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Effects of Heroin, Methadone, LAAM and Cyclazocine on Acquisition and Performance of Response Sequences in Monkeys[1]

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MOERSCHBAECHER, J. M., D. M. THOMPSON AND P. J. WINSAUER. *Effects of heroin, methadone, LAAM and cyclazocine on acquisition and performance of response sequences in monkeys.* PHARMACOL BIOCHEM BEHAV 19(4) 701–710, 1983.— In each of three components of a multiple schedule, monkeys were required to emit a different sequence of four responses in a predetermined order on four levers. Sequence completions produced food on a fixed-ratio schedule. Errors produced a brief timeout. One component of the multiple schedule was a repeated-acquisition task where the four-response sequence changed each session (learning). The second component of the multiple schedule was also a repeated-acquisition task, but acquisition was supported through the use of a stimulus fading procedure (faded learning). In a third component of the multiple schedule, the sequence of responses remained the same from session to session (performance). At high doses, each drug tested produced essentially the same effect. In all three components, response rate was substantially decreased and percent errors increased. At lower doses, however, their effects differed. Heroin and methadone produced dose-dependent sporadic periods of pausing, but had little or no effect on the accuracy of responding. LAAM also produced sporadic periods of pausing, but its effects on accuracy were variable. In contrast, cyclazocine produced no such pauses in responding but rather decreased the local rates of correct responding in a dose-related manner. These same doses of cyclazocine increased percent errors in the learning component, but not in the faded learning or performance components. The results are generally consistent with the view that putative mu opioid agonists do not affect the accuracy of a discrimination in monkeys except at those doses which produce a substantial decrease in the overall rate of responding.

Repeated acquisition Performance Multiple schedule Heroin Methadone LAAM Cyclazocine Lever press Monkeys

THERE have been numerous studies of the effects of morphine and morphine-like opioids, such as heroin, methadone and LAAM, on rate of responding maintained under various schedules of food presentation (see [5] for review). While small rate-increasing effects have on occasion been obtained (e.g., [4,12]), in general these drugs have been found to produce only dose-related decreases in the overall rate of responding in various species [1, 3, 4, 11, 12, 14]. In contrast, relatively few studies have reported the effects of these same drugs on the accuracy of a discrimination. The results of the few such studies have been mixed, and no clear generalization concerning the effects of these drugs can be made. For example, in rats morphine has been reported to produce dose-related decreases in both rate of responding and the accuracy of a discrimination [6]. In a pigeon study, Thompson, Glenn, Winston and Young [22] investigated the effects of methadone on both simple and conditional discriminations. They found that while response rates were decreased, the shape of a simple generalization gradient was unaffected by chronic methadone administration at doses ranging from 9 mg/kg/day to 90 mg/kg/day. Similarly, across this same range of doses, using a conditional discrimination procedure they found that while response rates were decreased, neither the overall accuracy of responding nor the shape of a generalization gradient was affected. In the pigeon the effects of morphine appear to be comparable to those obtained with methadone. For example, McMillan [3] investigated the effects of morphine on the accuracy of delayed matching-to-sample performance at several different delay durations (1–8 sec). At doses less than 3 mg/kg mor-

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phine had no effect on either accuracy or on running rate at any of the delay values studied. Only following a dose of 3 mg/kg at the 4 sec delay did morphine produce small decreases in accuracy. This effect was accompanied by a decrease in running rate. Using the repeated acquisition of behavioral chains as a baseline, Thompson and Moerschbaecher [21] reported that at low doses (e.g., 1.7 mg/kg) morphine produced small but reliable decreases in accuracy. However, at higher doses (e.g., 3–5.6 mg/kg) which produced a substantial decrease in overall rate of responding, errors were clearly increased. Thus, in the pigeon it would appear that morphine and morphine-like drugs (e.g., methadone) produce little or no effect on accuracy until doses are reached which produce a substantial decrease in the overall rate of responding. In general, in monkeys the effects of morphine appear to be similar [17,24]. For example, Moerschbaecher and Thompson reported that, across a range of doses which decreased response rates, morphine had no effect on accuracy of either the acquisition or the performance of conditional discriminations in patas monkeys. Only at higher doses (i.e., 1–1.8 mg/kg) which produced marked decreases in response rate was accuracy decreased.

It has been proposed that variations in stimulus control may function as a determinant of a drug's effect on behavior [10,20]. Inasmuch as previous studies have all involved discrimination procedures in which the discriminative stimuli were explicitly programmed, it may be that relatively strong control by such stimuli attenuated the effects of morphine on accuracy. The purpose of the present study therefore was to characterize in monkeys the effects of morphine-like drugs on responding under a procedure where there were no programmed discriminative stimuli for "correct" responding. A multiple schedule of repeated acquisition and performance of tandem response sequences was chosen for study because there are no programmed changes in the stimulus conditions during each sequence under this procedure. In addition, accuracy of responding under this procedure has previously been demonstrated to be sensitive to drugs [15]. Three morphine-like agonists, heroin, methadone and LAAM, were chosen for study. In addition the mixed agonist-antagonist cyclazocine was tested as a comparison drug.

