circles and solid lines represent percent change when the first clock stimulus was presented upon completion of the FR. Each point represents the mean over the last two clock stimulus sessions. In both conditions, reinforcer availability was withheld during clock stimulus illumination. Brackets represent ± 1 SEM of the control values.

of no drug availability [2,11] alter the rate and pattern of drug-maintained performance. The present study extends the range of contingent stimulus events which modify the rate of drug-maintained performance to include the presentation of clock stimuli differentially correlated with reinforcer availability.

The rate and pattern of responding maintained by codeine injection depend, in part, on the schedule contingencies and the dose per injection [3, 4, 5, 14]. Carney *et al.* [3] reported that under a VI 2 min schedule, maximum overall response rates and constant responding during a session are maintained by a unit codeine dose of 0.01 to 0.03 mg/kg: higher doses produce both lower rates and negatively accelerated patterns of responding. The present study replicated these results: Codeine doses of 0.025 or 0.05 mg/kg/infusion generated moderate response rates under the VI 2 min schedule; a higher dose decreased overall rates. The unit codeine dose available during the clock stimulus manipulations (0.05 mg/kg) maintained steady responding over both VI components, with little or no negative acceleration within or between components. Additionally, codeine injection maintained performance under a new schedule, a fixed interval with added clock stimuli.

The visual clock stimuli exerted discriminative control over fixed-interval responding maintained by either codeine or food presentation in the rhesus monkey. The monkeys usually made few responses during the initial two clock stimuli, then initiated lever pressing at moderate to high rates during the third or, more frequently, the fourth (final) clock stimulus and maintained these rates until reinforcer presentation. Clock stimuli control similar patterns of responding by pigeons key pecking under FI Clock schedules of food presentation [13, 18, 19, 24] and by rhesus monkeys lever pressing under shock postponement schedules [10]. Ferster and Zimmerman [7], however, reported difficulty in maintaining lever pressing by rhesus monkeys under a FI Clock schedule of food presentation with auditory and/or visual clock stimuli. Their subjects frequently paused for extended periods and rarely initiated lever pressing before the interval had elapsed. The use of a 10 sec limited hold and a prolonged exposure to shorter intervals in the present experiment may have contributed to the well-maintained lever pressing rates and patterns by rhesus monkeys under the FI Clock schedules.

When the clock stimuli were presented response-contingently, the behavioral effects of each stimulus depended on its position within the fixed interval, its duration and schedule of presentation, and the context in which it was presented. The position of a clock stimulus within the fixed interval determined the direction of the changes it produced in lever pressing rates during the VI component. The stimulus correlated with the initial segment of the interval reliably decreased response rates during the VI component, whereas the clock light correlated with the final 75 sec of the interval increased these rates. In general, the longer the illumination of a clock stimulus lamp, the greater its rate-altering effects. Decreasing the FR response requirement for stimulus presentation accentuated or did not alter the effects of the clock stimuli on response rate during the VI component. Finally, the rate-altering effects of response-contingent clock stimuli were most pronounced when different reinforcers were available in the two components of the multiple schedule. When either food or codeine was available in both schedule components, the clock stimuli did not markedly alter response rates in the VI component. The variables responsible for this possibly selective effect remain to be determined.

The clock stimuli may have exerted their rate-altering effects in a variety of ways. First, they may have exerted discriminative control over responding during their illumination. However, it is unlikely that the response rate changes were due to changes in rate during clock stimulus presentation, since lever presses and time during stimulus illumination were not used in the rate calculations. The rate-altering effects of brief clock stimulus presentations were not accompanied by changes in the total number of codeine injections delivered during the VI components. Therefore, the increased rate-altering effects of the stimuli as their duration increased or as the number of lever presses required for their illumination decreased cannot be attributed to a conditioning history of clock stimuli being associated with altered reinforcement density. Finally, the first and final clock stimuli may have served, respectively, punishing and reinforcing

functions. The response-contingent presentation of the first clock stimulus decreased ongoing rates, cf. [1]: the contingent presentation of the final clock stimulus increased rates during the VI component, cf. [6]. Although further work is needed to confirm this interpretation, the present results support Segal's [24] suggestion that stimuli differentially correlated with reinforcer availability may acquire reinforcing or punishing properties.

