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Effects of Opioids and Phencyclidine in Combination With Naltrexone on the 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 opioids and phencyclidine in combination with naltrexone on the acquisition and performance of response sequences in monkeys.* PHARMACOL BIOCHEM BEHAV 22(6) 1061–1069, 1985.—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 under 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). Heroin, methadone, cyclazocine and phencyclidine each produced dose-related decreases in overall response rate. At high doses which produced equivalent rate-decreasing effects, cyclazocine and phencyclidine generally produced greater disruption of accuracy in the learning component than did heroin or methadone. Naltrexone 5.6 μg/kg shifted to the right by approximately 1/2-log unit the heroin and methadone dose-effect curves, but produced little or no change in the cyclazocine dose-effect curves. At 56 μg/kg naltrexone completely antagonized both the rate-decreasing and error-increasing effects of heroin and methadone. The same dose of naltrexone tended to produce greater antagonism of the effects of cyclazocine on accuracy than on rate, which was shifted by only 1/4-log unit. In contrast, naltrexone failed to antagonize the effects of phencyclidine on either rate or accuracy. Thus it would appear that while cyclazocine and phencyclidine produce similar disruptions in the accuracy of a discrimination, the effects of each are differentially sensitive to antagonism by naltrexone.

Repeated acquisition Performance Multiple schedule Heroin Methadone Cyclazocine Phencyclidine Naltrexone Lever press Monkeys

THE effects of various opioid agonists on rate of responding maintained by simple schedules of food presentation are essentially the same. Each typically produces decreases in the overall rate of responding [7]. However, in regard to other behavioral properties, clear differences are apparent among the opioids. These differences have, in part, been attributed to their agonist action at distinct opioid receptors. For example, in monkeys *mu* agonists, such as morphine, will function as reinforcers while *kappa* agonists, such as ethylketocyclazocine, will not [34]. Similarly, the discriminative stimulus properties of the opioids differ depending upon whether they possess *mu* or *kappa* agonist activity [10,34]. In addition, *sigma* agonists, such as SKF 10,047, have been reported to produce discriminative effects which are comparable to those produced by the dissociative anesthetic agents phencyclidine and ketamine [10]. For example, in rats trained to discriminate saline from phencyclidine, SKF 10,047, but not morphine or ketocyclazocine will substitute for phencyclidine [12,27]. Finally, in monkeys, differences are also apparent among the opioids in terms of their effects on the accuracy of discriminations. Opioids with activity at the putative *sigma* receptor such as SKF 10,047, cyclazocine and pentazocine have been reported to exert a dose-dependent disruptive effect on the accuracy of discriminations, an action not shared by prototypical *mu* and *kappa* opioid agonists, at doses which produce approximately

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equivalent rate-decreasing effects [22–24]. These disruptive effects of *sigma* agonists are comparable to those obtained with phencyclidine under some of these same discrimination procedures [20,21].

The behavioral effects of various agonists are also differentially sensitive to the opioid antagonists [36]. For example, in rats responding under a fixed-interval schedule of food presentation, naltrexone produces approximately a 30-fold shift to the right of the morphine dose-effect curve [9]. This same dose of naltrexone, however, produces only about a 3-fold shift in the ethylketocyclazocine dose-effect curve and no shift in the SKF 10,047 dose-effect curve [9]. Similar limitations in the efficacy of opioid antagonists have been reported in relation to the discriminative stimulus properties of opioid agonists. In particular, naloxone and naltrexone generally have little or no effect on the phencyclidine-like discriminative stimulus properties of certain opioids (e.g., [2, 3, 12, 28]). On the basis of both similarities in their discriminative stimulus properties and the poor efficacy of opioid antagonists to block these same effects, it has been suggested that the action of the *sigma* agonists and phencyclidine may be mediated by a common nonopioid mechanism [12]. Data obtained *in vitro* support this notion [1, 25, 33, 37]. For example, neither ketocyclazocine, morphine nor naloxone displaces [^{3}H]phencyclidine, whereas *sigma* agonists such as SKF 10,047 displaces [^{3}H]phencyclidine in low concentrations [25].