METHOD

Subjects

Two adult female patas monkeys served. Both subjects had experimental histories involving the repeated acquisition of behavioral chains. Each subject was maintained at about 85% of its free-feeding weight (5.75 and 6.2 kg) on a diet consisting of Noyes banana-flavored food pellets, Purina Monkey Chow, fruit, and vitamins. The pellets were either earned during the experimental session or, when necessary, provided after the session. Monkey chow, fruit, and vitamins were given to each subject after the daily session. Water was continuously available.

Apparatus

Each subject was housed in a primate cage (Research Equipment Co., model LC-1004) measuring 76.2 cm by 71.1 cm by 96.5 cm. The bars were removed from one side of the cage and replaced with an aluminum panel. An array of four recessed levers (C.P. Clare Co., model C10647) was aligned horizontally to the left of the vertical midline of the panel. The levers were spaced 4 cm apart, center to center, and were 45 cm above the cage floor. Each lever required a minimum force of 0.98 N for activation. A relay mounted behind the panel clicked when any one of the four levers was pressed. An in-line projector (BRS/LVE, Model IC 901-696), mounted 4 cm above each lever, was used to project the different stimuli (colors). An additional lever, which operated the pellet dispenser, was mounted 11 cm to the right and 6 cm up from the center of the right-hand lever. A green pilot lamp (No. 1820) was mounted 6 cm below the food lever. A pellet aperture (8 cm by 8 cm) was located 3 cm to the right from the center of the food lever. The remaining devices (i.e., levers, stimulus lamps, water dispenser) that were mounted on the panel were not used during the present experiment. Solid-state scheduling and recording equipment was located in an adjacent room.

Procedure

Baseline. The baseline procedure consisted of a three-component multiple schedule. In each component the subject was required to emit a different sequence of four responses in a predetermined order on the four recessed levers. A different stimulus (red, blue, or green) was projected above the levers during each component. Within a component, however, the stimulus over the levers did not change; i.e., there was a tandem four-response sequence in each component of the multiple schedule. Following each completion of the four-response sequence, the stimuli over the levers were turned off and the green pilot lamp under the food lever was illuminated. A press on the food lever then operated the pellet dispenser. The food-pellet reinforcer (500 mg), however, was delivered after every second completion of the sequence (i.e., responding was maintained under an FR 2 schedule). This was accomplished by simply plugging every other delivery hole in the dispenser. Following operation of the dispenser, the green pilot lamp was turned off, the sequence reset, and the stimuli above the four levers were turned on. When the monkey pressed an incorrect lever (e.g., a press on lever 2 when lever 4 was correct), the error produced a 5-sec timeout. During the timeout, all stimuli were off and responses had no scheduled consequences. An error did not reset the sequence.

Components of the multiple schedule changed after the completion of 40 sequences (20 reinforcements) or 15 min, whichever occurred first. A 5-sec blackout separated each component change. The components occurred in the following order each session: learning, performance, faded learning, learning, performance, faded learning, etc. A daily session terminated after 180 reinforcements or 3 hr, whichever occurred first.

In the *performance* component of the multiple schedule, the sequence of correct responses was the same each session: lever 3, lever 1, lever 2, lever 4; food under the FR 2 schedule. During this component the stimulus over each of the four levers was blue for Monkey C and red for Monkey F. In the *learning* component of the multiple schedule, the four-response sequence was changed from session to session (repeated acquisition). During each session the monkey's task was to acquire a different four-response sequence by pressing the four levers in a particular order. For example, during one session the correct sequence of lever presses was 4-3-1-2, while during the next session the correct sequence was 3-2-4-1. The stimuli during this component were red for Monkey C and blue for Monkey F. The *faded-learning* component of the multiple schedule also consisted of a

repeated-acquisition task, where the four-response sequence changed each session. Acquisition in this component, however, was supported through the use of a stimulus-fading procedure. In the first step of the fading procedure, only the stimulus lamp over the correct lever was fully illuminated at each sequence position, while the lamps over the incorrect levers were off. In subsequent steps the luminance levels of the lamps over the incorrect levers increased, until at the final step the lamps over all four levers were fully illuminated. There was a total of eight steps in the stimulus-fading procedure which titrated under the following conditions: Completion of a correct sequence advanced the fading level one step; every fourth error within a single sequence decreased the fading level one step. A component change did not affect the fading level. For example, if the subject finished the first faded-learning component at step five, the next faded-learning component would resume with the fading level at step five. For each of the two acquisition components, different sequences were carefully selected to be equivalent in several ways and there were restrictions on their ordering across sessions (cf., [15]).

The data for each session were analyzed in terms of (a) the overall response rate (total responses/min, excluding timeouts) in each component and (b) the overall accuracy or percent errors [(errors/total responses) × 100] in each component. In addition to these measures based on session totals, within-session changes in responding were monitored by a cumulative recorder. For example, acquisition of the response sequence in each learning component was evidenced by a reduction in the frequency of errors as the session progressed.

