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Evaluation of the Effects of Opioid Agonists and Antagonists Under a Fixed-Consecutive-Number Schedule in Rats[1]

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PICKER, M., J. W. HEISE AND L. A. DYKSTRA. *Evaluation of the effects of opioid agonists and antagonists under a fixed-consecutive-number schedule in rats.* PHARMACOL BIOCHEM BEHAV **27**(1) 73–80, 1987.—The effects of several opioid agonists and the opioid antagonist naloxone were examined in rats responding under a fixed-consecutive-number (FCN) schedule. Under this schedule, a reinforced response run consisted of responding eight or more times on one response lever, and then responding once on a second response lever. In one component of this schedule, an external discriminative stimulus signalled the completion of the response requirement on the first lever, whereas no stimulus change was programmed in the other. Morphine, l-methadone, U50488, ketocyclazocine, phencyclidine, and (±)N-allylnormetazocine decreased the percent of reinforced response runs (accuracy) under the FCN schedule without the external discriminative stimulus, but had no effect under the FCN schedule with the external discriminative stimulus. Naloxone and bremazocine, in contrast, had no effect on the accuracy of the discrimination under either FCN schedule. With the exception of bremazocine and U50488, which increased rates of responding at low doses, all drugs produced comparable decreases in rates of responding under both FCN schedules. During tests of antagonism, a 0.1 mg/kg dose of naloxone reversed completely the accuracy-decreasing effects produced by U50488 and morphine. The rate-decreasing effects of morphine and U50488 were reversed completely by a 0.01 and 1.0 mg/kg dose of naloxone, respectively. These results suggest that the addition of an external discriminative stimulus can modulate the disruptive effects of opioids, and that mu, sigma and some kappa agonists produce similar effects when evaluated under the FCN schedules.

Fixed-consecutive-number Morphine l-Methadone Bremazocine U50488 Ketocyclazocine Phencyclidine (±)N-Allylnormetazocine Naloxone Opioids Conditional discriminations

INVESTIGATIONS extending across numerous species and preparations indicate that drugs acting at opioid receptor types can be differentiated in tests of analgesia [5–7], discriminative stimulus properties [6, 7, 12], reinforcing properties [31,32], and the ability of these drugs to produce physical dependence [8]. In general, the effects of opioid compounds can similarly be distinguished under simple schedules of food presentation. Although these drugs nonselectively decrease rates of responding under these schedules, the rate-suppressing effects produced by the mu agonists can be antagonized by doses of opioid antagonists (e.g., naloxone) that are considerably lower than those required to antagonize the effects of the kappa agonists [10,14]. The rate-suppressing effects produced by the sigma agonists, in contrast, are not significantly altered by the concomitant administration of opioid antagonists [10].

Recently, attempts have been made to determine whether operant tasks requiring complex conditional discriminations are differentially sensitive to the actions of the opioids. In monkeys and pigeons, for instance, the mu and kappa agonists have little effect on the accuracy of responding under various conditional discriminations [16, 20, 21, 24], while these compounds typically decrease the accuracy of rats responding [2, 3, 20]. The effects of the sigma agonists, in contrast, are consistent across these species in that these compounds nonselectively decrease the accuracy of responding [20,29].

One task that has been employed profitably to evaluate

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the effects of drugs on conditional discriminations is the fixed-consecutive-number (FCN) schedule (see [11,23]). Under this schedule, subjects are required to respond a fixed number of times on one operandum (work operandum), and then respond once on a second operandum (reinforcement operandum). Under one variant of the FCN schedule, an external discriminative stimulus signals the completion of the response requirement on the work operandum, while under the other no external stimulus change is programmed. Thus, the response requirements are the same under both variants of the FCN schedule. However, responding under one variant is controlled by an external discriminative stimulus, whereas responding under the other is controlled by an internal discriminative stimulus. Recent investigations indicate that drugs within several pharmacological classes can be distinguished under this procedure on the basis of the shape of their dose-effect curves [13, 19, 25, 26, 28] even when they have similar effects on rates of responding under simple schedules of food presentation [1, 4, 10, 18, 27]. Studies with the neuroleptics have shown, for example, that chlorpromazine nonselectively decreases accuracy under both variants of the FCN schedule, haloperidol has little effect on accuracy under either variant and pimozide selectively decreases accuracy under the FCN schedule without the external discriminative stimulus [13,28]. Such differential effects have also been reported with psychomotor stimulants, such as d-amphetamine, methylphenidate and caffeine, and the anticonvulsant compounds clonazepam, ethosuximide and valproic acid under the FCN schedules [13, 19, 24, 25].

