Psychopharmacology (2002) 163:345–351
DOI 10.1007/s00213-002-1201-4

ORIGINAL INVESTIGATION

J. H. Woods · G. D. Winger

Observing responses maintained by stimuli associated with cocaine or remifentanil reinforcement in rhesus monkeys

Received: 8 April 2002 / Accepted: 4 July 2002 / Published online: 29 August 2002

Abstract *Rationale:* The stimuli associated with drug reinforcement may be particularly relevant to drug abuse and relapse. *Objectives:* The study measured behavior maintained by conditioned reinforcing stimuli in an observing response procedure. *Methods:* The experiment was conducted with rhesus monkeys in three stages: 1) discriminative control was established by reinforcing responding on one lever with either intravenous cocaine or remifentanil in the presence of one stimulus and extinguishing the response in the presence of another stimulus, 2) discriminative control was suspended by not presenting the stimuli, and 3) a final stage was implemented wherein the stimuli from the first stage were presented only when one or more responses were made on a second (observing) lever. *Results:* Under FR1 conditions, observing responses were maintained at low rates, but increased markedly when the response requirement was increased. *Conclusions:* The procedure maintained observing responses quite well and may be useful to an analysis of conditioned reinforcement based on drug reinforcement.

Keywords Observing response · Cocaine · Remifentanil · Self-administration · Rhesus monkeys

Introduction

The reinforcing effects of discriminative stimuli that are presented along with primary reinforcers may be studied utilizing procedures that allow functional analysis of a response that produces discriminative stimuli but does not alter the rate of primary reinforcer delivery. One such arrangement has been designated as an observing response procedure following its introduction and use by Wyckoff (1952) for the analysis of discrimination learning. Subsequently, a number of commentators (e.g. Fantino 1977; Williams 1994) have recommended the observing response procedure for more general application to the study of conditioned reinforcement.

Through the process of conditioning and the establishment of conditioned reinforcers, the environmental context of drug reinforcement is likely to be strongly involved in the control of drug taking. Recently, Shahan (2002) drew attention to the utility of an observing response procedure in the study of conditioned reinforcement based on oral ethanol reinforcement in rats. He showed that discriminative stimuli associated with ethanol reinforcement were strong conditioned reinforcers, and that the reinforcing effects of these stimuli were weakened when ethanol reinforcement was discontinued. Further, he suggested that the reinforcing and discriminative effects of these stimuli could be investigated together because the observing response permits concurrent measures of both the discriminative control and the reinforcing effects of these conditioned reinforcers.

The present experiment extends Shahan's notions utilizing the observing response procedure in rhesus monkeys with intravenous opioid (remifentanil) or stimulant (cocaine) reinforcer delivery. Because this was an initial study of the application of the observing response technique using IV drug reinforcers in primates, the study emphasized basic parametric variations of presentation of the conditioned stimuli. Kelleher (1958) demonstrated that observing response rates and patterns may be modified by schedule-controlled delivery of the discriminative stimuli. Furthermore, the duration of the reinforcer (i.e. the observing stimulus) may affect its reinforcing effect (e.g. Auge 1973). Both the duration of the observing stimuli and the fixed-ratio schedule of their delivery were studied in the present experiment. It appeared that the procedure might be useful for a functional analysis of the conditioned reinforcing effects of schedule-correlated stimuli based on drug reinforcers.

J.H. Woods (✉) · G.D. Winger
Department of Pharmacology, 1301 MSRB III,
University of Michigan Medical School, Ann Arbor,
MI 48109-0632, USA
e-mail: jhwoods@umich.edu
Fax: +1-734-7647118

Materials and methods

Subjects

Five male rhesus monkeys were used in the experiment. They were prepared with chronic, indwelling venous cannulae (Silastic rubber; 0.08 o.d., 0.04 i.d., Moxmed, Portage, Wisc., USA); the cannulae were placed in major veins (e.g. jugular or brachial) as needed. The cannulae were passed subcutaneously from the vein insertion point to an exit point on the back between the shoulder blades. If a cannula became non-functional, as determined by a radical change in performance and confirmed by an uncharacteristic response to an ultrashort-acting barbiturate, methohexital, the nonfunctional cannula was surgically removed and a 2-week hiatus was followed by recannulation, which in turn was followed by the recovery of behavior in the last condition of the experiment prior to detection of the nonfunctional cannula.