Since cyclazocine and phencyclidine produce similar effects on the accuracy of discriminations in monkeys it is possible that the disruptive effects of these drugs might also be mediated by the same mechanism. The present study was therefore specifically designed to determine whether the effects of these drugs on the acquisition and performance of tandem response sequences were mediated by a naltrexone-sensitive mechanism. As a comparison the ability of naltrexone to antagonize the effects of heroin and methadone was also investigated.

METHOD

Subjects

Two adult female patas monkeys served. Both subjects had experimental histories involving the repeated acquisition of tandem response sequences. 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 76.2×71.1×96.5 cm. The bars were removed from one side of the cage and replaced with an aluminum response panel, the details of which have been previously described [20,24]. 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 FR2 (FR4:S) second-order 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 second-order 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, the details of which have been previously described [7,12]. 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., [20]).

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. Dose-effect data were obtained for cy-

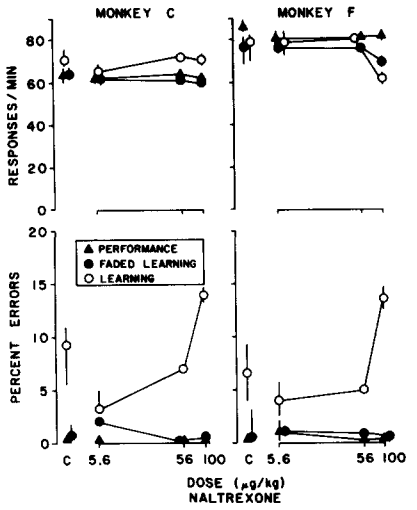

FIG. 1. Effects of varying doses of naltrexone on the overall response rate and percent errors in each component of the multiple schedule for each subject. The mean and range (vertical lines) of 4 saline control sessions (C) are shown at the left of each dose-effect curve. For each curve, the mean and 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.

clazocine (base), heroin (3,6-diacetyl-morphine) hydrochloride, methadone hydrochloride and phencyclidine hydrochloride in that order, both alone and in the presence of various doses of naltrexone hydrochloride. Cyclazocine was dissolved in three parts 8.5% lactic acid and two parts 1 N sodium hydroxide. All other drugs were dissolved in 0.9% sterile saline. Drug and control (saline or vehicle) injections were given IM (*gluteus m.*) either 5 min (phencyclidine), 15 min (cyclazocine, heroin and naltrexone), or 60 min (methadone) presession. These times were chosen on the basis of preliminary studies conducted in monkeys and/or on the basis of previously published studies [20,24]. The volume of injection was 0.05 ml/kg body weight. The doses (expressed in the forms described above) of each drug were tested in a mixed order. The dose-effect curve for a given drug was first determined alone. Various doses of that drug were then tested in combination with 5.6 μg/kg of naltrexone and then in combination with 56 μg/kg of naltrexone. Phencyclidine was only tested in combination with the higher dose of naltrexone. Finally, after the combined effects of a given drug and naltrexone were determined, the effects of various doses of that drug alone were redetermined. When determining the effects of a drug alone, drug sessions were generally conducted on Tuesdays and Fridays, with control injections on Thursdays. At the higher doses and when studied in combination with naltrexone, however, drug injections were given only once a week. 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.

RESULTS

The effects of varying doses of naltrexone on overall response rate and percent errors in each component of the multiple schedule are shown for each monkey in Fig. 1. Naltrexone had little or no effect, across the range of doses tested, in either the performance or faded-learning components. Note, however, that at the 5.6 μg/kg dose, naltrexone produced small but reliable decreases in percent errors in the learning component in monkey C; while at the 100 μg/kg dose, percent errors were increased in the same component in both monkeys. Response rate was also slightly decreased at this same dose in the learning component in monkey F. Only those doses which, when administered alone, had no error-increasing or rate-decreasing effect on behavior (i.e., 5.6 and 56 μg/kg) were tested in combination with the other drugs.