In the present investigation, we determined whether the behavioral effects of several opioid agonists and the opioid antagonist naloxone could be distinguished under the FCN schedule. In addition, the ability of naloxone to antagonize the effects of morphine and U50488 was investigated. By employing the FCN schedules with and without the added external discriminative stimulus we also determined the extent to which the disruptive effects of these opioid compounds could be modulated by an external discriminative stimulus.

METHOD

Subjects

Four experimentally naive male Long-Evans hooded rats, about 4 months old at the start of the experiment, were used. Rats were food deprived to approximately 80% of free-feeding weights (range across subjects 300–350 g) and were housed individually with unlimited access to water in a colony maintained on a 12 hr light-dark cycle.

Apparatus

Four plastic and aluminum operant conditioning chambers measuring 23 cm long, 19 cm high, and 20 cm wide were used. Each chamber was equipped with two centrally mounted 5 cm long response levers located 9 cm from the chamber floor and 1.3 cm from either wall. When operated, a pellet dispenser could deliver a 45 mg Noyes food pellet (P. J. Noyes Co., Lancaster, NH) into a pellet trough, which was centrally mounted under the two levers 1 cm above the chamber floor. Located approximately 15 cm from the floor and 2.5 cm above each lever were two stimulus lights. When illuminated, the lights located above the right lever were red and the lights above the left lever were white. Two white houselights were centrally mounted on the ceiling 2.5 cm from the rear wall. The chambers were also equipped with an exhaust fan which supplied ventillation and white noise to mask extraneous sounds. Scheduling of experimental events and data collection were accomplished through the use of a TRS model IV microcomputer interfaced with the chambers via an external Med Associates Interface Box.

TABLE 1

CONTROL VALUES FOR PERCENT OF REINFORCED RUNS, NUMBER OF REINFORCERS EARNED, AND RATES OF RESPONDING FOR INDIVIDUAL RATS RESPONDING UNDER A FCN 8-SD AND FCN 8 SCHEDULE

Rat (No.)	% Reinforced Runs (S.E.)	Reinforcers (S.E.)	Responses/sec (S.E.)
		FCN 8-SD	
1	99 (1.0)*	24 (0)	1.15 (0.08)
2	98 (1.0)	24 (0)	0.85 (0.03)
3	99 (0.54)	24 (0)	1.00 (0.04)
4	98 (0.71)	24 (0)	0.79 (0.02)
		FCN 8	
1	65 (4.2)	24 (0)	1.46 (0.07)
2	80 (2.1)	24 (0)	1.00 (0.03)
3	81 (3.0)	24 (0)	1.12 (0.04)
4	39 (3.4)	24 (0)	1.25 (0.02)

*Data are based on the mean control values for individual rats during all dose-effect determinations and tests of antagonism. Values in parentheses indicate the standard error.

Behavioral Procedure

After preliminary lever press training, four rats were exposed to a fixed-consecutive-number schedule with an external discriminative stimulus (FCN SD). During the initial training sessions, two red stimulus lights located above the left lever (work lever) were illuminated, and a single response on the left lever turned off the red stimulus lights and turned on the two white stimulus lights located above the right lever (reinforcement lever). A subsequent response on the reinforcement lever produced a food pellet, extinguished the right lever lights, and illuminated the left, red lever lights. Although recorded, multiple responses on the reinforcement lever had no scheduled consequences. Over the next few sessions the number of responses on the work lever before a response on the reinforcement lever was reinforced was gradually increased to eight. Under this schedule (FCN 8-SD), food was delivered only if the rat responded eight or more times on the work lever and then responded once on the reinforcement lever. Responding less than eight times on the work lever and then responding on the reinforcement lever reset the response requirement but had no effect on which stimulus lights were illuminated. The houselight remained darkened whenever the FCN 8-SD schedule was in effect. Under these conditions, sessions terminated after 50 reinforcers or 30 min, whichever came first.