Water was available at all times. The monkeys were fed twice daily about 2 h prior to each of the two, daily 2-h experimental sessions; a sufficient amount of Purina monkey chow was fed to maintain body weights. The diet was supplemented with fresh fruit daily and enrichment toys were rotated among the monkeys as well. The weights of individual monkeys ranged between 10.5 and 12.4 kg. Animals were weighed every 2 weeks when their cages were exchanged for sanitized cages, and drug doses were adjusted to weights as needed.

All monkeys had been in other experiments in which drugs were evaluated as reinforcers. Many of those experiments employed fixed-ratio schedules of drug delivery using right lever responding, and drug availability was traditionally indicated by illumination of the red light over the right lever and the green light was illuminated during injections. The studies were performed in AAALAC International accredited facilities using protocols approved by the University of Michigan Institutional Review Board for Use and Care of Laboratory Animals. Principles of laboratory animal care as promulgated by NIH publication No. 85-23, revised 1996 were followed.

Apparatus

The individual housing cages, constructed in over-and-under pairs, were custom built (Research Equipment Co., Bryan, Tex., USA); three walls and the ceiling were solid, stainless steel. The floor and the front wall were barred; the barred front wall allowed visual access to other monkeys in the same room. The inside dimensions of the cages were 30 inches wide×33 inches high×36 inches deep. Each cage contained a restraint device that consisted of two components: 1) a jacket made of Teflon mesh. These were individually fitted to the monkey and prevented the monkey's access to the cannulae, and 2) a flexible tubular stainless steel tether anchored to the back of the cage and connected to the back of the mesh jacket). This tether, which contained the cannula, was connected to a swivel at the back of the cage that prevented twisting of the cannula (Lomir, Malone N.Y., USA).

Injections were made by activating a Watson-Marlow roller pump (Model MHRK 55, Falmouth, UK) for 5 s; the pump speed delivered 1 cc of fluid during the 5 s.

A small section of one wall of the cage contained the two response levers (Model 121-07, BRS-LVE, Beltsville, Md., USA) capable of being activated by 0.01–0.15 N. They were mounted 10 inches above the floor and 1 inch apart. A vertically mounted steel plate placed between the levers prevented simultaneous responding by one paw on both levers. Three 1-inch diameter stimulus lights were mounted 2 inches above the levers. The center light was illuminated green during drug injections. The right and left stimulus lights were red when illuminated and were used as described below.

Programming of the schedules of reinforcement was accomplished by and responses were recorded with Med Associates (Fairfield, Vt., USA) software including Soft Cumulative Record. IBM PC computers with Med Associates and home-made interfacing served as the hardware base.

Drugs

Cocaine hydrochloride (NIDA, Rockville, Md., USA) and remifentanil hydrochloride (Glaxo-Wellcome, Research Triangle Park, N.C., USA) were used. Doses refer to the salts.

Procedures

Multiple schedule of drug reinforcement. All monkeys were exposed initially to a multiple variable-interval 3-min extinction schedule of reinforcement (mult VI3 EXT). Components of the multiple schedule were indicated by illuminating the right light constantly during the variable-interval and turning the right light on and off every second during extinction. The intervals that composed the variable-interval were selected randomly from a list: 0, 45, 90, 135, 180, 225, 270, 315, and 360 s. The components alternated on a variable temporal basis; the durations of the components were chosen randomly with replacement from a list of durations (450, 675, 900, 1350, and 1800 s). These durations assured that at least one reinforcer would be available in each component. The variable-interval and extinction conditions alternated and, over the course of several sessions, each component should have been available for the same amount of time, though not necessarily within a single session. Drug delivery was indicated by the illumination of the central green light and darkening of both of the other panel lights. The drug reinforcer consisted of either 0.01 mg/kg per injection cocaine in some monkeys and in the others, 0.0003 mg/kg per injection remifentanil. Sessions were 2 h in length. Performance was assessed after at least 20 sessions of exposure to the multiple schedule before the next contingency was introduced.