Figure 2 shows the effects of varying doses of heroin and cyclazocine, both alone and in combination with two different doses of naltrexone, on the overall response rate and overall accuracy (percent errors) in the performance component of the multiple schedule for each subject. In each subject, heroin alone produced dose-related decreases in overall response rate and, at the highest dose, small error-increasing effects. The 5.6 μg/kg dose of naltrexone attenuated both the error-increasing and rate-decreasing effects of heroin. In each monkey the heroin dose-effect curve for response rate was shifted by approximately 1/2-log unit to the right. The 56 μg/kg dose of naltrexone completely antagonized both the error-increasing and rate-decreasing effects of heroin across the range of doses tested. Like heroin, cyclazocine alone also produced dose-related decreases in the overall rate of responding and small error-increasing effects in the performance component. The effects of cyclazocine in combination with the 5.6 μg/kg dose of naltrexone were, however, mixed. In monkey C, little or no antagonism of the effects of cyclazocine on either rate or accuracy obtained. In monkey F, this same dose of naltrexone shifted the cyclazocine dose-effect curves for both rate and accuracy by approximately 1/4-log unit to the right. In monkey C, increasing the dose of naltrexone to 56 μg/kg produced somewhat greater antagonism of the error-increasing effects, but little or no additional antagonism of cyclazocine's rate-decreasing effects. Similarly, in monkey F the higher dose of naltrexone resulted in no further antagonism of cyclazocine's effects. Comparable results obtained in the faded-learning component in both subjects (not shown).

The effects of varying doses of heroin and cyclazocine, both alone and in combination with naltrexone, in the learning component of the multiple schedule are shown for each subject in Fig. 3. In general, the results are similar to those obtained in the performance component. Heroin alone produced dose-related decreases in the overall rate of responding and at the higher doses produced a modest error-increasing effect. The 5.6 μg/kg dose of naltrexone shifted the heroin dose-effect curves by about 1/4-log unit in both monkeys. Across the range of doses tested, the 56 μg/kg dose completely antagonized both the rate-decreasing and error-increasing effects of heroin. Cyclazocine alone also produced dose-related decreases in the overall rate of responding in the learning component. However, in comparison to heroin, cyclazocine produced greater error-increasing effects. As was the case in the performance component, the combined effects of cyclazocine and naltrexone in the learning component were somewhat variable between monkeys. In monkey C, the 5.6 μg/kg dose of naltrexone attenuated both the rate-decreasing and error-increasing effects of the lower (0.056 and 0.1 mg/kg) doses of cyclazocine, but not those produced by the highest dose (0.18 mg/kg). In monkey F, this same dose of naltrexone shifted the cyclazocine

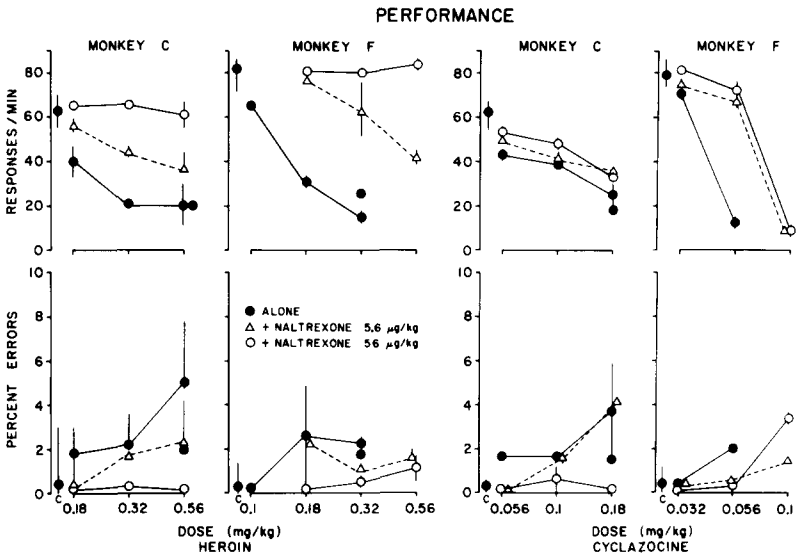

FIG. 2. Effects of varying doses of heroin and cyclazocine, both alone and in combination with two different doses of naltrexone, on the overall response rate and percent errors in the performance component of the multiple schedule for each subject. The mean and range (vertical lines) of 10 saline control 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. Unconnected closed circles represent the effects of each agonist after it was studied in combination with naltrexone.