When the percentage of reinforced response runs for individual rats showed no visually evident trend, rats were exposed to a multiple FCN schedule. Each experimental session started with the FCN 8-SD schedule, as described above, followed by the FCN 8 schedule. The contingencies

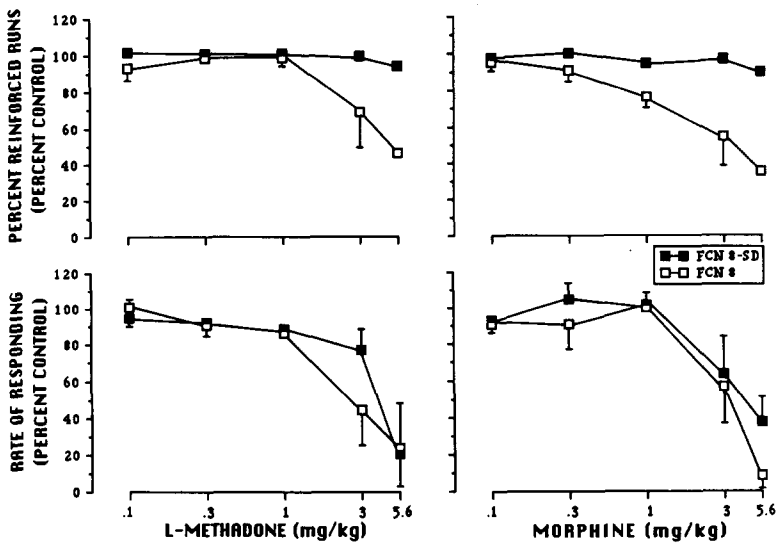

FIG. 1. Effects of l-methadone (left panels) and morphine (right panels) on the percent of reinforced runs and rates of responding in four rats responding under each of the FCN schedules. For ease of comparison, drug data represent mean group performances expressed as the percent of individual control performances during all vehicle control sessions prior to drug administration; vertical lines indicate the S.E. Those S.E.s that fell within the drug data point are not illustrated in the figure. Under each FCN schedule, drug data for percent of reinforced runs were included only when an individual rat earned five or more reinforcers during the session.

under the FCN 8 schedule were identical to those under the FCN 8-SD with the exception that when the FCN 8 schedule was in effect, the houselight was illuminated, the lever lights were darkened, and no stimulus change was associated with the completion of the response requirement on the work lever. During the initial training sessions, the response requirement on the work lever was gradually increased from 1 to 8. Each component of the multiple schedule was in effect for 5 min or until eight reinforcers were earned, whichever came first. If eight reinforcers were earned before the end of the 5 min component, all stimulus lights were darkened until the start of the next component. Sessions terminated after 30 min (3 components of each variant of the FCN schedule). Experimental sessions were conducted 5 days per week, at about the same time each day.

Pharmacological Procedure

After 60 sessions of exposure to the multiple FCN procedure just described, dose-effect curves were determined for morphine, (±)N-allylnormetazocine and U50488. Five doses of each drug, given at least once, were administered in an irregular order that varied across rats. At the termination of these acute dose-effect determinations, a 3.0 mg/kg dose of morphine and then a 5.6 mg/kg dose of U50488 were administered in combination with several doses of naloxone. These doses of morphine and U50488 were selected for antagonism studies because they produced marked suppression of rates of responding and percent reinforced runs, but did not completely eliminate responding in any rat. Subsequently, dose-effect curves were determined for naloxone, phencyclidine, l-methadone, bremazocine, and ketocyclazocine in that order. With the exception of ketocyclazocine, which was dissolved in 8.5% lactic acid and 1.0 sodium hydroxide in a ratio of 3:2, all drugs were dissolved in distilled water and are expressed as the salt.

Drugs were administered on Tuesday and Friday, whereas distilled water was injected on Thursday with the data obtained during these sessions serving as the non-drug control data. With the exception of ketocyclazocine, which was injected intraperitoneally (IP) 15 min prior to the experimental session, all drugs and vehicle control injections were administered IP 30 min prior to the session at an injection volume of 1.0 ml/kg. During tests of naloxone antagonism, the two drugs were injected on opposite sides of the peritoneal cavity. Otherwise all test conditions were identical to those during single administrations.

