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Effects of Mu, Kappa and Sigma Opioids on Fixed Consecutive Number Responding in Rats[1]

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BRONSON, M. E. AND J. M. MOERSCHBAECHER. *Effects of mu, kappa and sigma opioids on fixed consecutive number responding in rats.* PHARMACOL BIOCHEM BEHAV 27(4) 733–743, 1987.—Responding in rats was maintained under a fixed consecutive number 20 schedule. Under this schedule, at least 20 consecutive responses were required on one lever before a response on a second lever produced food. Morphine, buprenorphine, ethylketocyclazocine (ECK), N-allylnormetazocine (NANM) and *d*-cyclazocine all caused dose-dependent decreases in response rate. With the exception of buprenorphine and EKC, each drug also produced a decrease in the percent of reinforced runs. Differences among the drugs were more apparent, however, on the basis of the conditional probability of switching to the second lever after any given run length on the first lever. Morphine increased the probability of premature switching and decreased the probability of switching after run lengths greater than 20. Buprenorphine decreased the probability of switching at all run lengths and EKC produced occasional increases in premature switching. In sharp contrast to the other opioids tested, NANM and *d*-cyclazocine generally increased the probability of switching at all run lengths. Thus, it appears that the fixed consecutive number schedule may be a sensitive procedure for distinguishing among the behavioral effects of various opioid agonists.

Fixed consecutive number Rats Morphine EKC NANM *d*-Cyclazocine Buprenorphine *d*-Amphetamine

THE reinforcing and discriminative stimulus properties of the opioids have been characterized by various investigators [2, 5, 6, 17, 19, 20]. Data obtained under these procedures are generally consistent with the opioid receptor model proposed by Martin *et al.* [9]. Mu agonists have been found to function as positive reinforcers and share discriminative stimulus properties with morphin-like drugs, while kappa agonists are generally not self-administered and share discriminative stimulus properties with ethylketocyclazocine (EKC) [5,19]. The d-isomers of agonists which act at the putative sigma receptor (e.g., dexoxadrol) also function as reinforcers and share discriminative stimulus properties with N-allylnormetazocine (NANM) and phencyclidine [17].

Aside from their reinforcing and discriminative stimulus properties, it is difficult to distinguish among opioid agonists on the basis of their direct behavioral effects. For example, the opioids typically produce only dose-dependent decreases in the overall rate of responding under simple schedules of reinforcement [4]. Some differences among the opioids, however, have been reported in terms of their effects on the performance of complex discriminations. For example, in monkeys responding under a fixed ratio discrimination, at doses which produce approximately equivalent rate-decreasing effects, sigma agonists disrupt accuracy of responding while mu and kappa agonists do not [12]. However, in rats responding under a fixed-ratio discrimination [12], morphine, buprenorphine, EKC, NANM and cyclazocine all decreased response rate and, with the exception of EKC, all increased errors. Similarly, under other discrimination procedures, morphine has also been reported to disrupt accuracy of responding in rats [1,14], but not in monkeys [13]. Thus while these data suggest a difference between the rat and monkey in terms of the effects of mu agonists, they further emphasize the difficulty of distinguishing among the direct behavioral effects of various opioid agonists in the rat.

In a fixed consecutive number (FCN) procedure a predetermined number of consecutive responses are required on one lever before a subsequent response on a second lever is reinforced [7,10]. Previously this procedure has been used in an attempt to distinguish among the behavioral effects of different central nervous system stimulants [11]. Under this procedure amphetamine has been reported to produce decreases in both the overall response rate and in the percent of reinforced runs (accuracy). In addition, amphetamine also

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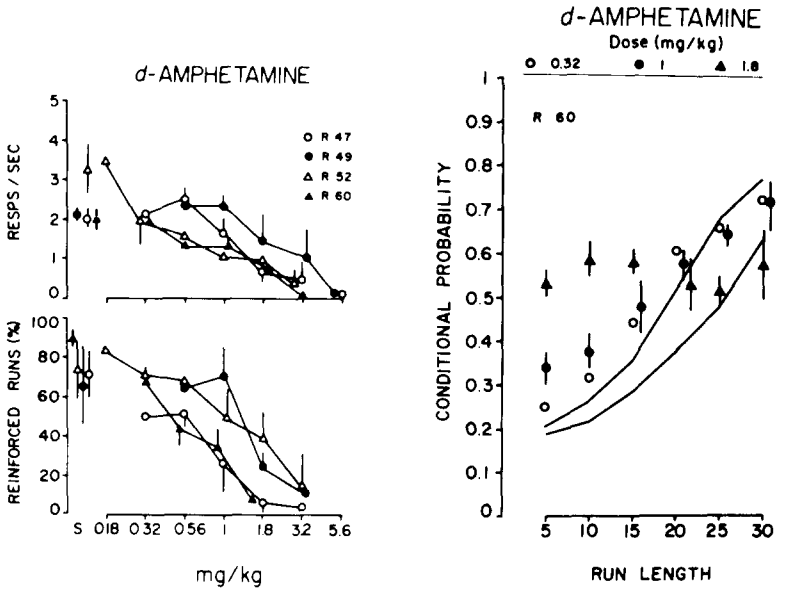