Mixed schedule of drug reinforcement

During the rather short exposure (usually ten sessions) to this schedule, the left stimulus light was introduced, and only this light was illuminated, except during injections when this light was darkened, and the center green infusion light was lighted. Drug delivery remained on the same VI3 EXT schedule for right lever responses as was the case in the previous multiple schedule; however, there was no visual indication of the current condition, i.e. variable-interval or extinction. Other conditions were the same as in the multiple schedule procedure.

Observing response schedules

Evaluation of the effects of changing the duration of observing stimuli. During this portion of the study, illumination of the left stimulus light indicated the beginning of each session. A single response on the left lever turned off the left lever light and illuminated the right lever light either flashing (indicating extinction component) or steady (indicating variable-interval component) for a period of 5 s. These conditions remained in effect for at least ten sessions, and usually somewhat longer. Then, the duration of the right light illumination was varied. Durations of 2, 10, and 20 s were studied subsequently, followed by replication of the 5-s condition. The sequence of the values of the light duration was unsystematic, except that it was initiated by the 5-s duration and this duration was repeated at the end of the sequence.

Observing response schedules

Evaluation of the effects of changing the fixed-ratio schedules with 5 or 20 s durations of the observing stimulus. A series of

Table 1 Mean response rates and their SEMs (in parentheses) for individual monkeys. Calculations are based on the last ten sessions under each condition

Subject	Drug/condition	Drug lever		"Observing" lever	
		S^D	S^Δ	S^D	S^Δ
Cocaine					
Hartmut	Multiple	0.35±0.03	0.02±0.01	0.25±0.02	0.01±0.00
	Mixed	0.26±0.03	0.21±0.03	0.06±0.02	0.05±0.01
Stony	Multiple	1.00±0.03	0.18±0.02	0.13±0.01	0.04±0.01
	Mixed	0.66±0.08	0.75±0.07	0.08±0.01	0.08±0.01
Remifentanil					
Pasquale	Multiple	0.98±0.10	0.01±0.005	0.004±0.002	0.001±0.00
	Mixed	0.85±0.07	0.99±0.08	0.004±0.004	0.005±0.001
Caligula	Multiple	0.18±0.04	0.00±0.00	0.03±0.00	0.00±0.00
	Mixed	0.12±0.02	0.24±0.06	0.05±0.01	0.08±0.02
Booker	Multiple	0.86±0.06	0.23±0.03	0.09±0.01	0.04±0.007
	Mixed	0.52±0.05	0.76±0.08	0.14±0.02	0.20±0.03

observations were then made of the maintenance of the observing response when the fixed-ratio value of the observing response was varied among 1, 5, 15, 30, and 60 responses. This manipulation was carried out using either 5 or 20 s duration of illumination of the right stimulus light as the reinforcer. One of these two durations was selected and the fixed-ratio values were changed systemically from 1 to 60; each condition was maintained for ten consecutive sessions. The other duration of stimulus light illumination was then used and the ratio values were changed again in the same manner. The initial duration was selected unsystematically among the subjects. For most monkeys these changes were made following the fixed-ratio 1 studies with various durations described above. One monkey (Caligula) did not participate in this part of the study.

Observing response schedules

Evaluation of the effects of high fixed-ratio schedules maintained by 3- or 60-s presentations. Three monkeys were studied under conditions in which the ratio size was larger (fixed ratio 100 or 300) with either 60 or 3 s durations of schedule-correlated stimuli as reinforcers. The durations were alternated; each was maintained for ten or more consecutive sessions before the preceding condition was returned.

