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Second-Order Schedules of Intravenous Drug Self-Administration in Rhesus Monkeys

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SANCHEZ-RAMOS, J. R. AND C. R. SCHUSTER. *Second-order schedules of intravenous drug self-administration in the rhesus monkey.* PHARMAC. BIOCHEM. BEHAV. 7(5) 443–450, 1977. — Lever-pressing behavior was generated and maintained in 3 rhesus monkeys by intravenous infusions of morphine or cocaine under a second-order schedule of reinforcement. Under this schedule, every tenth lever-press response (FR 10) during a fixed interval of time produced a 2 sec stimulus light. The first FR 10 completed after a 60 min interval had elapsed produced the stimulus light and an intravenous infusion of morphine or cocaine. The stimulus light remained on for the duration of the drug infusion (50–60 sec). Sessions of morphine or cocaine presentation, each with distinct stimulus light conditions, alternated on a daily basis. Under this schedule, single doses of morphine from 0.125 to 1.0 mg/kg maintained high overall response rates (maximum of 40 Rs/min) in the pattern characteristic of fixed interval (FI) schedules of reinforcement. There was no functional relationship between the response-rates and the doses of morphine tested. The simultaneous infusion of naloxone (0.125 mg/kg) with morphine (0.25 mg/kg) markedly decreased response rates. However, the infusion of the same dose of naloxone five min after the presentation of morphine failed to suppress self-administration behavior. Naloxone had no effects on cocaine-reinforced responding.

Second-order schedules Intravenous drug self-administration Morphine Cocaine Naloxone

UNDER a simple fixed ratio (FR) schedule of drug self-administration, an intravenous (IV) injection occurs after the emission of every nth response. When the injection dose of morphine or cocaine is increased, overall response rates diminish, and the total number of infusions per session decreases [4, 12, 17, 19]. Pretreatment with appropriate doses of morphine will, in general, suppress behavior controlled by drug or non-drug reinforcers [13, 16, 18]. Since the capacity of a drug injection to serve as a reinforcing event is confounded with other pharmacological effects of the drug under simple schedules of drug-taking behavior, other procedures have been devised to circumvent this problem. Second-order schedules, drug choice procedures and appropriate spacing of discrete trials have been used to avoid the influence of the rate-modifying effects of drugs [2, 8, 9, 10, 11, 14]. In this study, a second-order schedule of drug reinforcement has been chosen to separate the response-maintaining actions of morphine from its many other pharmacological actions which tend to suppress or interfere with lever pressing that follows each drug infusion [8, 9, 10, 11].

A second-order schedule treats a pattern of behavior engendered by a schedule contingency as a unitary response that is itself reinforced according to some schedule of reinforcement [15]. Under the specific schedule employed by Goldberg and colleagues [8, 10, 11], every nth lever-press response (FR n) during a fixed interval (FI) of time produces only a brief stimulus light without drug injection. The first FR n completed after the FI has elapsed produces the light which then remains on until the monkey has been given an IV or IM injection of either morphine or cocaine. Single, daily injections of morphine or cocaine are sufficient to maintain operant behavior under the control of second-order schedules [10,11]. Although response rates are generally constant across a broad range of dose changes, there are some graded effects at the lower doses [10,11]. This kind of schedule is well suited for the investigation of the role of stimuli associated with drug injections in the control of drug-seeking behavior [11] and for the study of the effects of prior drug treatments (e.g., antagonists) on drug-seeking behavior [10].

Our primary objective was to separate the reinforcing effects of morphine from its other pharmacological effects by using a second-order schedule similar to that employed by Goldberg *et al.* [10,11]. Our secondary objective, for which we report preliminary data, was to determine the dose ratio of morphine to naloxone required to extinguish self-administration behavior when the antagonist was administered either simultaneously with, or five minutes after, a morphine infusion. Cocaine was self-administered on alternate days in order to assess the specificity of the opiate antagonist interaction.

We report, in confirmation and extension of the findings of Goldberg *et al.* [8, 10, 11] that response rate remained relatively insensitive to morphine dose manipulations (from 0.125–1.0 mg/kg) under a second-order schedule of reinforcement. Despite the insensitivity of behavior to morphine dose manipulations under these conditions, naloxone (0.125 mg/kg) suppressed self-administration behavior when administered simultaneously with morphine. However, the infusion of the same dose of naloxone (0.125 mg/kg) five min after the termination of the morphine infusion had no effect on the rate and pattern of lever responding.