dose-effect curves by 1/4-log unit to the right. The higher dose of naltrexone further attenuated the rate-decreasing effects of intermediate doses of cyclazocine in both monkeys. Greater antagonism of the rate-decreasing effect also obtained at the highest dose in monkey C (0.18 mg/kg), but not in monkey F. In contrast to this relatively incomplete antagonism of cyclazocine's rate-decreasing effects, the 56 µg/kg dose of naltrexone antagonized the error-increasing effects of cyclazocine across the range of doses tested in both monkeys. In general, the effects of both heroin and cyclazocine alone were replicated after their combined administration with naltrexone (Figs. 2 and 3, unconnected closed circles).

The effects of varying doses of methadone and phencyclidine, both alone and in combination with naltrexone, on responding in the performance component are shown in Fig. 4. Though less potent (on a mg/kg basis) than heroin when administered alone, the effects of methadone were generally comparable to those produced by heroin (Fig. 2). In both monkeys each dose of naltrexone antagonized the rate-decreasing effects of methadone, shifting the dose-effect curves to the right by at least 3/4-log unit. It is of interest to note that while both heroin and methadone produced comparable decreases in overall response rate, the low dose (5.6 µg/kg) of naltrexone produced greater antagonism of the rate-decreasing effects of methadone than of heroin. Greater antagonism of the error-increasing effects of methadone was obtained with the 56 µg/kg than with the 5.6 µg/kg dose of naltrexone in monkey F. In monkey C the two doses of naltrexone were about equieffective in this regard. When administered alone, phencyclidine decreased response rate and increased percent errors at the highest dose tested (0.18 mg/kg) in both monkeys. The 56 µg/kg dose of naltrexone had no effect on the rate-decreasing effects of phencyclidine. In relation to the error-increasing effects obtained at the 0.18 mg/kg dose, naltrexone either produced slight attenuation (monkey F) or had no effect. In general, comparable effects obtained in the faded-learning component in both monkeys (not shown).

The effects of methadone and phencyclidine, alone and in combination with naltrexone, on responding in the learning component are shown for each subject in Fig. 5. The degree of antagonism obtained with a given dose of naltrexone in combination with methadone tended to be more dose responsive in monkey F than in monkey C. In general, however, as was obtained in the performance component, naltrexone (56 µg/kg) antagonized both the rate-decreasing and error-increasing effects of methadone shifting the dose-effect curves by approximately 3/4-log unit. When administered alone, phencyclidine decreased response rate and produced large error-increasing effects at doses of 0.1 and 0.18 mg/kg. While the error-increasing effects were slightly attenuated in both monkeys at the 0.1 mg/kg dose, in general, naltrexone failed to antagonize the effects of phencyclidine on either rate or accuracy. In general, the effects of both methadone and phencyclidine alone were replicated after combined administration with naltrexone (Figs. 4 and 5, unconnected closed circles).

The within-session effects of selected doses of each of the drugs tested alone (A) and in combination with naltrexone 56 µg/kg (B) are shown in the cumulative records for monkey F in Fig. 6. A cumulative response record for a session which was preceded by a saline injection is shown in the top left panel. The session began in the learning component (L), then changed to the performance component (P), which was then