Data analysis

Measures of rates of responding on both right and left levers were recorded in four session conditions: VI component, right light on; VI component, right light off; EXT component right light on; EXT component right light off. Cumulative records of responding were also obtained using Soft Cumulative Record. Total session average rates of responding were calculated along with standard errors of the means in individual monkeys usually for the last ten sessions under each condition. Response rates were calculated for the different stimulus conditions of the experiment with the exception that responses were not tallied during injections.

Results

Multiple schedule performance

The first phase of the experiment established discriminative control by the stimulus light conditions that signaled either a VI3 or an EXT period of IV drug delivery. The two monkeys that received cocaine had discrimination ratios (number of responses during the VI light condition/total responses) of 0.85 and 0.95. The three monkeys receiving remifentanil had discrimination ratios of 0.83, 0.99, and 1.00 over the last ten sessions in which this schedule was in effect. Variable-interval response rates maintained by cocaine were 0.35 and 1.0 responses/s, and rates of responding maintained by remifentanil were 0.18, 0.86, and 0.98 responses/s for the individual monkeys (Table 1). Response rate on the left (observing) lever, which at this point had no programmed consequence, was low in most cases, and lower than response rate on the right lever in all cases (Table 1).

Mixed schedule performance

The major effect of changing from a multiple to a mixed schedule was to increase responding on the right lever during the (unsignaled) extinction component of the session. Rates of right-lever responding during this period were increased in each of the five monkeys. Overall rates of responding were increased in four of the five monkeys, but to varying degrees (Table 1). Right-lever responding during the unsignaled variable-interval component was slightly and variably reduced compared with that occurring when this component was signaled in the previous portion of the experiment. Responding on the left (observing) lever increased in two cases to a small extent (Booker and Caligula, Table 1) and decreased in two other cases (Hartmut and Stony, Table 1).

Observing response schedules

Evaluation of the effects of changing the duration of observing stimuli. When each response on the left (observing) lever turned on the right stimulus light for 5 s, signaling either the variable-interval or the extinction component, four monkeys responded on the left lever sufficiently often to keep the multiple schedule in effect for almost 50% of the session. One monkey (Pasquale)

Table 2 Average response rates on drug and observing response keys and their SEs. Right column is the percentage of the session time that the discriminative stimuli were lit. Calculations are based on the last ten sessions under each duration condition

Subject	Drug/condition	Drug lever		Observing lever	% lights on
		S^D	S^Δ		
Cocaine (observing duration)					
Hartmut	2 s	0.79±0.06	0.30±0.03	0.15±0.02	31±3
	5[a]	0.43±0.06	0.05±0.01	0.12±0.005	42±2
	5[b]	0.55±0.04	0.23±0.02	0.12±0.01	61±2
	10	0.52±0.02	0.06±0.01	0.14±0.01	64±1
	20	0.39±0.03	0.16±0.02	0.14±0.02	83±3
Stony	2 s	1.47±0.06	0.38±0.03	0.11±0.01	22±1
	5[a]	0.98±0.05	0.22±0.02	0.04±0.00	21±1
	5[b]	1.18±0.20	0.04±0.01	0.17±0.04	41±9
	10	1.72±0.04	0.36±0.02	0.13±0.01	59±2
	20	1.22±0.11	0.17±0.02	0.15±0.03	63±8
Remifentanil (observing duration)					
Pasquale	2 s	1.79±0.05	0.25±0.02	0.10±0.01	17±1
	5 (a)	1.53±0.24	0.15±0.04	0.00±0.00	1±0
	5(b)	1.26±0.15	0.09±0.02	0.10±0.01	26±2
	10	1.35±0.04	0.04±0.01	0.13±0.01	46±2
	20	1.17±0.09	0.02±0.01	0.07±0.01	55±3
Caligula	2 s	0.70±0.05	0.80±0.08	0.06±0.01	12±1
	5[a]	0.65±0.05	0.22±0.04	0.05±0.01	26±1
	5[b]	1.07±0.08	1.26±0.13	0.04±0.00	23±1
	10	0.61±0.02	0.13±0.01	0.06±0.00	37±1
	20	0.32±0.02	0.09±0.03	0.05±0.00	50±1