REFERENCES

1. Azrin, N. H. and W. C. Holz. Punishment. In: *Operant Behavior: Areas of Research and Application*, edited by W. K. Honig. New York: Appleton-Century-Crofts, 1966, pp. 380–447.
2. Bigelow, G., I. Liebson and R. Griffiths. Alcoholic drinking: Suppression by a brief time-out procedure. *Behav. Res. Ther.* **12:** 107–115, 1974.
3. Carney, J. M., M. E. Llewellyn and J. H. Woods. Variable interval responding maintained by intravenous codeine and ethanol injections in the rhesus monkey. *Pharmac. Biochem. Behav.* **5:** 577–582, 1976.
4. Deneau, G., T. Yanagita and M. H. Seevers. Self-administration of psychoactive substances by the monkey: A measure of psychological dependence. *Psychopharmacologia* **16:** 30–48, 1969.
5. Downs, D. A. and J. H. Woods. Codeine- and cocaine-reinforced responding in rhesus monkeys: Effects of dose on response rates under a fixed-ratio schedule. *J. Pharmac. exp. Ther.* **191:** 179–188, 1974.
6. Ferster, C. B. and B. R. Skinner. *Schedules of Reinforcement*. New York: Appleton-Century-Crofts, 1957.
7. Ferster, C. B. and J. Zimmerman. Fixed-interval performances with added stimuli in monkeys. *J. exp. Analysis Behav.* **6:** 317–322, 1963.
8. Goldberg, S. R. The behavioral analysis of drug addiction. In: *Behavioral Pharmacology*, edited by S. D. Glick and J. Goldfarb. St. Louis: The C. V. Mosby Company, 1976, pp. 283–316.
9. Gollub, L. R. The relations among measures of performance on fixed-interval schedules. *J. exp. Analysis Behav.* **7:** 337–343, 1964.
10. Grabowski, J. and T. Thompson. Response patterning on an avoidance schedule as a function of time-correlated stimuli. *J. exp. Analysis Behav.* **18:** 525–534, 1972.
11. Griffiths, R., G. Bigelow and I. Liebson. Suppression of ethanol self-administration in alcoholics by contingent time-out from social interactions. *Behav. Res. Ther.* **12:** 327–334, 1974.
12. Grove, R. N. and C. R. Schuster. Suppression of cocaine self-administration by extinction and punishment. *Pharmac. Biochem. Behav.* **2:** 199–208, 1974.
13. Hendry, D. P. and P. V. Dillow. Observing behavior during interval schedules. *J. exp. Analysis Behav.* **9:** 337–349, 1966.
14. Hoffmeister, F. and U. U. Schlichting. Reinforcing properties of some opiates and opioids in rhesus monkeys with histories of cocaine and codeine self-administration. *Psychopharmacologia* **23:** 55–74, 1972.
15. Johanson, C. E. The effects of electric shock on responding maintained by cocaine injections in a choice procedure in the rhesus monkey. *Psychopharmacology* **53:** 277–282, 1977.
16. Kelleher, R. T. and S. R. Goldberg. Fixed-interval responding under second-order schedules of food presentation or cocaine injection. *J. exp. Analysis Behav.* **28:** 221–231, 1977.
17. Kelleher, R. T., S. R. Goldberg and N. A. Krasnegor (Eds.). *Control of Drug-Taking Behavior by Schedules of Reinforcement*. Baltimore: The William and Wilkins Company, 1976.
18. Kendall, S. B. Some effects of response-dependent clock stimuli in a fixed-interval schedule. *J. exp. Analysis Behav.* **17:** 161–168, 1972.
19. Laties, V. G. and B. Weiss. Influence of drugs on behavior controlled by internal and external stimuli. *J. Pharmac. exp. Ther.* **152:** 388–396, 1966.
20. Pickens, R., R. Hauck and W. Bloom. A catheter-protection system for use with monkeys. *J. exp. Analysis Behav.* **9:** 701–702, 1966.
21. Sanchez-Ramos, J. R. and C. R. Schuster. Second-order schedules of intravenous drug self-administration in rhesus monkeys. *Pharmac. Biochem. Behav.* **7:** 443–450, 1977.
22. Schuster, C. R. and C. E. Johanson. The use of animal models for the study of drug abuse. In: *Research Advances in Alcohol and Drug Problems, Vol. 1*, edited by R. J. Gibbins, Y. Israel, H. Kalant, R. E. Popham, W. Schmidt and R. G. Smart. New York: John Wiley and Sons, 1974, pp. 1–31.
23. Schuster, C. R. and T. Thompson. Self-administration of and behavioral dependence on drugs. *Ann. Rev. Pharmac.* **9:** 483–502, 1969.
24. Segal, E. F. Exteroceptive control of fixed-interval responding. *J. exp. Analysis Behav.* **5:** 49–57, 1962.
25. Smith, S. G. and W. M. Davis. Punishment of amphetamine and morphine self-administration behavior. *Psychol. Rec.* **24:** 477–480, 1974.
26. Thompson, T. and R. Pickens. An experimental analysis of behavioral factors in drug dependence. *Fedn Proc.* **34:** 1759–1770, 1975.