Drug testing. Before drug testing began, the multiple-schedule baseline was stabilized. The baseline was considered stable when the response rate and percent errors in each component no longer showed systematic change from session to session. After baseline stabilization (30 to 40 sessions), dose-effect data were obtained for heroin (3,6-diacetyl-morphine) hydrochloride, methadone hydrochloride, LAAM (l-alpha-acetyl-methadol) hydrochloride, and cyclazocine (base) in that order. Cyclazocine was dissolved in three parts of 8.5% lactic acid and two parts 1 N sodium hydroxide. Heroin, methadone, and LAAM were dissolved in 0.9% sterile saline. Drug and control (saline or vehicle) injections were given IM (*gluteus m.*) either 15 min (heroin and cyclazocine), 30 min (methadone), or 60 min (LAAM) presession. These times were chosen on the basis of preliminary studies conducted in monkeys and/or on the basis of previously published studies [2, 3, 17, 24]. The volume of injection for LAAM was 0.2 ml/kg body weight, while for the other drugs it was 0.05 ml/kg body weight. The doses (expressed in the forms described above) of each drug were tested in a mixed order. At least two weeks of baseline sessions intervened between the end of a series of injections with one drug and the start of a series with another. LAAM was administered only once a week on Wednesday, with control injections on Tuesday. For the other compounds, drug sessions were generally conducted on Tuesdays and Fridays, with control injections on Thursdays. At the higher doses, however, drug injections were given only once a week.

RESULTS

Effects of Heroin

The effects of heroin on rate of responding and percent errors in each component of the multiple schedule are shown for each subject in the dose-effect curves of Fig. 1. In both monkeys, heroin produced only dose-related decreases in the overall rate of responding. While Monkey F tended to be slightly more sensitive to the rate-decreasing effects of heroin than was Monkey C, there was little evidence that heroin selectively decreased rates between components of the multiple schedule in either subject. The only instance where a selective effect on rate was clearly evident was at the 0.056 mg/kg dose in Monkey F. In each of the three components of the multiple schedule heroin had no effect on percent errors except at those doses which also produced substantial decreases (i.e., less than 20 responses per min) in the overall rate of responding in that same component. This was generally true for both monkeys. For example, in Monkey F the 0.056 mg/kg dose increased errors and decreased rate in the learning component. In the faded learning and performance components this same dose produced small decreases in response rate but had no effect on errors. Higher doses (0.32–0.56 mg/kg) of heroin decreased rate and increased errors in each component of the multiple schedule in both monkeys. In summary, heroin generally increased percent errors only at those doses which produced large decreases in response rate; at lower doses rate was generally decreased while accuracy was unaffected.

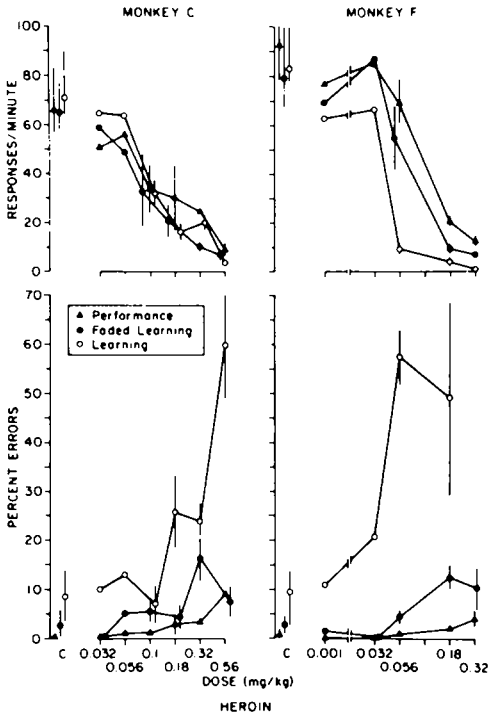

FIG. 1. Effects of varying doses of heroin on the overall response rate and percent errors in each component of the multiple schedule for each subject. The mean and range (vertical lines) of 7 saline control sessions (C) are shown at the left of each dose-effect curve. For each curve, the mean and range (vertical lines) for two determinations are shown. The data points shown without a range represent a single determination at that dose or an instance in which the range was encompassed by the data point. For monkey F no data point is shown for percent errors in the learning component at the 0.32 mg/kg dose since virtually no responses were made.