Data Analysis

The percentage of reinforced runs, overall rates of responding, and frequency distributions of run lengths were recorded during each of the FCN and FCN SD components. The percentage of reinforced runs reflect the proportion of response runs during which a rat made eight or more responses on the work lever and then responded once on the reinforcement lever. Responding less than the minimum requirement on the work lever and then responding once on the reinforcement lever was recorded as a nonreinforced run or error. Conditional probability functions were computed from run length distributions to determine possible drug-induced changes in response patterning. These functions reflect the conditional probability of switching to the reinforcement lever after completing individual response runs of any given length.

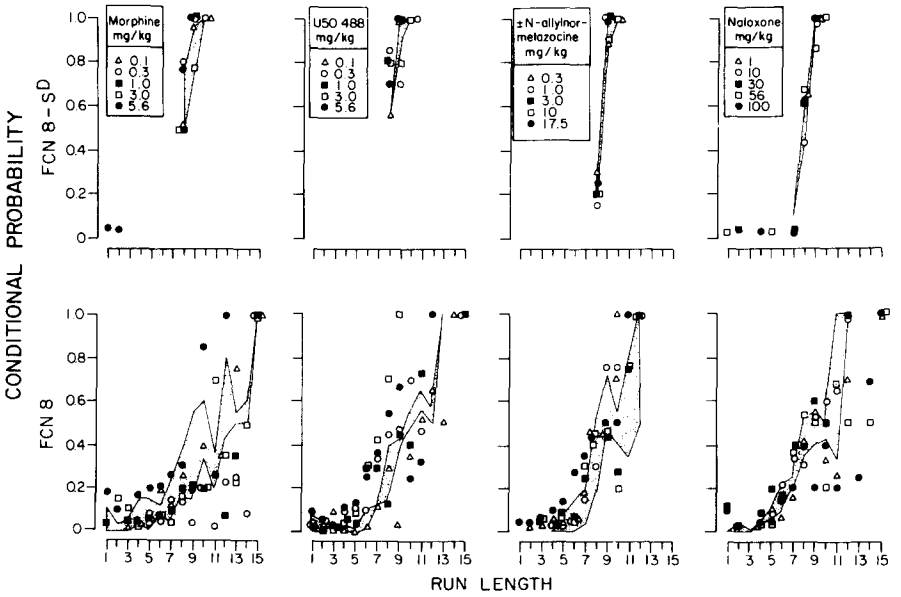

FIG. 2. Effects of morphine, U50488, (±)N-allylnormetazocine and naloxone on the conditional probability functions under each of the FCN schedules. The ordinate gives the probability that the rat will stop responding after a number of consecutive responses on the work lever, indicated on the abscissa, and respond on the reinforcement lever. The shaded areas represent the range over the water control sessions which preceded drug administrations. For simplicity, drug data were excluded from the figure when the conditional probability of switching to the reinforcement lever was zero. Under both FCN schedules, conditional probability functions after the administration of morphine, U50488, (±)N-allynormetazocine and naloxone represent data for rats 2, 3, 4 and 1, respectively.

RESULTS

Control Responding

Data obtained during baseline and vehicle control sessions indicated that the FCN 8-SD engendered a higher accuracy level (percent of reinforced response runs) than the FCN 8 (Table 1). Under control conditions, the mean accuracy levels under the FCN 8 was 67% with a range across rats of 39 to 81%. The mean accuracy levels under the FCN 8-SD was 98%, with a range of 98 to 99%. With the exception of one rat, whose accuracy levels decreased from a high of 58% to a low of 32%, accuracy levels were relatively stable over the course of the experiment. Between-schedule differences in rates of responding were apparent for each of the four rats, with the FCN 8 schedule consistently engendering a higher rate of responding. With the exception of one rat (Rat No. 4), the magnitude of these differences in rates of responding were relatively small. Across the course of the experiment, rates of responding did not change appreciably under either FCN schedule.