[a] Initial exposure, [b] replicated condition

failed to come into contact with the new contingency because his rate of left-lever responding was very low. When left-lever responses turned on the right stimulus light for 20-s, this monkey showed an increase in frequency of responding on this lever, and responding on this lever was subsequently maintained when the 5 s duration was repeated. In the other four monkeys, however, when responses on the left lever turned on the right stimulus light for 5 s, the response rates on the left lever were in most cases similar to the rates observed under the mixed schedule condition (compare Table 1 with Table 2 or Table 3; Left lever and observing response rates) in which these responses had no consequence. When the duration of the right stimulus light was varied from 2 to 20 s, response rates on the left lever were unrelated to the duration. One consequence of this consistency of rates was a positive relation between the programmed duration of the stimuli and the percent of the total session during which the right stimulus light was illuminated. (Table 2). There also appeared to be no general or consistent relationship between the duration of the observing stimuli and rates of right (drug) lever responding.

Observing response schedules

Evaluation of the effects of changing the fixed-ratio schedules with 5- or 20-s durations of the observing stimulus showed that the effect of increasing response requirements on the observing response lever was to increase response rates relative to the FR1 condition (Table 3). At FR requirements from 5 to 60, however, there were inconsistent effects across monkeys. These same results were obtained with both durations of observing stimuli. As was noted earlier under FR1 conditions (Table 2), the observing stimuli remained on for a larger portion of the session at 20 s than at 5 s for each of the FR conditions. Increasing the fixed-ratio requirement on the observing lever produced a decrement in the percent of the session that the stimulus light was on for both durations.

Altering the FR requirements and duration of the observing stimulus failed to alter discriminative control of drug-reinforced responding in the three monkeys evaluated in this procedure, with one exception. Rates of responding on the drug lever were consistently higher during the VI portion of the schedule as compared with the extinction portion as FR requirement was increased and for the two durations of discriminative stimuli (Table 4). This was the case even when the percent of time that the discriminative stimuli were illuminated was reduced to between 4 and 8% of the total session. The one exception was one monkey (Hartmut) that showed relatively poor discrimination between the VI and EXT portions of the schedule even under the FR1 condition with a 20-s duration of the discriminative stimuli, when these stimuli were illuminated for 83% of the total session time. Although he responded more than twice as fast in the VI as compared with the EXT components in this optimal condition, the other animals responded nearly 100 times faster in the VI component under these conditions. Under the condition in which the stimuli were illuminated for 5 s, Hartmut lost discriminative control by the

Table 3 Average response rates on the right (drug) and left (observing) response levers. Right hand column (and SEMs) is the percentage of the session time that the discriminative stimuli were lit. Entries for 5 and 20 s refer to observing stimuli duration. Calculations are based on the last ten sessions under each duration and ratio condition