METHOD

Animals

Three experimentally naive rhesus monkeys (M4138, M4139, M4140) weighing between 5 and 6 kg were housed in sound attenuating cubicles 68.6 cm wide, 76.2 cm high, and 83.5 cm deep. Food (Purina Monkey Chow) and water were available ad lib and supplemented with weekly vitamins and fruit.

Apparatus

Chronic intravenous double-lumen catheters (U.S. Catheters, No. 1100) were implanted in jugular or femoral veins as described by Johanson and Schuster [14]. Upon exiting the skin between the scapulae, the catheter was threaded into a stainless steel spring arm. A stainless steel harness (E and H Engineering, Chicago) connected with a spring arm to protect the catheter and to allow the monkeys relative freedom of movement. The distal ends of each luman of the catheter were connected to two Cole Parmer peristaltic infusion pumps (No. 7540 X) located outside the experimental cubicle. The use of double-lumen catheters permitted separate delivery of different solutions without intermixing. The two lever boxes (15.2 cm × 12.7 cm × 10.8 cm) were mounted on the door of the cubicle, 20 cm from the floor and 10 cm from the center line. Each box contained a lamp panel (two colored GE a.c. bulbs) protected by clear Plexiglas above each lever (Lehigh Valley Electronics, 121–07). All counting, timing, switching and recording operations were accomplished with standard electro-magnetic relay equipment in an adjacent room.

Procedure

The animals were conditioned to self-administer cocaine or morphine under a second-order schedule of drug reinforcement. Initially the animals were trained under a simple ratio schedule (FR 10) of cocaine self-administration. After two weeks, an interval requirement was superimposed such that each FR 10 completed produced only a brief stimulus light of 2 sec duration over the cocaine lever. Responses on the morphine lever (unlighted) had no consequences but were recorded. The first FR 10 completed after the fixed interval had elapsed produced a drug infusion and the infusion light. Gradually the interval requirement was extended from 3 to 60 min. The final schedule condition was a second-order fixed interval sixty min, fixed ratio 10 of drug presentation, which can be written as second-order FI 60′ (FR 10: S) in the notation of Kelleher [15].

The specific steps in the shaping of the subjects were as follows. After catheterization, the animals were trained on a continuous reinforcement schedule (CRF) of cocaine infusions. In the presence of orange light above the cocaine lever, each lever response was followed by an infusion of 0.1 mg/kg of cocaine dissolved in 0.1 ml/kg of 0.9% NaCl. The rate of infusion was 1 ml/10 sec. During the infusion, the orange light turned off, and a white light was illuminated over the lever. Within a few days the response requirement was raised to 10 (FR 10). Each daily session was of 60 min duration. After two weeks, an FR 3′ was superimposed such that each FR 10 completed was followed by the onset of the infusion light (white light) alone for 2 sec without the cocaine infusion. After 3 min had elapsed, the first FR 10 completed was followed by the cocaine infusion (0.1 mg/kg) and the infusion light. At this phase of training, cocaine and morphine were alternated on a daily basis. A green stimulus light indicating that morphine was available (S^D) appeared over the morphine lever. The morphine infusion light was red. Separate lever boxes were used to minimize generalization of responding when drugs were alternated. At this stage, the dose of morphine was 0.01 mg/kg/injection while the rate of the infusion remained 1.0 ml solution/10 sec and the volume 0.1 ml/kg body weight. The maximum morphine intake could not exceed 0.2 mg/kg in a session. The fixed interval was gradually extended to 60 min with a 3 min limited hold. That is, the first complete emission of FR 10 after 60 min had elapsed was followed by the drug infusion. If a complete FR 10 was not emitted between 60 and 63 min from the start of the session, the lever lights went off and the session was terminated. The gradual extension of the FI progressed from 3′ to 5′ to 15′ to 45′ and finally to 60′. The time required to make these progressions varied for individual animals and was determined by the animal's performance in sessions of morphine presentation. As these interval requirements were increased, the concentation of morphine and duration of infusion were correspondingly changed such that the total morphine intake could not exceed 0.20 mg/kg. The final volume administered upon reaching the FI 60′ (FR 10:S) was 1.0 ml of drug solution per kg body weight infused over 50 to 60 sec (10 sec/kg body weight).