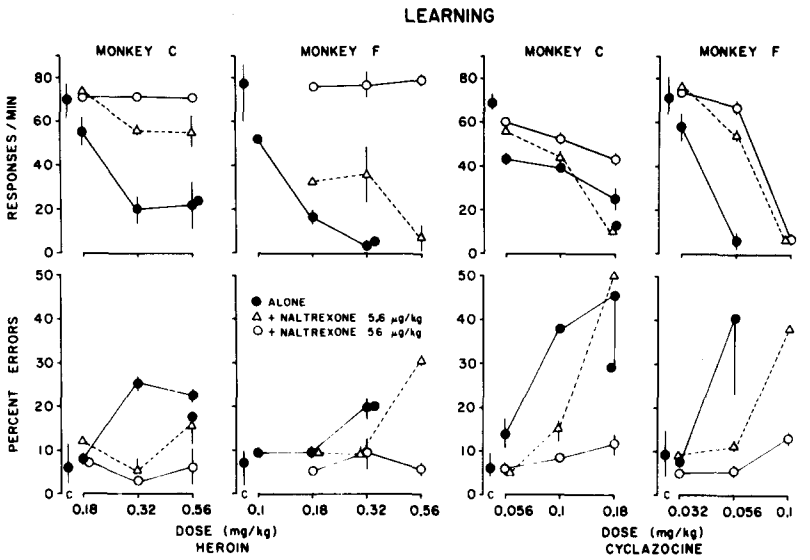

FIG. 3. Effects of varying doses of heroin and cyclazocine, both alone and in combination with two different doses of naltrexone, on the overall response rate and percent errors in the learning component of the multiple schedule for each subject. The mean and range of 10 saline control sessions (C) are shown at the left of each dose-effect curve. Other details are the same as in Fig. 2.

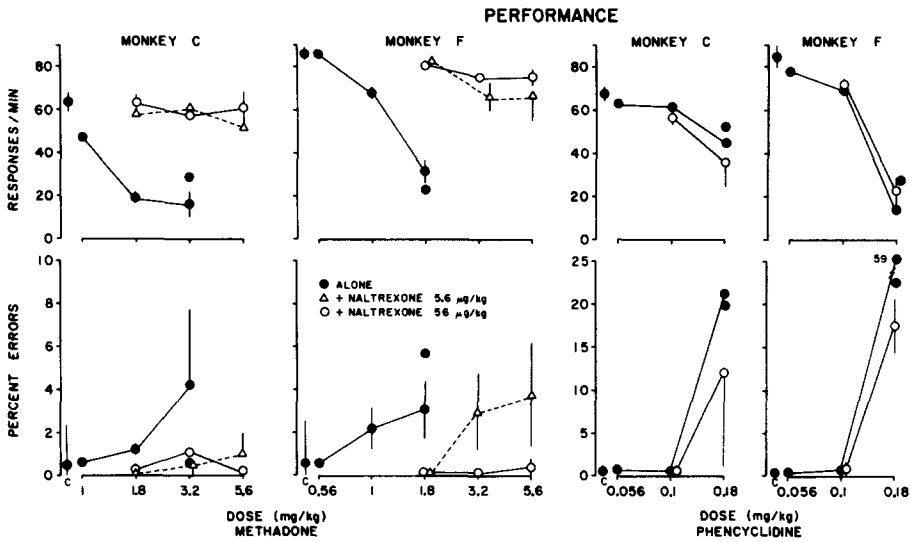

FIG. 4. Effects of varying doses of methadone and phencyclidine, both alone and in combination with naltrexone, on the overall response rate and percent errors in the performance component of the multiple schedule for each subject. The mean and range of 6–10 saline control sessions (C) are shown at the left of each dose-effect curve. Other details are the same as in Fig. 2.

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, though errors decreased as the session progressed. 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, naltrexone 56 µg/kg administered alone had virtually no effect on responding under the multiple schedule. In contrast, when heroin (0.32 mg/kg) or methadone (1.8 mg/kg) was administered alone, the local rate of correct responding in each component of the multiple schedule was decreased. Sporadic pauses in responding were also evident during the sessions. When administered in combination with naltrexone the effects of each of these drugs within each session were antagonized and the cumulative records were virtually indistinguishable from the control sessions (saline). In comparison to heroin and methadone, when cyclazocine (0.056 mg/kg) was administered alone the local rates of correct re-