A comparison of the conditional probability functions obtained during control sessions showed that performance under the two FCN schedules was characterized by different patterns of responding (see control performance in Fig. 2). Responding under the FCN 8-SD schedule was predominantly characterized by response runs consisting of between eight and 10 consecutive responses on the work lever, with very few longer or shorter response runs. Much flatter conditional probability functions were obtained under the FCN 8 schedule, where the conditional probability of switching to the reinforcement lever increased as a function of the number of consecutive responses on the work lever, with consecutive responses on the work lever rarely exceeding 12 or 13.

Effects of the Mu Agonists l-Methadone and Morphine

Figure 1 shows the effects of l-methadone and morphine on the percent of reinforced runs (top panels) and rates of responding (bottom panels). Under the FCN 8 schedule, l-methadone and morphine produced dose-dependent decreases in the percent of reinforced runs. These accuracy-decreasing effects were evident at the two highest doses of l-methadone and at the four highest doses of morphine. With the exception of the 5.6 mg/kg dose of each drug, where only one rat earned all available reinforcers, all rats earned the maximum number available at each dose administered.

As illustrated in Fig. 2, drug-induced disruption of stimulus control was also apparent in the conditional probability functions under the FCN 8 schedule. At doses that produced large decreases in accuracy, morphine typically increased the conditional probability of switching to the reinforcement lever before completing the minimum response requirement on the work lever. In contrast to the disruptive effects observed under the FCN 8 schedule, no accuracy-decreasing effects or disruption of the conditional probability functions were observed for morphine under the FCN 8-SD schedule. Although not graphically depicted, the effects of l-methadone on the conditional probability functions were qualitatively similar to those produced by mor-

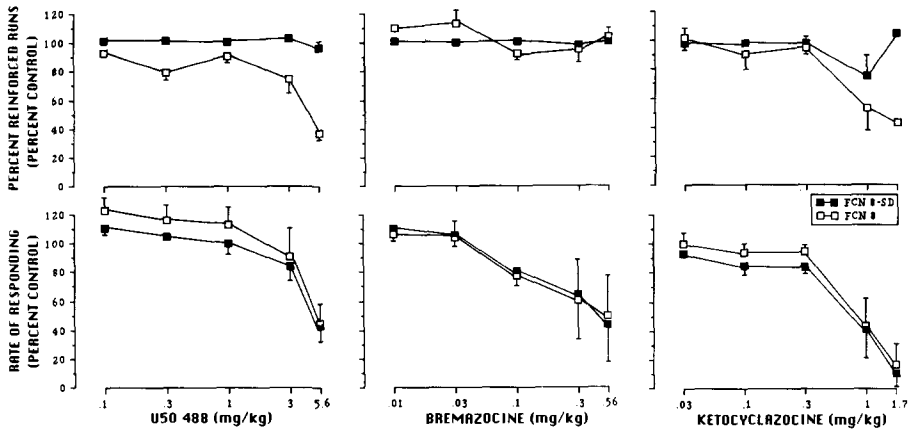

FIG. 3. Effects of U50488 (left panels), bremazocine (middle panels), and ketocyclazocine (right panels) on the percent of reinforced runs and rates of responding in four rats responding under the FCN schedules. Details are as described in Fig. 1.

phine. Morphine and l-methadone decreased rates of responding under both variants of the FCN schedule in a dose-dependent fashion.

Effects of the Kappa Agonists U50488, Bremazocine and Ketocyclazocine

Figure 3 shows the effects of U50488, bremazocine and ketocyclazocine on the percent of reinforced runs and rates of responding. U50488 and ketocyclazocine selectively decreased accuracy under the FCN 8 schedule, whereas bremazocine had no effect on accuracy under either FCN schedule. With few exceptions, all available reinforcers were earned at the low and intermediate doses of each drug administered. At the highest dose of ketocyclazocine and bremazocine, three and two rats, respectively, earned the maximum number of available reinforcers; all rats earned the maximum number at this dose of U50488. At doses that produced large decreases in accuracy under the FCN 8 schedule, U50488 (see Fig. 2) and ketocyclazocine typically increased the conditional probability of switching to the reinforcement lever before completing the minimum response requirement on the work lever. This effect was not consistently observed at any dose of bremazocine. U50488 and bremazocine typically increased rates of responding at low doses and decreased rates of responding at the higher doses. For U50488, but not bremazocine, these rate-increasing effects were largest under the FCN 8 schedule. Ketocyclazocine, in contrast, decreased rates of responding in a dose-dependent fashion under both FCN schedules.