Fixed-ratio value	Drug lever				Observing lever			
	S^D		S^Δ		Overall rate		% light on	
	5 s	20 s	5 s	20 s	5 s	20 s	5 s	20 s
Cocaine								
Hartmut								
FR1	0.55±0.04	0.39±0.03	0.23±0.02	0.16±0.02	0.12±0.01	0.14±0.02	61±2	83±3
FR5	0.39±0.03	0.30±0.03	0.31±0.01	0.08±0.02	0.27±0.02	0.48±0.06	40±1	64±3
FR15	0.26±0.03	0.21±0.02	0.56±0.03	0.04±0.01	0.39±0.02	0.48±0.05	37±2	37±4
FR30	0.31±0.09	0.26±0.01	0.59±0.08	0.04±0.01	0.21±0.03	0.59±0.04	8±1	27±1
FR60	0.34±0.04	0.27±0.05	0.26±0.04	0.07±0.01	0.24±0.04	0.50±0.04	2±0	13±1
Stony								
FR1	1.18±0.20	1.22±0.11	0.04±0.01	0.17±0.02	0.17±0.4	0.15±0.03	41±9	63±8
FR5	0.70±0.01	1.79±0.07	0.08±0.01	0.13±0.01	0.90±0.05	0.36±0.01	44±1	66±2
FR15	0.60±0.06	0.74±0.03	0.08±0.02	0.12±0.02	0.63±0.14	0.78±0.09	16±3	44±3
FR30	0.66±0.03	0.74±0.02	0.05±0.01	0.13±0.02	1.23±0.09	0.86±0.08	52±2	34±2
FR60	0.51±0.06	0.57±0.06	0.07±0.01	0.07±0.02	1.13±0.12	0.72±0.12	8±1	18±3
Remifentanil								
Pasquale								
FR1	1.26±0.15	1.17±0.09	0.09±0.02	0.02±0.01	0.1±0.01	0.07±0.01	26±2	55±3
FR5	1.77±0.06	0.45±0.03	0.12±0.02	0.01±0.00	0.32±0.03	0.18±0.02	21±1	42±2
FR15	1.40±0.08	0.47±0.02	0.05±0.01	0.02±0.00	0.74±0.02	0.47±0.03	18±1	39±1
FR30	0.82±0.04	0.51±0.04	0.06±0.01	0.02±0.00	0.53±0.04	0.40±0.02	9±1	23±1
FR60	1.01±0.06	0.50±0.02	0.15±0.01	0.02±0.00	0.35±0.02	0.39±0.02	4±0	15±0
Booker								
FR1	0.72±0.04	0.80±0.07	0.56±0.04	0.25±0.03	0.04±0.00	0.05±0.00	33±2	47±2
FR5	0.82±0.06	0.90±0.06	0.55±0.06	0.11±0.01	0.04±0.01	0.08±0.01	17±4	21±2
FR15	0.82±0.09	0.75±0.06	0.51±0.06	0.48±0.05	0.04±0.01	0.12±0.02	3±0	13±1
FR30	0.35±0.04	0.44±0.04	0.19±0.02	0.14±0.02	0.07±0.01	0.17±0.01	2±1	9±1
FR60	0.47±0.05	0.59±0.07	0.32±0.06	0.19±0.02	0.07±0.01	0.19±0.03	0±0	6±1

Table 4 Mean responses and standard errors of the mean on the observing response lever when reinforcement duration was either 3 or 60 s duration. Response rates are calculated only for the periods when the mixed schedule was in effect, during either the variable-interval or extinction condition. *R* replication

Monkey (fixed ratio)	Observing lever				Correlated stimuli: % of session	
	60 s		3 s			
	VI	EXT	VI	EXT	60 s	3 s
Stony (FR300)	0.44±0.07	0.58±0.08	0.36±0.07	0.32±0.05	9±1	1±0
R	0.57±0.06	0.62±0.07	–	–	9±1	
Pasquale (FR300)	0.45±0.05	0.36±0.03	0.51±0.03	0.49±0.02	11±1	0±0
R	0.39±0.02	0.31±0.03	–	–	10±1	
Hartmut (FR100)	0.71±0.05	0.70±0.08	0.30±0.04	0.24±0.04	25±1	1±0
R	0.43±0.11	0.48±0.11	–	–	17±2	

observing stimuli as the fixed-ratio requirement for presentation of these stimuli increased. Rates of responding on the drug lever during the VI schedule were no higher than, and sometimes lower than rates of responding during EXT at FR values above 1. Interestingly, with an FR of 100 and a 60-s duration of the discriminative stimuli, this animal's discriminative control was much improved. Whether this reflects additional training or a repeatable individual difference remains to be determined. A cumulative record of his performance under this schedule condition is shown in Fig. 1. As explained in the figure caption, the drug-reinforced response shows a relatively high rate of steady responding in the variable-interval portion of the schedule alternating with a lower rate of responding during extinction.