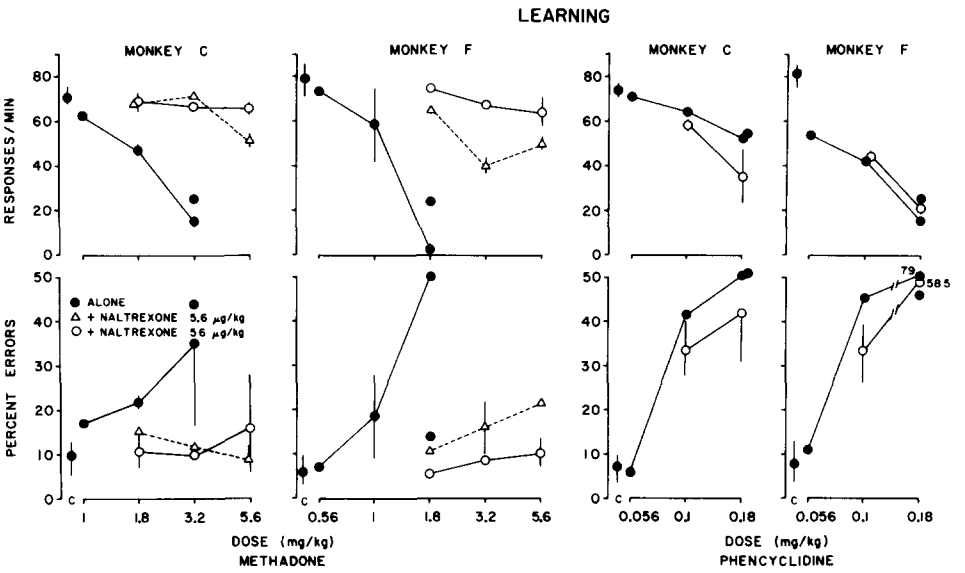

FIG. 5. Effects of varying doses of methadone and phencyclidine, both alone and in combination with naltrexone, on the overall response rate and percent errors in the learning component of the multiple schedule for each subject. The mean and range of 6–10 saline control sessions (C) are shown at the left of each dose-effect curve. Other details are the same as in Fig. 2.

sponding were also decreased. However, cyclazocine produced less pausing and a greater disruption of accuracy in each component of the multiple schedule than did either heroin or methadone. Note that the greatest increase in errors occurred in the learning component. Naltrexone antagonized both the rate-decreasing and error-increasing effects of this same dose of cyclazocine. Finally, when administered alone phencyclidine (0.18 mg/kg) produced large error-increasing effects in each component of the multiple schedule. While a long pause in responding occurred at the start of the session (not shown), once the monkey began to respond, further pausing occurred infrequently. Though the error-increasing effects of phencyclidine were slightly attenuated when this same dose was administered in combination with naltrexone, in general, no antagonism obtained and the within-session effects were comparable to those obtained with phencyclidine alone. The within-session effects of each drug, alone and in combination with naltrexone, were similar for monkey C though in some cases the doses varied slightly.

DISCUSSION

In the present study, heroin and methadone each produced dose-related decreases in overall response rate and at the higher doses increased percent errors in each component of the multiple schedule. Both the rate-decreasing and error-increasing effects of heroin and methadone were antagonized by doses of naltrexone that had no effect when administered alone. The dose-effect curves of the agonists were shifted progressively to the right as the dose of naltrexone was increased. These results are comparable to those previously reported with both naltrexone and naloxone in combination with morphine in monkeys, pigeons and rats (e.g., [5, 6, 9, 18, 19]) responding under various schedules of food presentation. Similarly, naloxone has been reported to antagonize the rate-decreasing effects of methadone in pigeons and rats [16, 18, 19]. There have been, however, few previous reports regarding the efficacy of either naloxone or naltrexone as antagonists of the effects of various opioids on either the acquisition or performance of discriminations. In one such study we investigated the combined effects of morphine and naloxone in pigeons responding under a repeated acquisition task [32]. When either morphine or naloxone was administered alone, the overall response rate decreased with increasing doses. The rate-decreasing effect was accompanied by an increase in percent errors with morphine but not with naloxone. Both effects of morphine were antagonized by doses of naloxone that were ineffective when given alone. At certain dose combinations, however, the antagonism was selective in that naloxone (3 mg/kg) completely blocked the error-increasing effect but not the rate-decreasing effect of the higher doses of morphine (17–30 mg/kg). Similarly, instances of selective antagonism also obtained at certain dose combinations in the present study. For example, in monkey F the 5.6 μg/kg dose of naltrexone completely blocked the error-increasing but not the rate-decreasing effects of the 0.32 mg/kg dose of heroin (Fig. 2). In summary, the present data are in general agreement with the results obtained in previous studies of the efficacy of naltrexone as an antagonist of *mu* opioid agonists.