Effects of the Sigma Agonists Phencyclidine and (±)N-Allylnormetazocine

The effects of phencyclidine and (±)N-allylnormetazocine on the percent of reinforced runs and rates of responding are shown in Fig. 4. Both drugs decreased the percent of reinforced runs under the FCN schedule, while having little or no effect on the accuracy of responding under the FCN 8-SD schedule. With the exception of the 17.5 mg/kg dose of (±)N-allylnormetazocine, where only two of the rats earned all available reinforcers, all four rats earned the maximum number of reinforcers across the dose range evaluated. When phencyclidine was administered, three rats earned all available reinforcers at the 3.0 mg/kg dose, whereas no rat earned the maximum at the 5.6 mg/kg dose. Although the highest dose produced small increases in the frequency of making response runs shorter then the minimum response requirement, these drugs had little consistent effect on the conditional probability functions (see Fig. 2). (±)N-Allylnormetazocine produced dose-dependent decreases in rates of responding that were similar under both FCN schedules. While systematically decreasing rates of responding under the FCN 8 schedule, phencyclidine decreased responding only at the highest dose under the FCN 8-SD schedule.

Effects of Naloxone Alone and in Combination With Morphine and U50488

As shown in Fig. 5, when administered alone naloxone had no effect on accuracy levels under either FCN schedule. In addition, naloxone had little consistent effect on the conditional probability curves (Fig. 2). Under both schedules, naloxone decreased rates of responding. Figure 6 shows the effects of naloxone when administered in combination with a 3.0 mg/kg dose of morphine and 5.6 mg/kg dose of U50488. When administered alone, these doses of morphine and U50488 markedly decreased rates of responding and percent reinforced runs, but did not eliminate responding in any rat. The degree of rate-suppression engendered by the 5.6 mg/kg dose of U50488 under both FCN schedules was slightly larger than those produced by the 3.0 mg/kg dose of morphine. Doses of naloxone that had no effect when administered alone dose-dependently antagonized the disruptive behavioral effects of these drugs under both FCN schedules. Complete antagonism (i.e., when accuracy levels were within or above the control range) of morphine's and U50488's accuracy-decreasing effects were obtained with the 0.1 mg/kg dose of naloxone. In contrast, the rate-decreasing effects produced by morphine were antagonized by the 0.01 mg/kg dose of naloxone, whereas 1.0 mg/kg naloxone only partially antagonized (i.e., rates of responding were slightly below the control range) U50488's rate-decreasing effects.

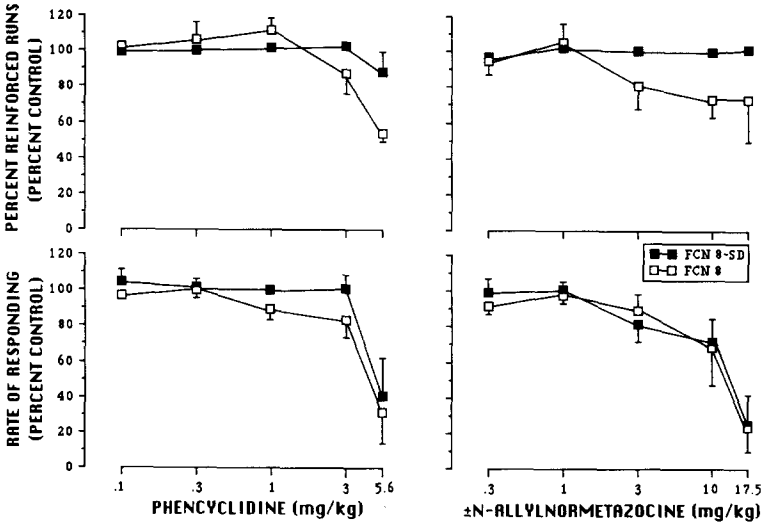

FIG. 4. Effects of phencyclidine (left panels) and (±)N-allylnormetazocine (right panels) on the percent of reinforced runs and rates of responding in four rats responding under the FCN schedules. Details are as described in Fig. 1.