Observing response schedules

The effects of high ratios maintained by 3 or 60 s presentations of stimuli were evaluated. Since the observing responses appeared to be maintained well

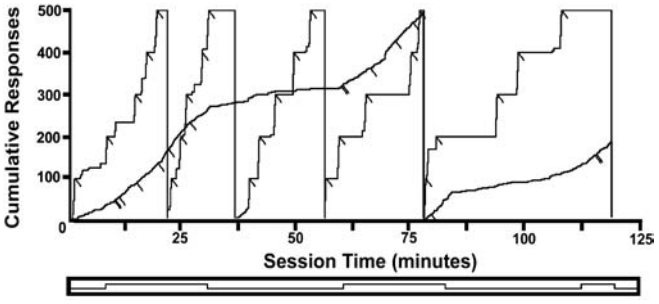

Fig. 1 For monkey Hartmut, a cumulative record of behavior maintained on the observing lever (high rates, "break-and-run" pattern) overlayed on a cumulative record of behavior maintained on the lever producing the drug reinforcement (lower rates). The *ordinate* is number of responses: the pen lines for both records increased with each lever press to a maximum of 500 responses, and then reset. The *abscissa* is time; the session lasted 120 min. The event pen on the bottom of the record is in the down position when the schedule was extinction and in the up position when the schedule was a VI 3 min of 0.01 mg/kg per injection of cocaine. The conditions shown in the record are an FR100 schedule for 60 s presentation of the discriminative stimuli. On the drug-reinforced record, drug delivery is shown by the *downward blips*. The *downward blips* on the observing response record indicate presentation of the conditioned light stimulus signaling either drug availability or extinction on the drug-reinforced lever. Overall rates of responding on the drug-reinforced lever during the VI portion of the session were 0.16 responses per second; on the EXT component of the session, these decreased to 0.03 responses per second. Rates of responding on the observing response lever were 0.45 responses per second when the discriminative stimuli were not illuminated

under the fixed-ratio and duration conditions described above, an attempt was made to "strain" observing performance by increasing ratio requirements and shortening the duration of the stimuli. In addition, we extended the exposure under the most demanding condition to 20 sessions. The major results of these manipulations are shown in Table 4. These manipulations were carried out in three monkeys, and the findings appeared uniform in each monkey. Responding continued to be maintained well under these conditions regardless of duration of the observing stimuli. In addition, responding on the observing lever is reported under both the variable-interval and the extinction conditions. As can be seen in Table 4, responding was maintained at equal rates under these conditions. This is shown as well in Fig. 1, where responding on the observing lever can be seen to occur about equally often in the variable-interval condition as in the extinction condition.

Discussion

Under conditions in which IV drugs (cocaine or remifentanil) served as primary reinforcers on a mixed VI 3-min EXT schedule, rhesus monkeys developed and maintained responding that resulted in the illumination of stimuli that indicated whether or not the schedule of drug delivery was in effect. To the best of our knowledge, this is the second report of observing responses being maintained by stimuli associated with drug delivery (Shahan 2002 being the first), and the first such report using behavior maintained by IV drug delivery in non-human primates.

The effect of changes in the FR schedule on the observing response was generally to increase rates of responding on the observing lever. Kelleher (1958) used a similar observing procedure in two chimpanzees where the primary reinforcer was food. He found that increasing the fixed-ratio requirement on the observing lever resulted in increased rates of responding on this lever that were directly related to the ratio value at fixed ratios of 1, 10, 20, and 30. No further rate increases were observed at an FR of 60. In general, our findings agree with those of Kelleher. There was typically a large increase in rates of responding on the observing lever when the fixed ratio was increased from 1 to 5; further increases occurred with higher ratios, although not necessarily at the next higher FR value (Table 3).