Like heroin and methadone, cyclazocine and phencyclidine each produced dose-related decreases in overall response rate in each component of the multiple schedule. The drugs differed, however, in terms of their effects on accuracy of responding. At doses which produced approximately equivalent rate-decreasing effects, cyclazocine and phencyclidine generally produced greater disruption of accuracy in the learning component than did heroin or methadone. The maximum shift in the cyclazocine dose-effect curves produced by naltrexone (56 μg/kg) was approximately 1/4-log unit to the right. This same dose of naltrexone did not alter the phencyclidine dose-effect curves. This result is in agreement with our previous report in pigeons responding under a

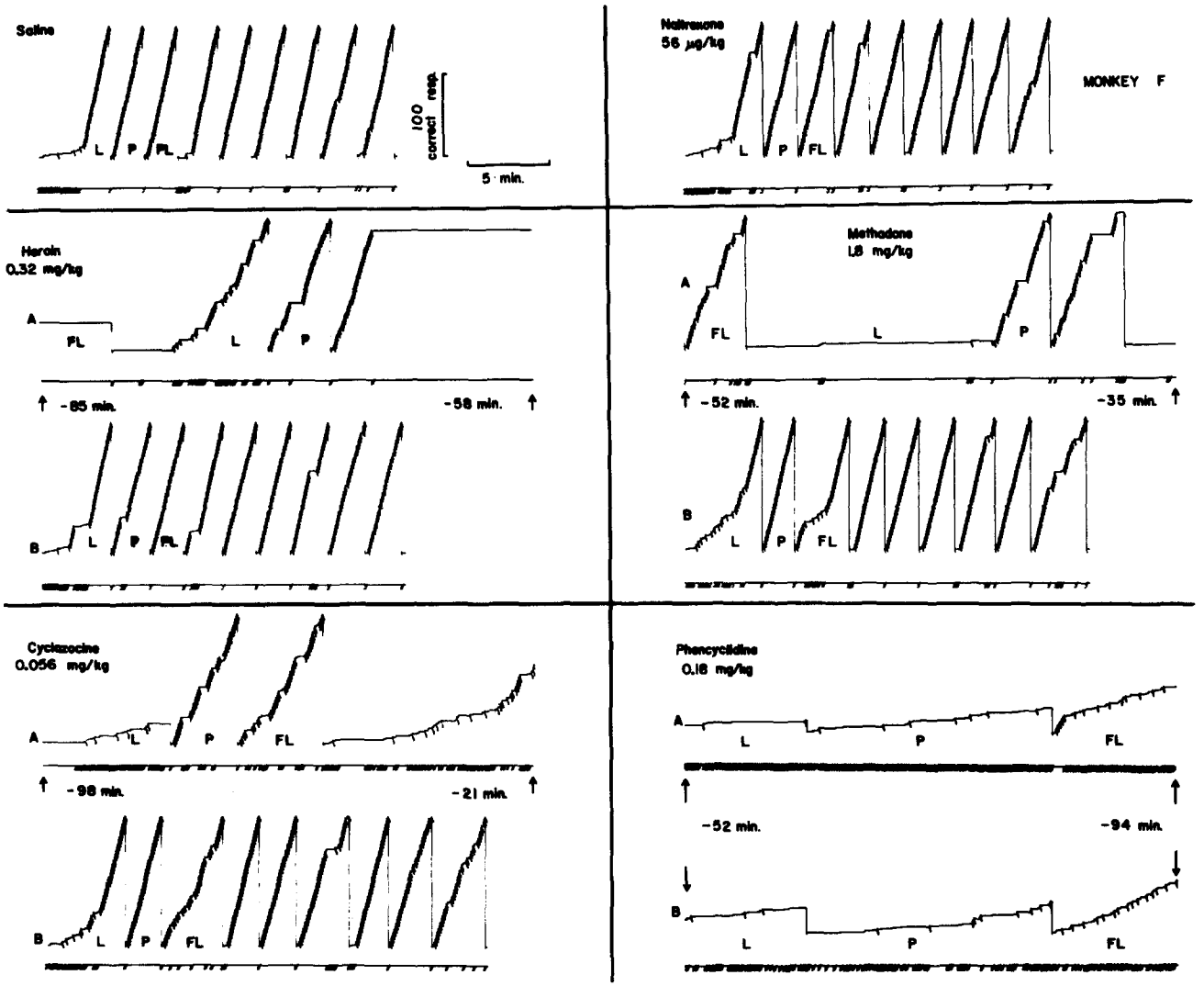

FIG. 6. Cumulative response records for monkey F showing the pattern of responding during a control session (saline), a session preceded by the injection of naltrexone (56 µg/kg) alone, and sessions preceded by the injection of each agonist alone (labeled A) and by the same dose of each agonist in combination with naltrexone 56 µg/kg (labeled B). 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.