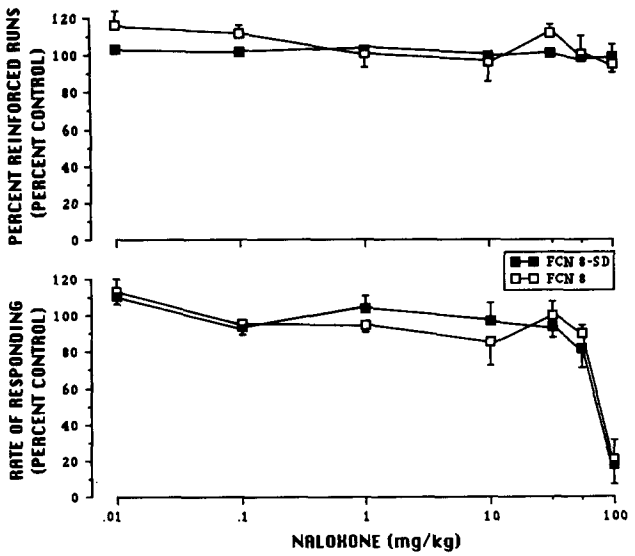

FIG. 5. Effects of naloxone on the percent of reinforced runs and rates of responding in four rats responding under the FCN schedules. Details are as described in Fig. 1.

DISCUSSION

In the present investigation, the mu agonists morphine and l-methadone, the kappa agonists U50488 and ketocyclazocine, and the sigma agonists phencyclidine and (±)N-allylnormetazocine decreased accuracy under the FCN 8 schedule at doses that had no effect on the accuracy of responding under the FCN 8-SD schedule. The opioid antagonist naloxone and the kappa agonist bremazocine, in contrast, had no effect on accuracy under either FCN schedule even at doses that markedly suppressed responding. That the opioids evaluated in the present investigation decreased accuracy in the FCN 8, but not in the FCN 8-SD, is consistent with a growing body of literature which indicates that the addition of an external discriminative stimulus can serve to modulate the disruptive behavioral effects of some psychoactive drugs [11, 13, 20, 25, 26, 28].

In addition, the finding that the opioid agonists evaluated in the present investigation decreased rates of responding under both FCN schedules is similar to those reported previously in rats, monkeys and pigeons performing under simple schedules of food presentation as well as various conditional discriminations [1, 4, 10, 15, 18]. Although cross-study and cross-species comparisons are often difficult to make, the relative potency of these drugs in terms of their rate-decreasing effects obtained in the present investigation are comparable to those reported previously in rats and monkeys (e.g., [1, 6, 20, 22]).

That morphine and l-methadone decreased the accuracy of responding is consistent with the effects of morphine when evaluated in rats responding under other conditional discrimination tasks [2, 3, 9, 20, 29]. The accuracy-decreasing effects of these drugs are, however, in contrast to those typically reported in monkeys and pigeons [17, 20, 23]. Recent evidence suggests, for example, that mu and kappa agonists have little effect on the accuracy of pigeons responding under delay matching-to-sample tasks [16,24] or monkeys responding under repeated acquisition and fixed-ratio discrimination tasks [21,22]. In rats responding under visual, shock, and fixed-ratio discrimination tasks, however, morphine produces dose-dependent decreases in accuracy [9, 21, 29].

In contrast to the interspecies differences observed with the mu agonists, the sigma agonists decrease the accuracy of responding in rats, monkeys and pigeons performing under various conditional discriminations [16, 17, 21, 23]. The present finding that phencyclidine and (±)N-allylnormetazocine decreased accuracy levels is in agreement with these investigations. Moreover, the present findings extend previous investigations by demonstrating the disruptive behavioral effects of these drugs can be modulated by the addition of an external discriminative stimulus.