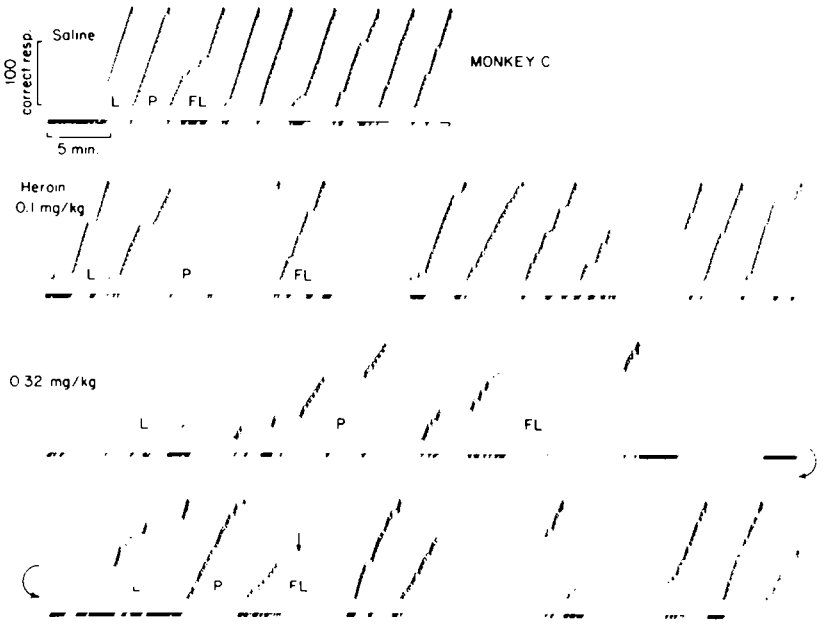

FIG. 2. Cumulative response records for monkey C showing the pattern of responding during a control session (saline) which approximated the mean for both percent errors and response rate, and during two sessions preceded by injections of heroin. The learning (L), performance (P) and faded learning (FL) components occurred in the same order throughout the session. The response pen stepped upward with each correct response and was deflected downward each time the four-response sequence was completed. Errors are indicated by the event pen, which was held down during each timeout. A change in components of the multiple schedule reset the stepping pen. The event pen was also displaced downward during the delay that separated a component change. Due to an apparatus failure, the components did not change on the basis of time on two occasions in the lower records. The arrow in the bottom record indicates a period of approximately 6.5 min which was omitted and during which no responses were made.

A cumulative response record for a session which was preceded by a saline injection is shown for Monkey C at the top of Fig. 2. The session began in the learning component (L), then changed to the performance component (P), which was then followed by the faded-learning component (FL). This order (L-P-FL) was the same throughout the session. Notice that the greatest number of errors (event pen) occurred in the learning component and the fewest in the performance component. Although errors decreased as the session progressed in both the learning and faded-learning components, fewer errors were made in acquiring the sequence with the fading procedure. By the end of the session (last three excursions of the response pen), the rates of correct responding in each of the three components were similar, though a few errors still occurred in the learning component. In comparison to saline, the major effect of the 0.1 mg/kg dose of heroin was to decrease overall rate of responding. As can be seen in the cumulative record, this was primarily due to sporadic pauses in responding which occurred in each of the components of the multiple schedule. As is also evident in the cumulative record, this same dose had little effect on the within-session distribution of errors. The disruptive effects of heroin on responding were more pronounced at the 0.32 mg/kg dose (lower records). In comparison to the 0.1 mg/kg dose, the frequency of pauses in responding was increased. In addition, in comparison to the saline record the local rates of correct responding were also decreased in each of the components and the within-session distribution of errors was also affected at this dose. In the learning component the frequency of errors was increased during the first two cycles of the multiple schedule. Note that in both the learning and faded-learning components there were instances where the subject would complete several sequences without an error, as if the sequence had been acquired. This cohesive run of correct responses would then abruptly change to a pattern of responding where errors again predominated. This biphasic pattern of responding is most evident in the first learning component that is shown in the bottom record of Fig. 2. Though the doses varied slightly, the within-session effects of heroin were similar for Monkey F.

Effects of Methadone

Generally, the effects of methadone on overall rate of responding and percent errors were similar to those of heroin. These data are shown in Fig. 3. In both subjects, response rate in each component of the multiple schedule decreased with increasing doses of methadone. There was little evidence of selective rate-decreasing effects between components of the multiple schedule in either monkey. Like heroin, at the lower doses methadone decreased response

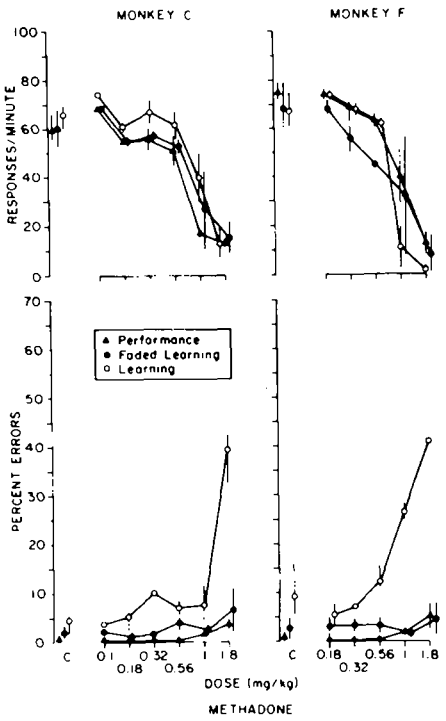

FIG. 3. Effects of varying doses of methadone on the overall response rate and percent errors in each component of the multiple schedule for each subject. The mean and range (vertical lines) of either 7 (monkey C) or 6 (monkey F) saline control sessions (C) are shown at the left of each dose-effect curve. Other details are the same as in Fig. 1.

rates but had no effect on percent errors in any of the schedule components. The small increase in errors in the learning component for Monkey C at the 0.32 mg/kg dose constitutes the single exception to this finding. At the higher doses (1 and 1.8 mg/kg) percent errors in any given component of the multiple schedule were increased only when response rate in that same component was substantially decreased (20 responses/min). For example, at the 1 mg/kg dose in Monkey F, response rate was decreased and errors increased in the learning component. In the faded learning and performance components, however, the rate-decreasing effects of methadone were attenuated and percent errors were unaffected. The highest dose tested (1.8 mg/kg) produced large decreases in response rate and increased percent errors in each component in both monkeys.