repeated acquisition task [32]. In that study naloxone also failed to antagonize the disruptive effects of phencyclidine.

The efficacy of naloxone and naltrexone as antagonists of the effects of cyclazocine varies depending upon the behavioral task under which they are tested. For example in pigeons and rats responding under schedules of food presentation both naltrexone and naloxone produce little or no antagonism of the rate-decreasing effects of cyclazocine [9,19]. Under continuous avoidance schedules, however, naloxone has been reported to antagonize both the rate-increasing and rate-decreasing effects of cyclazocine in the squirrel monkey and rat [11,14]. Similarly, in subjects trained to discriminate injections of cyclazocine from saline, naltrexone will antagonize the discriminative stimulus properties of cyclazocine [26, 30, 31]. However, in subjects trained to discriminate injections of phencyclidine from saline, neither naloxone nor naltrexone will antagonize the phencyclidine-like discriminative stimulus properties of cyclazocine [2, 12, 13, 28]. Of particular interest is the fact that the rate-decreasing effects produced by cyclazocine at high doses are particularly resistant to antagonism [2, 9, 19, 35]. Young and Stephens [35] have pointed out that in macaques, antagonism of the discriminative stimulus properties of high cyclazocine doses by naltrexone is limited by a lack of antagonism of its rate-decreasing effects. The present data suggest that this may also be the case in relation to cyclazocine's error-increasing effects; naltrexone tended to produce greater antagonism of cyclazocine's disruptive effects on accuracy than on rate.

We have previously reported that in patas monkeys, opioids with activity at the putative *sigma* receptor, such as SKF 10,047 and cyclazocine, exert a dose-dependent disruptive effect on the accuracy of discriminations, an action

not shared by prototypical *mu* and *kappa* opioid agonists, at doses which produce approximately equivalent rate-decreasing effects [22]. Furthermore, *sigma* agonist activity is generally considered to be insensitive to the opioid antagonists, since neither naloxone nor naltrexone will block the effects of SKF 10,047 [3, 12, 29]. The present data, however, suggest that the error-increasing effects of certain opioids, such as cyclazocine, which may mimic those effects produced by both SKF 10,047 and phencyclidine are mediated by a different naltrexone-sensitive mechanism. Martin [4,17] has proposed the existence of two subtypes of *sigma* receptors. These receptors, *sigma 1* and *sigma 2*, were hypothesized to mediate the agonist effects of cyclazocine and SKF 10,047, respectively. Naloxone was proposed as an antagonist at *sigma 1*, but to have little or no affinity for *sigma 2*. In addition, it was suggested that phencyclidine is an agonist at *sigma 2*. Though speculative, it may be the case that the error-increasing effects of cyclazocine are mediated by the putative *sigma 1* receptor, while those of SKF 10,047 and phencyclidine are mediated by the putative *sigma 2* receptor. Traditionally, the *sigma* receptor has been associated with the "psychotomimetic" properties of opioids [17]. We have previously suggested that the technique of repeated acquisition may be useful in identifying such behavioral properties of novel opioids. Consistent with this notion cyclazocine has been reported to produce "psychotomimetic" effects in man [8]. Jasinski *et al.* [15] have also reported that naloxone will antagonize both the behavioral and subjective effects of cyclazocine in man. The present data are in agreement with these findings. Martin [17] has noted that there is a "functional redundancy for opioid receptors." For example, both *mu* and *kappa* agonists produce analgesia, hypothermia and miosis. The present data suggest that the error-increasing effects of opioids may also be mediated by two distinct mechanisms, consistent with the concept of opioid "receptor dualism."

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