FIG. 1. Effects of varying doses of *d*-amphetamine on the overall response rate, percent of reinforced runs and conditional probability. The points with vertical lines in the dose-response curves indicate the mean and the range for at least two determinations. The points without vertical lines indicate either a single determination or an instance in which the range is encompassed by the point. For overall response rate and percent of reinforced runs (left panel), the points and vertical lines above S indicate the mean and the range for at least six saline doses. When response rate for any particular dose is zero, no data point for that dose is shown for percent of reinforced runs. For conditional probability (right panel), the ordinate gives the probability that the rat will stop after the number of consecutive responses on the abscissa and switch to the right lever. Only run lengths reaching or exceeding twenty were reinforced. The saline range is indicated by the solid lines. It should be noted that not all doses which affected conditional probability are plotted. These data are shown in the corresponding tables.

increases the probability of prematurely switching to the second lever [7, 8, 16]. Recently this procedure has also been used to study the effects of various anticonvulsant drugs [15].

A procedure which could distinguish among the direct behavioral effects of the prototypical opioid agonists in the rat would provide a basis on which the behavioral properties of other opioids might be compared. In addition, such a procedure might be of value in further elucidating the mechanism(s) responsible for mediating the behavioral effects of the opioids in the rat. Preliminary results in this laboratory suggested that the FCN procedure might be useful in both of these regards [3]. In one phase of the present study *d*-amphetamine was tested in order to determine whether its effects under an FCN 20 schedule would be similar to those obtained by other investigators using an FCN 8 schedule [7, 8, 11, 16]. The major purpose of the study was, however, to characterize the effects of morphine, a mu agonist; buprenorphine, a partial mu agonist; EKC, a kappa agonist; and NANM and *d*-cyclazocine, which are sigma agonists, on responding under an FCN 20 schedule in the rat.

METHOD

Subjects

Ten naive adult male Long Evans hooded rats served as subjects. Each was shaped to respond under a fixed consecutive number schedule. Subjects were maintained at approximately 80% of their free-feeding weights by presentation of food pellets (Bio-Serve, Product No. 0021, 45 mg) during the sessions and by supplemental post-session feeding (Purina Rat Chow). Water was continuously available in the individual home cages. The home cages were kept in a temperature-controlled room under a 12 hr light-12 hour dark cycle.

Apparatus

A standard sound-attenuated experimental chamber was used. Mounted on one wall of the chamber were two response levers (Coulbourn No. E21-03) spaced approximately 8 cm apart. A pilot lamp was mounted 5 cm above each lever. A food pellet cup, houselight and pellet dispenser were mounted on the same wall but 5 cm to the right of the right lever. Solid-state equipment (Coulbourn Instruments) was used to program the procedure and the data were recorded on counters and a cumulative recorder.

Behavioral Procedure

The baseline procedure consisted of a fixed consecutive number schedule [10,11]. Under this procedure the subject was required to make at least 20 consecutive responses on the left lever before a subsequent response on the right lever was reinforced with presentation of a food pellet. Presenta-

TABLE 1

EFFECTS OF *d*-AMPHETAMINE* ON CONDITIONAL PROBABILITY OF SWITCHING

Subject	Dose		Run Length 5	10	15	20	25	30
R41	saline	high	0.41	0.6	0.75	0.85	1	0.8
	saline	low	0.29	0.39	0.42	0.66	0.76	0
	1 mg/kg		*0.55*	*0.69*	*0.83*	*0.87*	*0.5*	0
	1.8 mg/kg		*0.68*	*0.66*	0.68	0.83	*0.5*	0
R47	saline	high	0.27	0.47	0.57	0.83	1	1
	saline	low	0.23	0.3	0.43	0.63	0.7	0
	1 mg/kg		*0.37*	0.45	*0.59*	0.7	0.78	0.9
R49	saline	high	0.29	0.41	0.61	0.82	0.76	1
	saline	low	0.2	0.27	0.38	0.54	0.62	0.56
	1.8 mg/kg		*0.37*	*0.43*	0.49	*0.5*	*0.46*	0.68
	3.2 mg/kg		*0.5*	*0.51*	0.41	*0.36*	*0.46*	0.65
R52	saline	high	0.28	0.33	0.43	0.6	0.82	0.82
	saline	low	0.19	0.23	0.26	0.36	0.46	0.66
	3.2 mg/kg		*0.36*	*0.4*	*0.45*	0.56	0.69	*0.84*
R60	saline	high	0.23	0.26	0.36	0.52	0.69	0.76
	saline	low	0.17	0.23	0.29	0.37	0.49	0.65
	0.56 mg/kg		*0.3*	*0.36*	*0.45*	*0.56*	0.63	*0.81*