We also studied the effect of different durations of stimulus presentation. This variable has not been studied frequently. Auge (1973) evaluated the effect of two different durations of observing stimuli using pigeons responding on an FR1 schedule to turn on stimuli that signaled different magnitudes of grain delivery. The grain was available on an FI 1 min schedule, and the stimuli indicating the magnitude of the reinforcer were either illuminated for 10 s or for the duration of the interval. Only responding that turned on the longer duration stimuli maintained observing responses. This is in contrast to the current conditions in which the duration of the observing stimuli had no marked effect on the rate of responding to obtain these stimuli. All durations from 5 to 20 s were effective reinforcers. Although one monkey (Hartmut) showed a consistently higher rate of observing when the stimuli were illuminated for 20 s as compared with 5 s, the two other monkeys did not show consistent duration-related changes in rates of observing. Although the difference between our results and those of Auge (1973) might be due to different species, different reinforcers, different schedules of primary reinforcement, or different FR values for stimuli presentation, our data remain curious. One might assume that increasing the duration of the observing stimuli is effectively increasing the magnitude of the reinforcer that maintains responding on the observing lever. One might therefore expect higher rates of responding when the longer duration was presented. Nevertheless, it is quite possible that our procedure was not optimal for detecting the effects of duration of the observing stimulus. Dinsmoor et al. (1981) used a procedure in which two responses concurrently available, presented an observing stimulus (the SD only) for different durations. The response alternative presenting the longer duration was preferred.

Although the current report deals with several changes in the parameters governing responding on the observing lever, changes in the effects of responding on the drug lever may be instructive in understanding more about conditioned reinforcers associated with drug delivery that maintain an observing response. The effects of replacing

the drugs with saline as well as the effects of different doses of cocaine and remifentanil will be helpful in this regard. Using an observing response procedure, Shahan (personal communication) noted increased responding on both the observing and the primary lever as concentration of the sucrose reinforcer was increased. With oral ethanol as a reinforcer, however, Shahan (2002) noted that decreases in observing responses occurred slowly when ethanol was removed from the reinforcing fluid. Further studies will determine the effects of changing the magnitude of the primary reinforcer on behavior maintained by a conditioned reinforcer using IV drug reinforcers in rhesus monkeys.

In conclusion, this initial investigation of the use of IV drug delivery in rhesus monkeys to reinforce responding maintained by conditioned reinforcers suggests that this procedure may be useful in reflecting the strength of these conditioned reinforcers. The likely impact of conditioned reinforcement in directing the behavior of drug abusers is sufficiently high to warrant continued study of this interaction.

Acknowledgements The animals used in this study were maintained in accordance with the USPHS Guide for Care and Use of Laboratory Animals and all procedures were approved by the appropriate Institutional Animal Care and Use Committees. This research was funded by USPHS grants DA-00254 and DA-09161.

References

Auge RJ (1973) Effects of stimulus duration on observing behavior maintained by differential reinforcement magnitude. J Exp Anal Behav 20:429–438

Dinsmoor JA, Mulvaney DE, Jwaideh AR (1981) Conditioned reinforcement as a function of duration of stimulus. J Exp Anal Behav 36:41–49

Fantino E (1977) Conditioned reinforcement: Choice and information. In: Koenig WK, Staddon R (eds) Handbook of operant behavior. Prentice-Hall, Englewoods Cliffs, N.J. pp 313–339

Kelleher RT (1958) Stimulus-producing responses in chimpanzees. J Exp Anal Behav 1:87–102

Shahan TA (2002) The observing-response procedure: a novel method to study drug-associated conditioned reinforcement. Exp Clin Psychopharmacol 10:3–9

Williams BA (1994) Conditioned reinforcement: experimental and theoretical issues. Behav Anal 17:261–285

Wyckoff LB Jr (1952) The role of observing responses in discrimination learning. Psychol Rev 59:431–442