Changes in Magnitude of Morphine Reinforcement

When the FI 60′ (FR 10: S) was reached and performance was under schedule control as indicated by a typical scallop performance seen in the cumulative response record [5] and determined by the index of curvature to be a pattern of positive acceleration [7], then various doses of morphine (0.125, 0.25, 0.5 and 1.0 mg/kg) were systematically investigated. Each dose was kept constant for ten morphine sessions. On alternate days, cocaine was the reinforcer at a dose of 0.5 mg/kg which was held constant throughout the study. Note that a total of 20 sessions (20 days) were required before a change of morphine dose was made.

Saline Extinction

Saline was substituted for morphine for ten sessions. For reasons to be described in the results, cocaine alternation was discontinued, and saline extinction sessions were repeated for 10 consecutive sessions.

Addition of Graded Doses of Naloxone to the Morphine Solution

The following manipulations were performed on one animal (M4138). After repeating the saline extinction for 10 consecutive sessions, morphine-maintained responding was reinstated with a dose of 0.250 mg/kg/injection. To this dose of morphine (0.250 mg/kg) was added graded amounts of naloxone (0.0625 or 0.125 mg/kg). The volume of the morphine plus naloxone solution infused per session remained the same as the morphine alone: 1.0 ml/kg body weight infused over a duration of 60 sec. A given dose ratio of morphine to naloxone was tested each day for ten consecutive sessions. Observations for the presence of opiate abstinence signs (e.g., vomiting, salivation, diarrhea) were made following each session. It should be emphasized, that for each dose manipulation performed, ten consecutive sessions were run. When a dose ratio of morphine to naloxone was found which produced extinction on the morphine lever, then post-morphine infusions of naloxone were tested.

Postmorphine Infusions of Naloxone

Five min after the termination of the morphine infusion, a dose of naloxone shown to extinguish morphine-reinforced responding was infused through a separate lumen of the catheter in a volume of 1 ml saline in 15 sec. At the time the naloxone was infused, the one hour session had terminated, five min had elapsed since the termination of the morphine infusion and no stimulus lights were illuminated.

Addition of Graded Doses of Naloxone to the Cocaine Solution

To test for the specificity of the naloxone effect on reinforced responding, 10 consecutive sessions of cocaine (0.5 mg/kg) presentation were run followed by 10 sessions of cocaine plus naloxone (0.125 or 0.5 mg/kg) presentation.

Data Analysis

Response rates were computed as responses per minute (total number of responses in the session/60 min). The index of curvature was calculated using the method of Fry, Kelleher and Cook [7]. The 60 min interval was divided into 6 ten min bins and the index was computed from:

$$I = \frac{5R_t - 2\sum_{i=1}^{5} R_i}{6\,R_t}$$

where R_t = total number of responses in the 60′ interval
R_i = number of responses in a specific 10 min bin

Drugs

All doses refer to the salt of the drug used: morphine sulfate, cocaine hydrochloride and naloxone hydrochloride. Naloxone solutions were prepared freshly each week.

RESULTS

The representative cumulative response records (Fig. 1) illustrate the development of performances from those characteristic of simple ratio schedules to those generated by second-order FI 60′ (FR 10: S). The rapid, constant rate engendered by fixed ratio schedules was evident under the schedule condition of FI 10′ (FR 10: S) (Fig. 1a). The response rate, however, was decreasing as the hour progressed due to multiple morphine infusions within the session. By the time the final condition of FI 60′ (FR 10: S) was reached through the gradual extension of the interval to 60 min (Fig. 1b), the pattern of responding was similar to responding generated by a ratio schedule. This high, steady rate of responding was maintained by only one injection of morphine (0.125 mg/kg) at the end of each session. Following each presentation of the two second stimulus, there was a brief pause, then a resumption of lever responding. After 25 morphine sessions (50 days) on this same schedule, the pattern of responding began to assume the curvature characteristic of fixed interval schedules of reinforcement (Fig. 1c). At the start of the session, there was a pause followed by steadily increasing response rates (positive acceleration) and a progressive decrease in the duration of the pauses following each 2 sec light presentation. Towards the terminal part of the session, a high, constant rate of responding was emitted. Fig. 1d depicts the final performance generated by this schedule before changing dose of reinforcement. The pause from the start of the session to the first completion of the FR 10 was approximately 30 min; after that point the overall pattern of responding showed the positive acceleration characteristic of simple fixed interval schedules of reinforcement. Table 1 represents the development of response patterning characteristic of interval schedules when quantified by the index of curvature in 3 animals. An index of 0.0 would represent a constant rate of responding throughout the interval. A positive sign indicates a positive acceleration in response rate as the session progresses. If all responding were to occur in the last bin (of the 6 bins in the 60 min interval) the index would equal a maximum value of +0.83. For all 3 animals responding under this schedule, the rate of responding was positively accelerated, and after at least 30 morphine sessions, the index approached a stable value of +0.60 (Table 1). This index of curvature corresponds to the pattern of responding illustrated in Fig. 1d.