*Each value is the mean of two determinations in each subject. Values in italics are outside saline range.

tion of the food pellet was accompanied by a brief timeout (3 seconds) during which the house light was on and the pilot lamps above the levers were off. Premature responses on the right lever reset the requirements on the left lever. The session duration was 30 minutes.

Pharmacological Procedures

Before drug testing began, the fixed consecutive number schedule baseline was stabilized. The baseline was considered stable when the response rate, percent of reinforced runs and conditional probabilities no longer showed systematic change from session to session. After baseline stabilization, dose-effect data were obtained for *d*-amphetamine sulfate (0.18–5.6 mg/kg), morphine sulfate (0.18–10 mg/kg), EKC methane sulfonate (0.032–0.56 mg/kg), buprenorphine HCl (0.01–1 mg/kg), NANM HCl (0.56–18 mg/kg) and *d*-cyclazocine (0.56–18 mg/kg). Doses were administered at least two times in most cases, although in some instances only a single determination was made. The drugs were given in a mixed order and at least ten days of baseline sessions intervened between the end of a series of injections with one drug and the start of injections with another. The doses of each drug were also tested in a mixed order. *d*-Cyclazocine was dissolved in three parts of 8.5% lactic acid and two parts 1 N sodium hydroxide, buprenorphine was dissolved in sterile water and the other drugs were dissolved in saline. Drug and control (saline) injections were given IP 10 minutes presession and the volume of injection was 2 ml/kg body weight. Drug testing was conducted on Tuesdays and Fridays, with control injections on Thursdays.

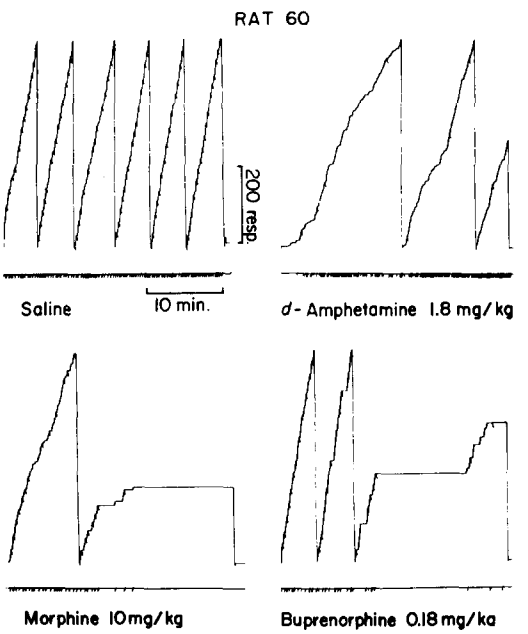

FIG. 2. Cumulative response records for rat 60 showing the pattern of responding during a control session (saline) and during sessions preceeded by either *d*-amphetamine, morphine or buprenorphine. The response pen stepped upward with each left-lever response and was deflected downward with each reinforcement. Right-lever responses are indicated by the event pen.