The effects of methadone on the within-session pattern of responding are shown for Monkey C in Fig. 4. In comparison to saline the 1 mg/kg dose of methadone produced sporadic pauses in responding, primarily in the learning and performance components. This pattern of sporadic pausing is similar to that obtained with heroin at intermediate doses (see Fig. 2, 0.1 mg/kg). As was stated previously (see Procedure), when the subject completed the four-response sequence the stimuli over the levers were turned off and a green pilot lamp under the food lever was illuminated. This lamp signalled food availability since when it was illuminated a press on the food lever operated the pellet dispenser. While the green "food" lamp was illuminated, the stepping pen on the cumulative recorder was deflected down. Note that many of the pauses in responding produced by methadone occurred in the presence of this stimulus. For example, in the first cycle of the multiple schedule, most of the pauses in responding during the performance component occurred in the presence of the food light. While the within-session distribution of errors in the faded-learning and performance components was generally unaffected, there was, in comparison to saline, a small increase in errors at the beginning of each learning component. At the 1.8 mg/kg dose methadone virtually eliminated responding in each component during the first hour of the session. During approximately the last hour of the session (bottom record), the rate of correct responding was decreased in both the faded-learning and performance components. Little or no responding occurred during the learning component until the last cycle of the multiple schedule. During this cycle, errors were increased substantially and there was virtually no indication of acquisition until nearly the end of the component where a slight acceleration in the rate of correct responding was evident. Methadone produced similar within-session effects on both the distribution of errors and rate of responding (i.e., sporadic pausing) in Monkey F, though this subject never paused in the presence of the food stimulus.

Effects of LAAM

The effects of LAAM on rate of responding and percent errors in each component of the multiple schedule are shown for each subject in the dose-effect curves of Fig. 5. At low doses (1–1.8 mg/kg) LAAM had no effect on the overall rate of responding in Monkey F. Small rate-increasing effects were occasionally obtained in Monkey C at these doses. At the 3.2 and 5.6 mg/kg doses, response rates in each component decreased in a dose-related manner in each subject. The effects of LAAM on accuracy (i.e., percent errors) were variable both between and within monkeys. In Monkey C, doses of 1.8 and 3.2 mg/kg increased percent errors in the learning component. While these increases were not accompanied by any substantial reductions in response rate in the same component, it should be noted that the increases in percent errors were relatively small and did not always replicate. A similar effect can be seen, in a few instances, in the data of Monkey F (e.g., 1 mg/kg dose). At the highest dose tested (5.6 mg/kg) LAAM increased percent errors in each component of the multiple schedule in each monkey. This effect was similar to those obtained with both heroin and methadone, in that the error-increasing effects were accompanied by substantial decreases in the overall rate of responding. At the higher doses each of the three drugs produced comparable rate-decreasing effects. However, in both monkeys the maximum increase in percent errors produced by LAAM was less than that produced by either methadone or heroin.

The within-session effects of LAAM are shown for Monkey C in Fig. 6. The 3.2 mg/kg dose of LAAM decreased the overall rate of responding primarily because of sporadic pauses in responding during each of the three components. This effect is similar to that obtained with both heroin (Fig. 2, 0.1 mg/kg) and methadone (Fig. 4, 1 mg/kg). Note that these pauses in responding occurred almost exclusively in the presence of the green "food" light. In addition, the local rates of responding were also slightly decreased at this dose. Other than a small increase in the frequency of errors during the first learning component there was little effect on the within-session distribution of errors. At the 5.6 mg/kg dose a

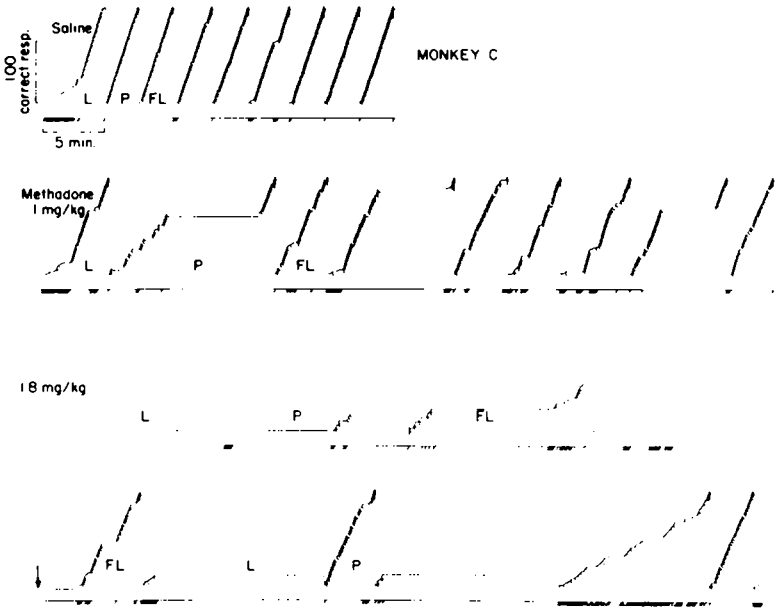

FIG. 4. Cumulative response records for monkey C showing the pattern of responding during a control session (saline) which approximated the mean for both percent errors and response rate, and during two sessions preceded by injections of methadone. At the 1.8 mg/kg dose only the first and third hours of the session are shown. The arrow indicates the beginning of the third hour. The recording details are the same as in Fig. 2.