TABLE 1

INDEX OF CURVATURE

Morphine Sessions	M4138	M4139	M4140
1	+0.38	+0.24	+0.32
5	+0.33	+0.38	+0.24
10	+0.42	+0.39	+0.30
15	+0.36	+0.52	+0.38
20	+0.57	+0.58	+0.48
25	+0.59	+0.48	+0.30
30	+0.60	+0.59	+0.47
35	—	—	+0.56
40	—	—	+0.62

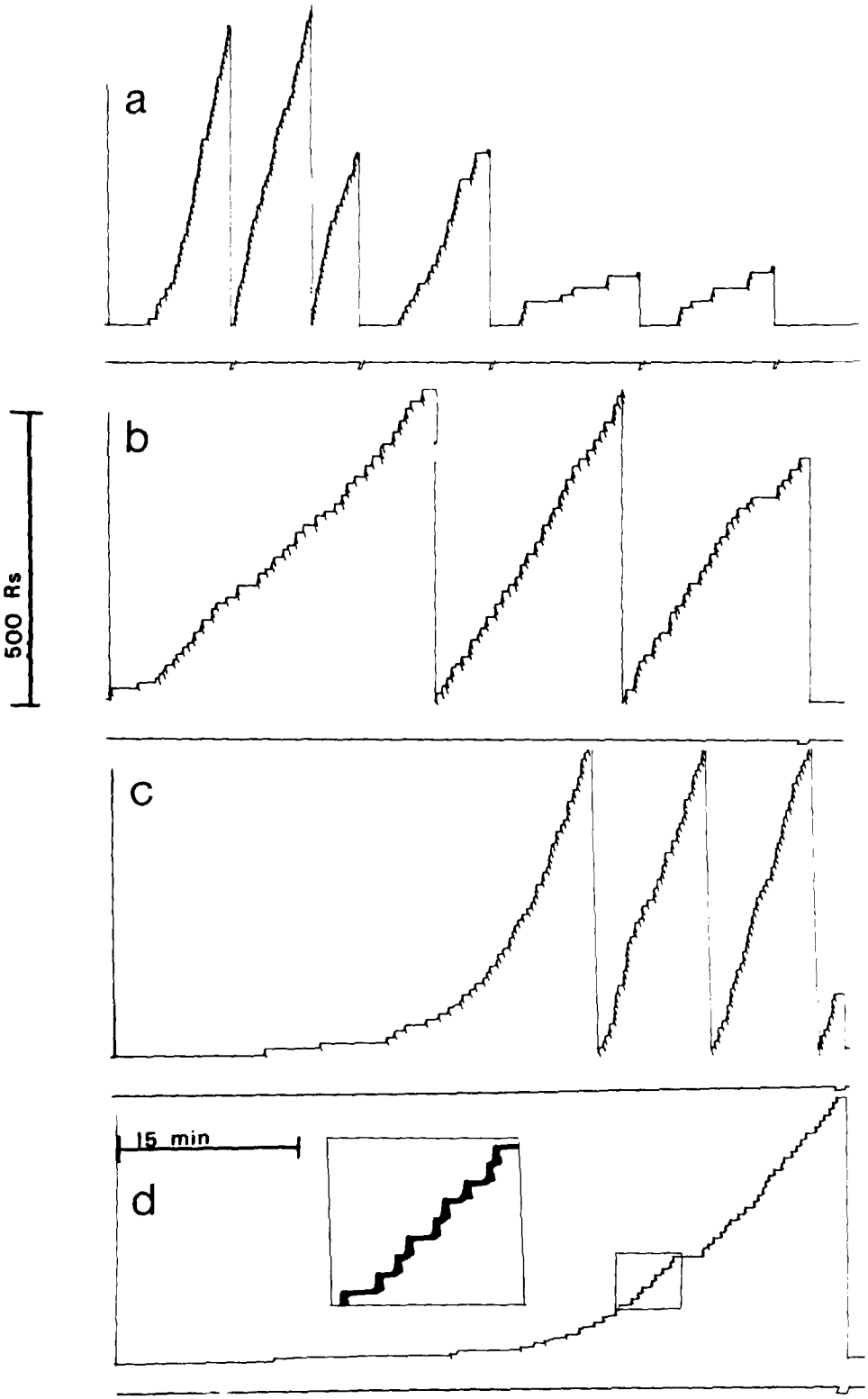

FIG. 1. Representative cumulative response records (from M4138) demonstrating the development of performance leading to the pattern generated by the second order FI 60′ (FR 10: S). Each session is of 60′ duration, with a 3′ limited hold. Each FR 10 completed is marked with a short diagonal slash representing the 2 sec stimulus infusion light alone. The event pen directly below the response record marks the onset and duration of the infusions. (a) The pattern of lever responding generated by FI 10′ (FR 10: S) of 0.035 mg/kg morphine reinforcement. (b) The attainment of the final condition, FI 60′ (FR 10: S). (c) The peformance generated under the same schedule conditions as in (b), but 25 morphine sessions later (or total of 50 days later). (d) The same schedule conditions as (b) and (c), but 8 morphine sessions later than (c). (Index of curvature + 0.60.) Inset depicts pauses after each brief stimulus presentation.

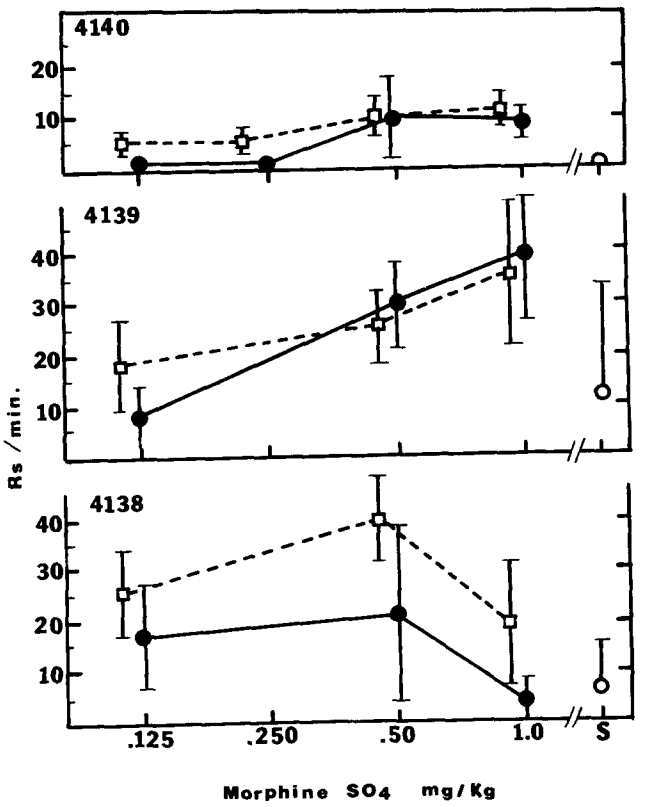

FIG. 2. Response rate plotted against the dose of morphine reinforcement for 3 animals: M4138, M4139, M4140. The ordinate scales the overall response rate (Rs./min). The abscissa scales the dose of morphine–SO_4 reinforcement in mg/kg. Each solid point represents the mean response rate of the last 3 morphine reinforced sessions; the brackets represent the range. Each square represents the mean response rate