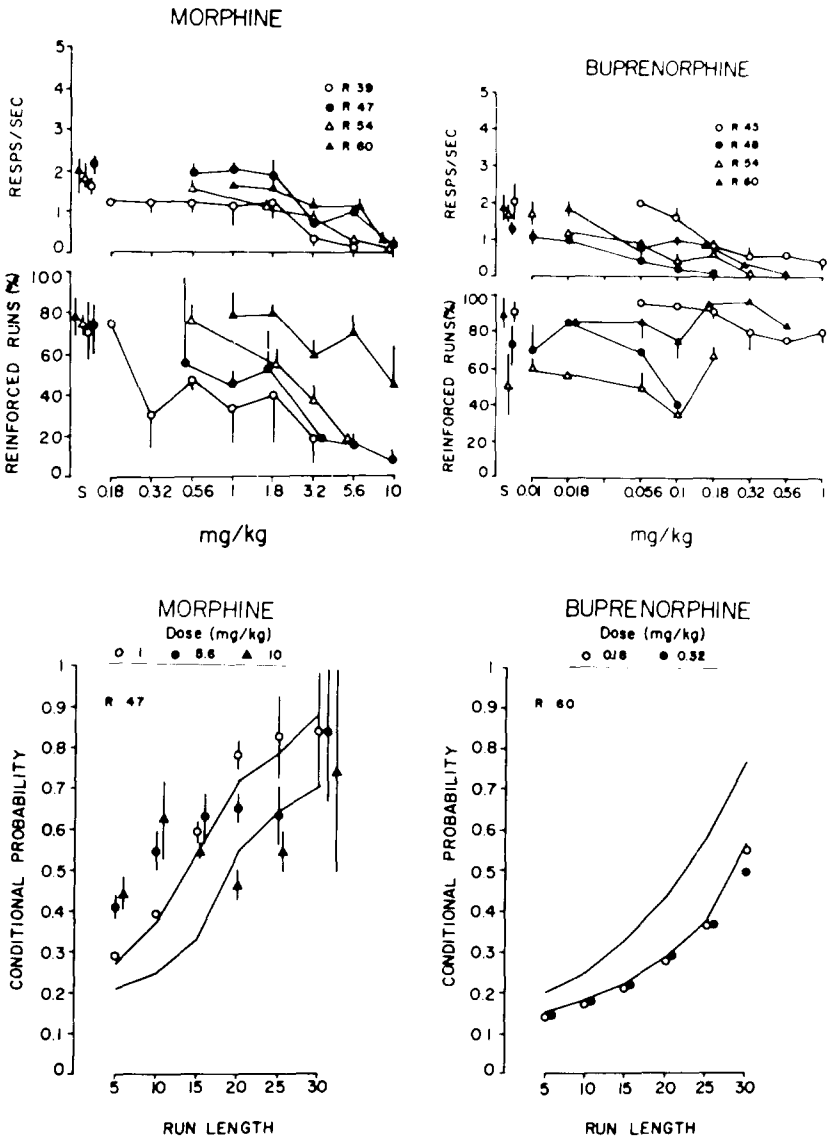

FIG. 3. Effects of varying doses of morphine (left panels) and buprenorphine (right panels) on overall response rate, percent of reinforced runs and conditional probability. Details are the same as in Fig. 1.

At the higher doses of buprenorphine, however, drug injections were given only once a week.

Data Analysis

The data for each session were analyzed in terms of the overall response rate, percent of reinforced runs and conditional probability. Overall rate was calculated by dividing the number of responses on the left lever by the session time (30 minutes minus the reinforcement time-outs). Percent of reinforced runs was calculated by dividing the number of runs which reached or exceeded 20 by the total number of runs. A run was initiated by the first response on the left lever and was terminated by the first response on the right lever. Data concerning run length were collected in 5-run bins (e.g., [5, 10, 15, 20, 25, 30]). Conditional probability was defined as the probability that the subject will switch to the right lever (the reinforcement lever) after any given run length on the left lever. This was calculated by dividing the frequency of the run length in question by the number of times that run length was reached or exceeded during the session [10]. Conditional probability was calculated on this basis from the data collected in the 5-run bins. Conditional probability data was not used if the overall number of runs during a drug session was less than 20% of the mean overall runs made during control sessions.

RESULTS

Effects of d-*Amphetamine*

d-Amphetamine produced dose-dependent decreases in

TABLE 2

EFFECTS OF MORPHINE* ON CONDITIONAL PROBABILITY OF SWITCHING

Subject	Dose		Run Length 5	10	15	20	25	30
R39	saline	high	0.27	0.4	0.59	0.75	0.84	1
	saline	low	0.22	0.27	0.38	0.55	0.69	0.8
		1.8 mg/kg	*0.31*	*0.45*	0.58	0.73	0.81	1
		3.2 mg/kg	*0.37*	*0.53*	*0.75*	0.72	*1*	0
R47	saline	high	0.28	0.38	0.55	0.72	0.79	0.89
	saline	low	0.21	0.25	0.33	0.55	0.65	0.71
		3.2 mg/kg	*0.39*	*0.51*	*0.66*	*0.76*	*0.5*	*0.6*
R54	saline	high	0.25	0.33	0.49	0.73	0.94	1
	saline	low	0.23	0.3	0.42	0.58	0.77	0.89
		3.2 mg/kg	*0.31*	*0.41*	*0.57*	0.66	*0.62*	*0.68*
		5.6 mg/kg	*0.39*	*0.53*	*0.62*	0.7	*0.33*	*0.5*
R60	saline	high	0.24	0.32	0.43	0.54	0.73	0.85
	saline	low	0.2	0.26	0.34	0.45	0.56	0.7
		10 mg/kg	*0.28*	*0.35*	*0.46*	0.5	*0.46*	*0.65*