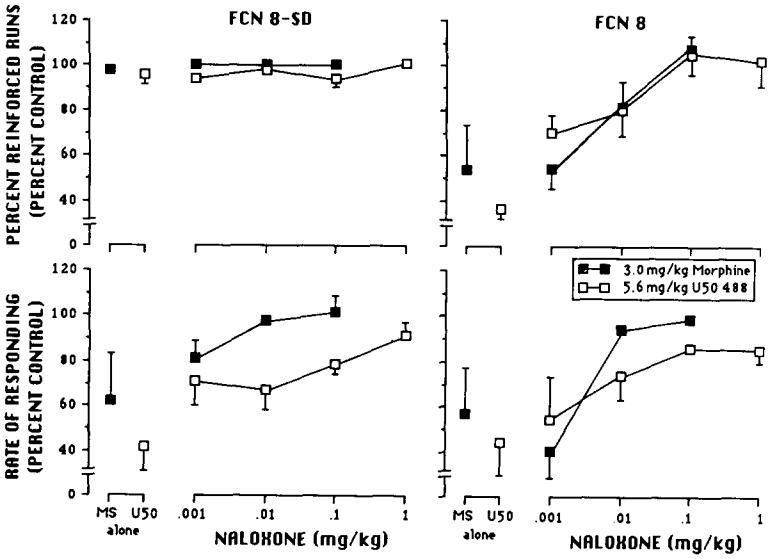

FIG. 6. Effects of naloxone in combination with a selected dose of morphine and U50488 on percent of reinforced runs and rates of responding. This dose of morphine and U50488 produced the greatest suppression of rates of responding and percent of reinforced runs without completely eliminating responding in any rat. Data portrayed in the left most panels represent mean group performance of rats responding under the FCN 8-SD schedule, while data in the right most panels represent responding under the FCN 8 schedule. Data points directly above MS and U50 (left most side of each panel) represent the effects of the selected dose of morphine and U50488 in the absence of any dose of naloxone.

In the present study, the kappa agonists U50488 and ketocyclazocine each decreased the accuracy of responding under the FCN 8 schedule at doses that had no effect on accuracy under the FCN 8-SD schedule. These findings are in sharp contrast to those obtained with bremazocine: even at doses that substantially reduced rates of responding this drug had no effect on accuracy. The evaluation of the effects of other kappa agonists in rats responding under conditional discrimination tasks have similarly yielded inconsistent findings. For example, ethylketocyclazocine has been reported to decrease the accuracy of rats responding under FCN schedules similar to those used in the present experiment [2], whereas this drug, like ketocyclazocine, has little consistent effect on accuracy under a fixed-ratio discrimination procedure [3,20]. Given these apparent discrepancies, it would be of interest to determine if the accuracy-altering effects of the kappa agonists are specific to certain discrimination tasks. Moreover, a kappa agonist classification system based on whether these drugs decrease accuracy under discrimination tasks may provide further insight into the behavioral mechanism of action underlying these processes.

Like bremazocine, the opioid antagonist naloxone had no effect on the accuracy of responding across an extensive range of doses. However, doses of naloxone that had no behavioral effects when given alone produced a dose-dependent antagonism of the accuracy- and rate-decreasing effects associated with the administration of selected doses of morphine and U50488. These results are in agreement with an extensive literature which indicates that the effects of mu and kappa opioids can be surmounted by the concomitant administration of opioid antagonists [12, 14, 23, 30]. In addition, it has been consistently reported that a distinguishing characteristic of the effects mediated by the mu, kappa and sigma receptors is the extent to which opioid antagonists are able to antagonize their effects. For instance, when contrasted with the mu agonists, substantially higher doses of opioid antagonists are required to antagonize the discriminative [12], rate-suppressing [3, 10, 14, 18], analgesic [5], and accuracy-decreasing [2, 3, 23] effects of the kappa agonists when evaluated in rats and monkeys. In the present study, this differential sensitivity was reflected in the finding that a 0.01 mg/kg dose of naloxone completely antagonized the rate-decreasing effects of morphine, whereas a dose 2 log-units larger antagonized U50488's rate-decreasing effects. Even at this dose of naloxone complete antagonism of U50-488's rate-suppressing effects were not obtained, in that rates of responding remained below the control range under both FCN schedules. These differential effects were selective in that a 0.1 mg/kg dose of naloxone antagonized completely the accuracy-decreasing effects produced by both of these drugs. Differential antagonism of morphine's accuracy- and rate-decreasing have similarly been reported in pigeons responding under a repeated acquisition procedure [30]. In that study, however, morphine-induced decreases in accuracy were blocked by doses of naloxone that had no effect on morphine-induced decreases in rates of responding.

ACKNOWLEDGEMENTS

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