of the last 3 cocaine reinforced sessions and the brackets the range. The S represents the substitution of saline for morphine. The open circles represent the mean response rate of the last 3 saline substitution sessions and the brackets the range. Cocaine reinforced sessions alternated with morphine or saline sessions throughout all the above dose manipulations. The cocaine dose of reinforcement remained constant at 0.5 mg/kg.

When the dose of morphine per injection was varied in an ascending sequence, the response rates remained insensitive to the changes in morphine doses (0.125–1.0 mg/kg) in 2 of the 3 monkeys (Fig. 2). In one of the monkeys (M4139) there was some indication of a linear relationship between response rates and dose of morphine. However, there was considerable overlap in the range of responses engendered by all doses of morphine.

The response rates generated in the alternating sessions maintained by a constant dose of cocaine paralleled the response rates during sessions of morphine presentation in 2 of 3 monkeys (Fig. 2). In the third animal response rates during sessions of cocaine presentation were approximately twice the response rates generated during sessions of morphine presentation (0.5–1.0 mg/kg). When saline was substituted for morphine, only one of the 3 monkeys (M4140) ceased responding on the morphine lever. Since extinction of responding on the morphine lever was difficult to obtain when sessions of cocaine presentation were available every other day, alternation was ceased. Under these conditions, lever responding could readily be extinguished in all 3 animals by 10 consecutive sessions (Table 2).