*Each value is the mean of two determinations in each subject, except in those instances in which only a single determination was made. Values in italics are outside saline range.

the overall response rate and in the percent of reinforced runs. These results are shown for 4 of the 5 subjects tested in the left panel of Fig. 1. The effects of *d*-amphetamine on the conditional probability of switching to the right lever after any given run length on the left lever are shown for one rat (R60) in the right panel of Fig. 1. The effects of selected doses of *d*-amphetamine on conditional probability measures for the other subjects are listed in Table 1. In general, the probability of switching to the right lever after the shorter runs was increased by *d*-amphetamine while the probability of switching after the longer runs (20 and greater) was unaffected. The effects of *d*-amphetamine on the within-session pattern of responding are shown in the cumulative record for R60 in Fig. 2. *d*-Amphetamine decreased the overall response rate by decreasing the local rates of responding, rather than by producing pauses in responding.

Effects of Morphine

Like amphetamine, morphine produced dose-dependent decreases in the overall rate and percent of reinforced runs. The data are shown for each subject tested in the top left panel of Fig. 3. The effects of selected doses of morphine on the conditional probability measures for the other subjects are listed in Table 2. The effects of morphine on the conditional probability of switching is also shown in the bottom left panel of Fig. 3 for R47. In general, morphine increased the probability of switching at the shorter run lengths while decreasing the probability at the longer run lengths. The cumulative record for one representative rat is shown in Fig. 2. Like amphetamine, morphine produced its rate-decreasing effects by decreasing the local rate of responding. In addition, morphine also produced sporadic pausing. Although only one dose is shown for morphine, it should be noted that the frequency of the pauses increased as a function of the dose. Figure 2 also shows a difference in morphine and amphetamine in terms of their effects on accuracy; *d*-amphetamine tended to produce a much greater decrease in the number of reinforcements than did morphine.

Effects of Buprenorphine

Buprenorphine also produced dose-dependent decreases in the overall response rate as is shown for 4 of the 5 subjects tested in the top right panel of Fig. 3. Across this same range of doses the percent of reinforced runs was relatively unaffected. There was, however, a general tendency for buprenorphine to decrease the conditional probability across all run lengths (Fig. 3, bottom right, and Table 3). Thus, accuracy was affected in that the subject was making runs that were longer than necessary. The cumulative record for one representative rat is shown in Fig. 2. In contrast to both amphetamine and morphine, buprenorphine had very little effect on the local rate of responding. Instead, it produced its rate-decreasing effects by causing sporadic pausing. Although not shown, the length of the pauses increased as a function of the dose.

Effects of Ethylketocyclazocine

With EKC, two general trends were seen among the subjects, as shown in Fig. 4. In three of the rats (Fig. 4, top left), there was a gradual dose-dependent decrease in the overall rate of responding. The rate-decreasing effects obtained in these subjects was due to a dose-related pause at the beginning of the session (data not shown). In addition when responding resumed it was comparable to that observed under control conditions, hence there was little (R47) or no effect on the percentage of reinforced runs. For the other subjects, however, the dose-response curves for the overall rate were very steep (Fig. 4, top right) and percent of reinforced runs

TABLE 3

EFFECTS OF BUPRENORPHINE* ON CONDITIONAL PROBABILITY OF SWITCHING

Subject	Dose		Run Length 5	10	15	20	25	30
R45	saline	high	0.53	0.33	0.48	0.63	0.75	0.85
	saline	low	0.15	0.19	0.24	0.31	0.41	0.51
	0.18 mg/kg		0.19	0.19	*0.21*	*0.27*	*0.36*	0.55
R52	saline	high	0.33	0.33	0.36	0.41	0.54	0.69
	saline	low	0.2	0.2	0.23	0.29	0.37	0.55
	0.56 mg/kg		*0.12*	0.2	*0.2*	*0.25*	*0.33*	*0.5*
	1 mg/kg		*0.17*	*0.17*	*0.21*	*0.25*	*0.32*	*0.51*
	1.8 mg/kg		0.2	0.2	*0.2*	*0.25*	*0.34*	*0.49*
R54	saline	high	0.31	0.43	0.69	0.94	1	1
	saline	low	0.26	0.35	0.54	0.81	0.75	0
	0.18 mg/kg		*0.25*	*0.34*	*0.51*	*0.78*	1	0

*Each value is the mean of two determinations in each subject, except in those instances in which only a single determination was made. Values in italics are outside saline range.

was unaffected except in R60 where there was a decrease at the 0.18 mg/kg dose. The conditional probabilities for all but rats 47 and 60 were unaffected. Although the dose-response curves for overall rate differed for these two rats, their conditional probability profiles are almost identical (Fig. 4, bottom left and bottom right). In both rats, EKC produced a slight increase in the probability of switching after the shorter runs while the probability of switching after the longer runs was unaffected.