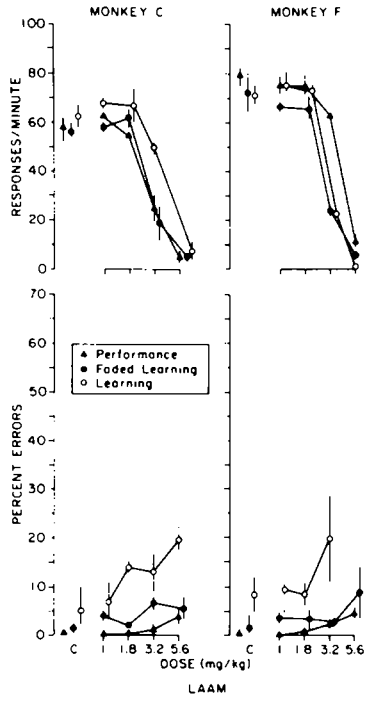

FIG. 5. Effects of varying doses of LAAM on the overall response rate and percent errors in each component of the multiple schedule for each subject. The mean and range (vertical lines) of either 5 (monkey C) or 6 (monkey F) saline control sessions (C) are shown at the left of each dose-effect curve. For monkey F no data point is shown for percent errors in the learning component at the 5.6 mg/kg dose since virtually no responses were made. Other details are the same as in Fig. 1.

similar effect was evident during the first hour of the session. During this time sporadic pausing occurred primarily in the presence of the green "food" light, while there was little or no effect on either the distribution or frequency of errors. During approximately the last hour of the session (bottom record) the pauses were longer and few responses were made other than those which occurred shortly following a change in the component of the multiple schedule. Based upon this finding it would appear that LAAM may not have been approaching its peak effect until approximately three hours after its injection. Similar within-session effects were obtained in Monkey F, though again this subject never paused in the presence of the green lamp.

The effects of various doses of LAAM were also investigated 24 hr following their administration. In both monkeys, small rate-increasing effects were evident in the learning component at doses ranging from 1–3.2 mg/kg. Rate of responding in the other components was generally unaffected at these same doses. Similarly, these doses had virtually no effect on accuracy in any of the components. The 5.6 mg/kg dose, however, produced substantial decreases in overall response rate and increased percent errors in each component of the multiple schedule in both subjects. In summary, these data suggest that at low to intermediate doses (1-3.2 mg/kg) the disruptive effects of LAAM on the acquisition and performance of a discrimination are most apparent during the first 24 hr following its administration. At higher doses (5.6 mg/kg), however, these disruptive effects of LAAM persist and can be easily detected after 24 hr (not shown).

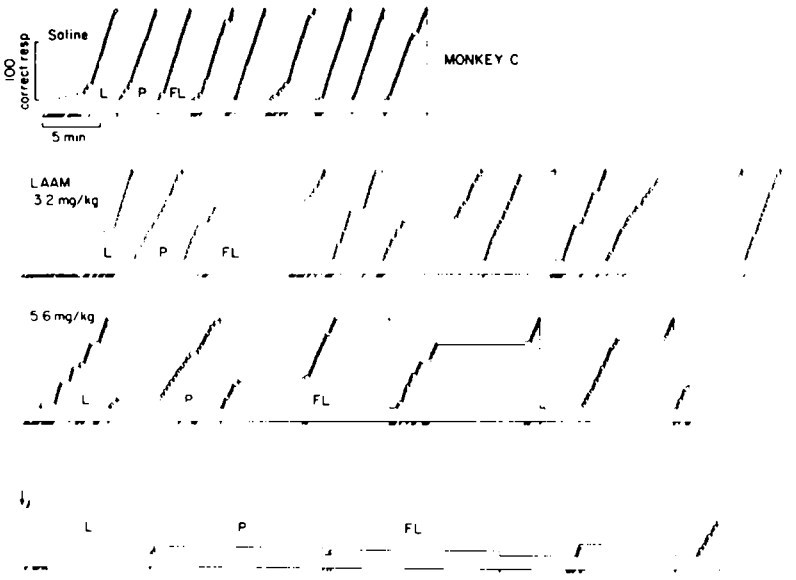

FIG. 6. Cumulative response records for monkey C showing the pattern of responding during a control session (saline) which approximated the mean for both percent errors and response rate, and during two sessions preceded by injections of LAAM. At the 5.6 mg/kg dose only the first and third hours of the session are shown. The arrow indicates the beginning of the third hour. The recording details are the same as in Fig. 2.