TABLE 2

SALINE EXTINCTION, RESPONSES/MINUTE

Consecutive Sessions	M4138	M4139	M4140
1	44	6	0.5
2	8	3	12
3	33	33	6
4	32	21	0.5*
5	8	65	0.0*
6	21	46	8
7	17	43	2
8	12	0.5*	0.5*
9	5	0.0*	0.0*
10	0.5*	0.3*	0.0*

*indicates failure to self-administer the solution.

The following results were obtained from manipulations performed on one monkey (M4138). After morphine-reinforced responding was reinstated for 10 consecutive sessions with a dose of 0.25 mg/kg/injection, saline was again substituted for 10 consecutive sessions. Response rates decreased from the morphine baseline of 18.8 ± 4.9 to 11.1 ± 3.4 responses per minute (Table 3), a decrease of 41% (Fig. 3). When a mixture of morphine (0.25 mg/kg) and naloxone (0.0625 mg/kg) was presented there was a 29% decrease in response rates. Increasing the dose of naloxone to 0.125 mg/kg decreased responding to 2.7 ± 2.5 responses/min, a statistically significant decrease ($p<0.05$) of 86% from the morphine baseline (Fig. 3). However, the addition of up to 0.5 mg/kg of naloxone to the cocaine solution for 10 consecutive sessions failed to significantly change response rates. At no time following naloxone administration were opiate abstinence signs observed.

After reinstating morphine-reinforced responding with a dose of 0.25 mg/kg/injection, naloxone (0.125 mg/kg) was infused five min after the termination of the morphine infusion. Response rates increased to a mean of 24.6 ± 7.2 responses/min, an increase of 31% over morphine baseline (Fig. 3).

DISCUSSION

The results presented here demonstrate the capacity of single IV infusions of morphine (0.125–1.0 mg/kg) or cocaine (0.5 mg/kg) to maintain relatively high rates of responding within an hour long session. We confirm and extend the finding of Goldberg *et al.* [10] and Goldberg and Tang [11] that infrahuman primates would emit repeated sequences of rapid responding in a second-order FI 60′ (FR n: S) of morphine or cocaine presentation. The schedule used by Goldberg *et al.* [10] was identical to the one reported in the present paper with the following exceptions. In Goldberg's study, the shaping procedure differed considerably, the drugs were delivered intramuscularly, sessions were conducted only 3 times per week, and higher drug doses (up to 6.0 mg/kg/injection) were adminis-

TABLE 3

RESPONSES/MINUTE*

Morphine (0.25 mg/kg)	18.8 ± 4.9	Cocaine (0.5 mg/kg)	56.2 ± 8.0
Sal	11.1 ± 3.4		
Morphine (0.25 mg/kg) + Naloxone (0.0625 mg/kg)	13.4 ± 3.4		
Morphine (0.25 mg/kg) + Naloxone (0.125 mg/kg)	2.7 ± 2.5†	Cocaine (0.5 mg/kg + Naloxone (0.125 mg/kg)	46.1 ± 6.7
Morphine (0.25 mg/kg)	19.8 ± 3.8	Cocaine (0.5 mg/kg) + Naloxone (0.5 mg/kg)	51.8 ± 10.7
M 5′ → Nx (0.25 mg/kg) (0.125 mg/kg)	24.6 ± 7.2		

*mean ± SE of the overall response rates of last five sessions.
†statistically significant change ($p<0.05$) from morphine baseline using a one-tailed t-test.