Effects of N-Allylnormetazocine

N-Allylnormetazocine produced dose-dependent decreases in the overall rate and percent of reinforced runs. The results are shown for 3 of the 5 subjects tested in Fig. 6 (top left). Conditional probability data for R39 are shown at the bottom left of Fig. 6. Conditional probability data for the other 4 rats are presented in Table 4. Generally, the probability of switching was increased in a dose-dependent manner at run lengths of 20 or less. With the exception of R49, the conditional probabilities at the longer run lengths were either unaffected or increased by NANM. As is shown in Fig. 5, the within-session pattern of responding for NANM was characterized by sporadic pausing and a decrease in the local rate of responding early in the session. Although only one dose is shown, the duration of this decrease was dose-dependent.

Effects of d-*Cyclazocine*

The effects of *d*-cyclazocine were similar to those produced by NANM. Overall rate and percent of reinforced runs generally decreased in a dose-dependent manner. These data are shown for 3 of the 4 subjects tested in the top right panel of Fig. 6. In one of the rats (R52), *d*-cyclazocine produced a dose-dependent decrease in the overall rate of responding, but had no effect on the percent of reinforced runs. In the other two rats (R45 and R46), the opposite effect was seen; that is, at doses which had little or no effect on the overall rate, there was a dose-dependent decrease in the percent of reinforced runs. Although not as striking as the effect produced by NANM, the general effect of *d*-cyclazocine (Fig. 6, bottom right, and Table 5) was similar in that the probability of switching after run lengths of 20 or less was increased while longer run lengths were generally unaffected.

The effects of cyclazocine on the pattern of responding is illustrated by the cumulative record in Fig. 5. Like NANM, *d*-cyclazocine produce pausing and a decrease in the local rate of responding early in the session. Later in the session overall rate of responding approached control levels, however, the rate of reinforcement was greatly decreased relative to the control. A dose of EKC which produced a decrease in overall rate comparable to those produced by NANM and *d*-cyclazocine is also shown for this same subject in Fig. 5. Note that EKC, unlike NANM and *d*-cyclazocine, had little effect on the rate of reinforcement once responding resumed.

DISCUSSION

One purpose of this study was to determine whether increasing the ratio requirement under the FCN to 20 would alter the effects of *d*-amphetamine previously reported under an FCN 8 [7, 8, 11, 16]. The higher FCN requirement did not change the effects of *d*-amphetamine. As was previously found, dose-related decreases in the overall respones rate and percent of reinforced runs were also obtained under the larger ratio requirement. In addition, the conditional probability results obtained in the present study were also similar to those previously reported in rats in that the probability of premature switches was increased [8,16]. Thus it appears that similar results are obtained with amphetamine even when the FCN requirement is increased by as much as two and a half fold.

The primary purpose of the study was to determine whether various opioid agonists would differ in terms of their