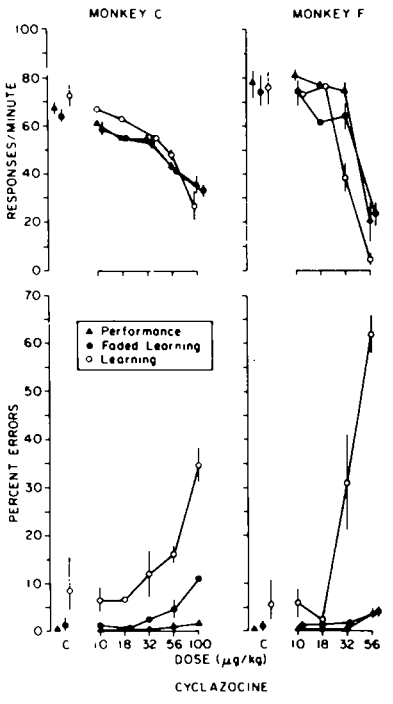

FIG. 7. Effects of varying doses of cyclazocine on the overall response rate and percent errors in each component of the multiple schedule for each subject. The mean and range of 7 vehicle control sessions (C) are shown at the left of each dose-effect curve. Other details are the same as in Fig. 1.

Effects of Cyclazocine

The dose-effect curves for cyclazocine are shown for each subject in Fig. 7. In both monkeys cyclazocine produced only dose-related decreases in overall response rate. For Monkey C, there were no systematic differential rate-decreasing effects between components of the multiple schedule. In Monkey F, however, the greatest rate-decreasing effects tended to occur in the learning component. Cyclazocine also increased percent errors in a dose-related manner. A selective error-increasing effect was obtained in Monkey F at the 32 μg/kg dose. Errors were increased in the learning but not in the faded-learning or performance components. At the highest dose tested in each subject errors were increased in each component of the multiple schedule. Finally, note that in both monkeys certain doses of cyclazocine (e.g., Monkey C, 100 μg/kg; Monkey F, 32 μg/kg) increased errors in the learning components while producing smaller decreases in overall response rate than did the other drugs tested.

The within-session effects of cyclazocine for Monkey C are shown in Fig. 8. At the 56 μg/kg dose, rate of correct responding was slightly decreased in each of the components. As is evidenced by the cumulative record, however, this dose produced no pauses in responding, but rather decreased the local rate. Other than a large increase in the frequency of errors in the first learning component, this dose had little effect on the within-session distribution of errors. The 100 μg/kg dose of cyclazocine produced even greater decreases in the local rates of correct responding but did not produce any noticeable pausing. The frequency of errors was substantially increased in both the faded-learning and learning components during the first two cycles of the mul-

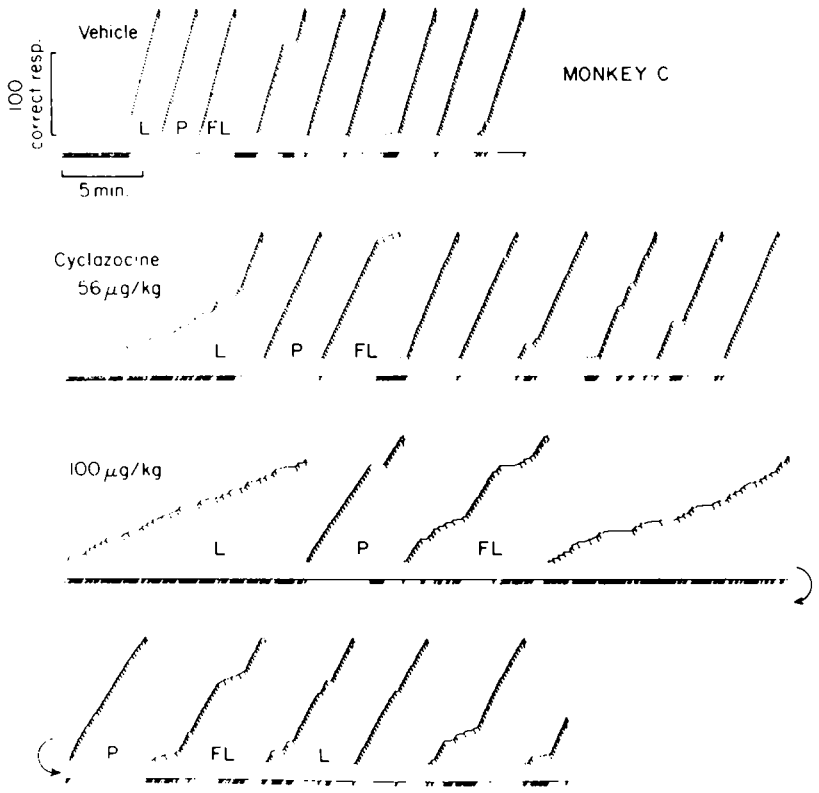

FIG. 8. Cumulative response records for monkey C showing the pattern of responding during a control session (vehicle) which approximated the mean for both percent errors and response rate, and during two sessions preceded by injections of cyclazocine. The recording details are the same as in Fig. 2.

tiple schedule. There was virtually no evidence of acquisition of the sequence in the learning component until the third cycle of the multiple schedule (bottom record). The within-session effects of cyclazocine in Monkey F were similar, though the doses varied slightly. The only instance of pausing in this subject was following the administration of the 56 μg/kg dose, where the subject failed to respond for approximately the first hour of the session. There was, however, no subsequent pausing once the subject began to respond.