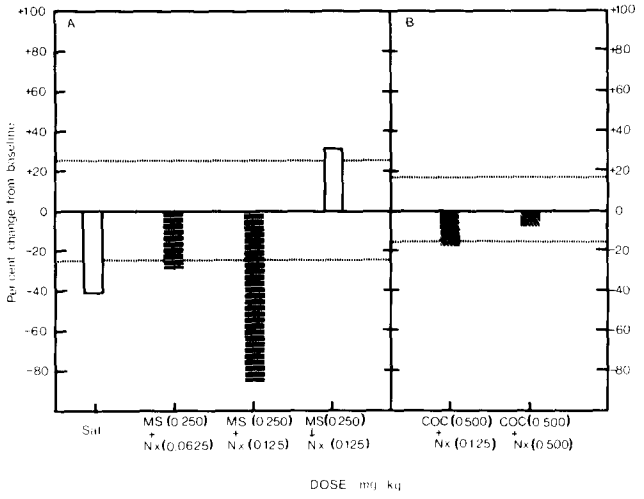

FIG. 3. A. Effects of the presentation of morphine and naloxone combinations on response rates (expressed as per cent change from control). The ordinate represents the per cent change from baseline morphine (0.25 mg/kg/injection) response rates. The horizontal dashed lines represent one standard error of the mean response rates of the last five sessions maintained by morphine alone (0.25 mg/kg/injection). The abscissa indicates the effects of the presentation of (from left to right) saline, morphine (0.25 mg/kg/injection) plus naloxone (0.0625 mg/kg/injection), morphine (0.25 mg/kg/injection) plus naloxone (0.125 mg/kg/injection), naloxone (0.125 mg/kg/injection) infused 5 min after the morphine (0.25 mg/kg/injection). B. Effects of the presentation of cocaine and naloxone combinations on response rates (expressed as percent of control). The abscissa indicates the presentation of cocaine (0.5 mg/kg/injection) plus naloxone (0.125 and 0.5 mg/kg/injection).

tered. The maximum response rates generated by IV administration of morphine or cocaine in the present report were approximately 2–3 times greater than response rates maintained by IM injections of morphine or cocaine under the similar schedule conditions employed by Goldberg *et al.* [10]. In the more recent study by Goldberg and Tang [11], morphine (in a dose up to 6.0 mg/kg) was self-administered intravenously by both rhesus and squirrel monkeys under a second-order FI 60′ (FR 30: S). Response rates generated under this schedule were comparable, though slightly higher to the rates generated in the present study. The slightly higher rates may be attributed to a higher ratio requirement (FR 30) and, in part, to the different species of monkey employed by Goldberg and Tang [11]. In the present study, extinction of responding on the morphine lever was achieved within 4 to 10 sessions by eliminating sessions of cocaine presentation. By contrast, extinction of responding maintained by IM injections was readily attained within 4 to 10 sessions without ceasing alternation with sessions of cocaine presentation [10]. When saline was substituted for IV morphine in the study by Goldberg and Tang [11], response rates decreased fairly rapidly (within five sessions). It should be pointed out that in that study, cocaine was not available on alternate days.

Despite these small differences, the results of Goldberg *et al.* [10] and Goldberg and Tang [11] are similar to those reported here in one important aspect; response rates maintained by either IV or IM routes of morphine or cocaine administration remained relatively constant across a wide range of doses tested. Although there were small increases in response rates as the dose of morphine was increased from 0.3 to 1.0 mg/kg/injection, dose increases from 1.0 to 6.0 mg/kg/injection failed to change response rates in either direction [11]. Similarly, in the present study, increases in morphine dose from 0.125 to 1.0 mg/kg/injection produced small increases in response rates in only one of three monkeys. The response rates in the remaining 2 monkeys bore no consistent relationship to the doses of morphine tested.

The absence of a graded, dose-dependent effect of morphine on response rates may be a result of the elimination of the direct rate-modifying effects of morphine on behavior. Rates of responding maintained by drug injections are determined not only by the capacity of the drug to reinforce behavior that preceded it but also by the direct effects of the drug on behavior that follows it [14]. Under simple schedules where multiple morphine or cocaine injections are self-administered, response rates bear a biphasic relationship to the dose per injection [3, 4, 12, 17, 19]. In most cases, response rates increase to a maximum as dose is increased. Further increases in dose lead to a decrease in response rates. Pretreatment with appropriate doses of morphine will produce dose-dependent suppression of schedule-controlled behavior in general [13, 16, 18]. Experimental attempts to separate the response-maintaining effects of a drug from its other pharmacological effects have imposed limits to drug intake by employing schedules where the frequency of drug injections is independent of response rates and where a timeout period (responses have no consequences) follows each injection [2, 8, 9, 10, 11, 14]. Under the second-order schedule employed in this study, drug infusions occurred only at the end of each session, and the drug could not directly act to suppress or interfere with lever responding. Moreover, drug presentations were 24 hr apart, long enough for any

disruptive effects on the following session to have dissipated. Balster and Schuster [2], by employing an FI 9′ schedule of cocaine self-administration with 15 min timeout following each injection, found the rate of responding increased as the cocaine dose was increased from 0.025 to 0.8 mg/kg/injection. In contrast, Dougherty and Pickens [3], using a FI 15′ schedule of cocaine self-administration without a timeout period after each injection, reported that the rate of responding decreased as the dose of cocaine was increased. Clearly, the imposition of a timeout allowed time for metabolism of the drug to take place and minimized the response-rate suppressant effects of the drug.