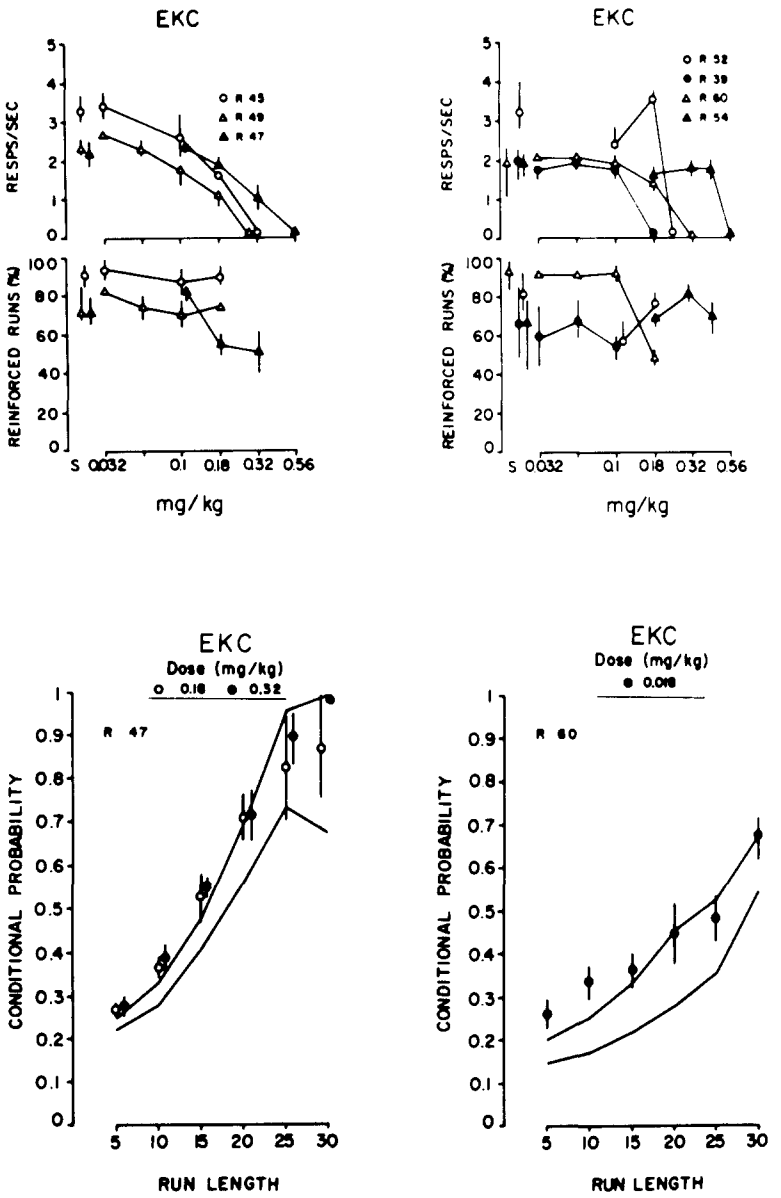

FIG. 4. Effects of varying doses of EKC on overall rate, percent of reinforced runs and conditional probability. Details are the same as in Fig. 1.

TABLE 4

EFFECTS OF NAMN* ON CONDITIONAL PROBABILITY OF SWITCHING

Subject	Dose		Run Length 5	10	15	20	25	30
R48	saline	high	0.22	0.29	0.39	0.5	0.65	0.8
	saline	low	0.12	0.2	0.25	0.31	0.41	0.51
	5.6 mg/kg		0.22	*0.35*	*0.41*	*0.55*	*0.7*	*0.85*
R49	saline	high	0.23	0.35	0.45	0.65	0.8	0.92
	saline	low	0.21	0.3	0.35	0.53	0.72	0.72
	1.8 mg/kg		*0.26*	*0.36*	*0.52*	*0.75*	0.75	*0.56*
	3.2 mg/kg		*0.26*	*0.4*	*0.62*	*0.78*	0.72	*0.66*
	5.6 mg/kg		*0.3*	*0.41*	*0.6*	*0.78*	*0.56*	*0.57*
	10 mg/kg		*0.35*	*0.45*	*0.55*	*0.62*	0.75	0.84
R54	saline	high	0.27	0.38	0.61	0.84	1	1
	saline	low	0.23	0.3	0.4	0.55	0.82	0
	5.6 mg/kg		*0.45*	*0.57*	*0.75*	0.84	1	0
	10 mg/kg		*0.52*	*0.68*	*0.79*	*0.4*	*0.66*	1
R60	saline	high	0.21	0.25	0.31	0.38	0.5	0.68
	saline	low	0.18	0.21	0.26	0.33	0.42	0.58
	5.6 mg/kg		*0.28*	*0.32*	*0.38*	*0.45*	*0.6*	0.66
	10 mg/kg		*0.4*	*0.5*	*0.65*	*0.63*	*0.75*	*1*

*Each value is the mean of two determinations in each subject. Values in italics are outside saline range.

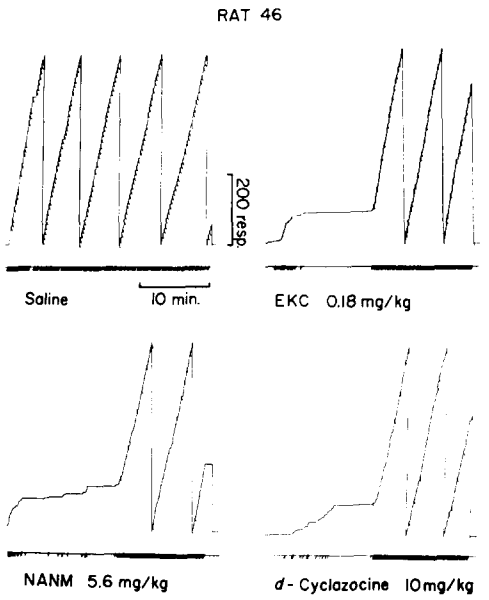

FIG. 5. Cumulative response records for rat 46 showing the pattern of responding during a control session and sessions preceeded by EKC, NANM and *d*-cyclazocine. Other details are the same as in Fig. 2.