In summary, the within-session effects of cyclazocine differed from those produced by heroin, methadone, and LAAM. At doses which produced approximately equivalent overall rate-decreasing effects (25–40 responses/min) heroin (Fig. 2, 0.1 mg/kg), methadone (Fig. 4, 1 mg/kg), and LAAM (Fig. 6, 3.2 mg/kg) each produced sporadic pauses in responding, while cyclazocine (Fig. 8, 56 and 100 μg/kg) only decreased the local rates. In addition, at these same doses cyclazocine generally produced a larger error-increasing effect and a greater disruption of the within-session distribution of errors than any of the other drugs tested.

DISCUSSION

In general each of the drugs tested produced only dose-dependent decreases in the overall rate of responding. These decreases occurred in each component of the multiple schedule; there was little evidence of differential rate-decreasing effects between components. These data are consistent with previous reports of the effects of these same drugs on rate of responding maintained under both simple schedules of food presentation and other discrimination procedures [1, 2, 3, 4, 6, 11, 12, 14, 22]. While the effects of each of these drugs on overall rate of responding were essentially the same, there were some differences in terms of their effects of the pattern of responding within the session. The mu agonists, heroin, methadone and LAAM, each produced sporadic periods of pausing. Both the frequency and duration of these pauses tended to increase with increasing doses of drug (Figs. 2, 4 and 6). These sporadic periods of pausing contributed substantially to the overall decreases in rate which were obtained with each of these drugs. In contrast, the mixed agonist-antagonist cyclazocine produced no such pauses in responding; rather it decreased the local rates of correct responding (Fig. 8).

The effect of heroin, methadone, and LAAM on accuracy of responding also tended to differ from those of cyclazocine. In general, heroin and methadone increased percent errors only at those doses which produced substantial decreases in the overall rate of responding (i.e., when rate was decreased to 20 responses/min or less). The effects of LAAM on accuracy in the learning component were variable both between and within monkeys. Small increases in percent er-

rors were, however, occasionally obtained. In contrast, cyclazocine was found to produce large error-increasing effects in the learning component at doses which produced relatively small rate-decreasing effects. These same doses, however, generally had little or no effect on accuracy in the faded-learning and performance components.

The results of the present study are similar to those obtained with other opioids in patas monkeys responding under a multiple schedule of repeated acquisition and performance of conditional discriminations [17]. Under this procedure monkeys were required to respond on a right or left lever depending upon the stimulus combination (a color and geometric form) presented. Reinforcement of a response in the presence of one stimulus (the form) was conditional upon the other stimulus (the color). One component of the multiple schedule was a repeated-acquisition task where the discriminative stimuli for left- and right-lever responses changed each session (learning). In the other component, the discriminative stimuli were the same each session (performance). The results obtained with the prototypical mu agonist morphine were similar to those obtained in the present study with heroin and methadone. Namely, morphine produced dose-related decreases in the overall rate of responding which were primarily a result of sporadic periods of pausing. Similarly, accuracy was unaffected except at the highest dose which produced a substantial decrease in the overall rate of responding [17]. In contrast, cyclazocine was found to disrupt accuracy of the discrimination in the learning component in a dose-related manner. In comparison to morphine, the error-increasing effects of cyclazocine were apparent at doses which produced much smaller decreases in overall response rate. Furthermore, as was observed in the present study the decreases in overall rate of responding obtained at low to moderate doses of cyclazocine were attributable to a decrease in the local rate of correct responding rather than to periods of sporadic pausing. It could be argued that the mu agonists disrupted accuracy across a wider range of doses in the present study than in our previous study [17]. Apart from the fact that the particular mu agonists investigated differed between studies, there were numerous procedural differences. One such procedural difference which may account for this discrepancy is the use of a tandem versus a chain schedule procedure. It is possible that in monkeys a tandem schedule is simply more sensitive to disruption by mu agonists than is a chain schedule because the discriminative stimuli in the chain schedule attenuate the disruptive effects of these drugs due to the relatively strong control they exert over responding (cf., [19]).

In addition to its pharmacological actions as an antagonist, cyclazocine has also been reported to have agonist activity at the putative sigma receptor [9]. It has been proposed that the discriminative stimulus properties of cyclazocine and other putative sigma agonists (e.g., SKF 10,047) may be mediated by a nonopioid mechanism of action, which also mediates the action of phencyclidine [7,8]. For example, in the monkey cyclazocine and its *d* and *l* enantiomers have been reported to possess discriminative stimulus properties similar to those of phencyclidine [8,25]. Similarly, under both the tandem schedule procedure used in the present study and under the chain schedule used in our previous study [17], the disruptive effects of cyclazocine on responding in the learning component are comparable to those produced by phencyclidine [15,16]. These studies are consistent with studies *in vitro* which suggest that cyclazocine and phencyclidine may be acting at a distinct nonopioid binding site [18, 23, 26, 27]. Moerschbaecher and Thompson [17] have proposed that in monkeys putative sigma opioid agonists, such as cyclazocine, exert a dose-dependent disruptive effect on the accuracy of a discrimination, an action not shared by putative mu and kappa opioid agonists, at doses which produce approximately equivalent rate-decreasing effects. While the cyclazocine dose-effect curves for accuracy obtained in the present study were steep, the data are generally consistent with this notion.

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