In studies where the response-maintaining effects of a drug were measured by variables other than response rate, i.e., two lever choice procedures, higher doses of cocaine were preferred to lower doses [14]. However, when both doses of cocaine were greater than 0.5 mg/kg/injection, no preference for responding on one lever over the other was shown [14]. These results suggest that beyond a certain dose level, the capacity of a drug to serve as a reinforcer remains constant or becomes aversive. The flat dose-response curves obtained using second-order schedules of drug self-administration are consistent with these results and support the hypothesis that the absence of a graded, dose-dependent effect of morphine on response rates may simply be a result of the elimination of the depressant component of morphine action on behavior.

Another factor which plays an important role in maintaining behavior in the second-order schedule employed in this study is the 2 sec stimulus presented after every 10 responses emitted by the monkey. The presentation of a stimulus intermittently associated with reinforcement has been shown to enhance performance in components of an extended sequence of schedules such as chained schedules [6] or second-order schedules [8, 9, 10, 11, 15]. Goldberg and Tang [11] have reported that omission of the brief light presentation following each FR component resulted in a decrease in response rates and in a loss of the FR pattern of responding within 3 days. When saline injections were substituted for morphine, but the brief light continued to be presented following each FR, responding decreased to very low rates. Thus, the brief light is important in controlling the ratio pattern of responding, but it is not sufficient to maintain behavior in the absence of the drug. Kelleher [15], in his analysis of the role of conditioned reinforcers in food maintained second-order schedules, found that the amount of food paired with a stimulus did not alter the effectiveness of the stimulus in maintaining behavior, at least not over the range of values utilized in that study.

Despite the insensitivity of response rates to morphine dose manipulations under second-order schedules, it was found that naloxone (0.125 mg/kg) antagonized the reinforcing effects of morphine (0.25 mg/kg). Similar results were reported by Woods *et al.* [20] who found that response-contingent delivery of a mixture of codeine and naloxone in monkeys conditioned to self-administer codeine under a FR 1 schedule of reinforcement resulted in suppression of responding. In the present study, infusion of naloxone (0.125 mg/kg) five min after the termination of the morphine infusion failed to decrease response rates. It appeared that 5 min of morphine action presented each day was sufficient to maintain behavior over 10 consecutive sessions. The actions of morphine that occurred after the effects of naloxone had dissipated cannot have been consequential in maintaining behavior since simultaneous presentation of morphine and naloxone in the same dose ratio suppressed response-rates. This strongly suggests that it was the effects of morphine which occurred within five min following the infusion that served as the reinforcing event. The longer term effects of morphine, i.e., analgesia or relief of abstinence distress, cannot be invoked as explanation of morphine reinforcement in this situation.

The observation that the morphine and naloxone mixture decreased response rates to a greater degree than saline substitution (Fig. 3), may have two explanations. First, the animal had several experiences with the extinction by the time the naloxone mixture was presented. Second, the mixture may have been more than a neutral solution, and may have served as a punishing event. In this context, the failure of naloxone to suppress behavior when infused five min after the termination of the morphine infusion can be understood as an effect of the delay of punishment. It is known that as the time between the presentation of the punishing stimulus and the behavior to be suppressed increases, the effectiveness of the punishing stimulus is diminished. In other words, the most effective punishment follows immediately the behavior to be suppressed [1]. Since the simultaneous administration of cocaine and naloxone did not suppress or alter the pattern of responding, it can be concluded that the effects of naloxone were specific to behavior maintained by morphine presentation. Regardless of the interpretation (extinction or punishment), the fact remains that morphine acting alone for 5 min was sufficient to maintain self-administration behavior, in contrast to the inability of a mixture of morphine and naloxone to maintain behavior. However, IM injections of morphine, with slower onset of action, will also maintain behavior under similar schedule conditions. Clearly, the immediate onset and brief time course of a drug effect is a sufficient but not necessary condition for a drug to serve as a reinforcer of behavior. It should be pointed out that the results on morphine and naloxone interaction were based on data derived from one animal, and as such the generality of this phenomenon remains to be demonstrated. Nevertheless, pharmacological interventions at various times following delivery of reinforcing drugs may help identify the biochemical and physiological components of drug action which maintain or suppress behavior under the control of second-order schedules.

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