behavioral effects in rats responding under an FCN procedure. In other behavioral paradigms where responding is maintained by food presentation, opioids produce a decrease in response rate [4]. Similar results were obtained with all of the opioids tested in the present study. It should be noted, however, that EKC, NANM and *d*-cyclazocine tended to have relatively steep dose-response curves in comparison with morphine and buprenorphine. With the exception of buprenorphine, and EKC in the majority of the subjects, all of the opioids included in this study also produced a decrease in the percent of reinforced runs. In terms of their effects on overall response rate and the percent of reinforced runs, the results obtained in the present study are generally consistent with those obtained with some of these same opioids in rats responding under a fixed-ratio discrimination procedure [12]. In that study morphine, buprenorphine, NANM and cyclazocine each disrupted accuracy at doses that had little or no effect on overall rate of responding. Thus, if overall rate and percent of reinforced runs were the only dependent variables considered, the behavioral effects of the different opioids would generally appear similar in the rat.

In contrast to the similarities in drug effects observed on overall response rate and percent of reinforced runs, the effects of the various opioid agonists on conditional probability were quite different. For example, buprenorphine, a partial agonist at the mu receptor, produced decreases in all run lengths. EKC, a kappa agonist, had little or no effect on conditional probability except in a few rats in which there was a slight increase in the shortest runs. That EKC had no effect on accuracy in this procedure is similar to results obtained in rats responding under a fixed ratio discrimination [12]. Morphine, a mu agonist, and two sigma

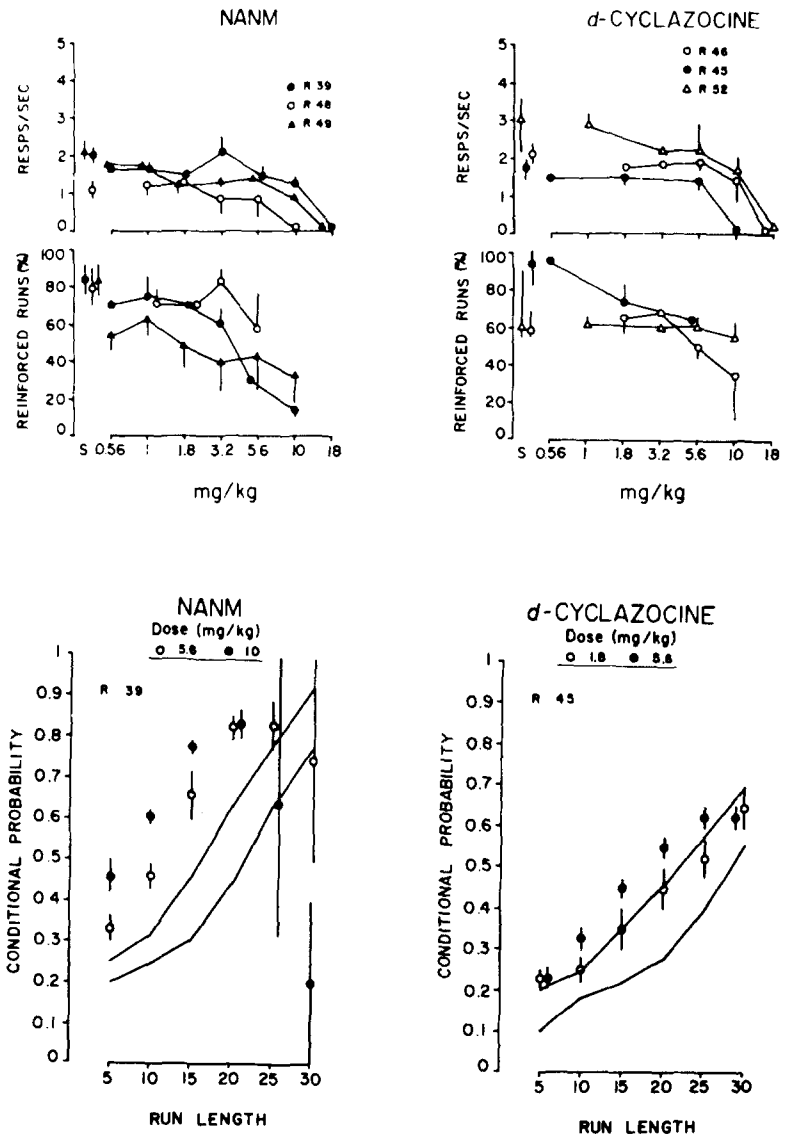

FIG. 6. Effects of varying doses of NANM (left panels) and *d*-cyclazocine (right panels) on overall rate, percent of reinforced runs and conditional probability. Details are the same as in Fig. 1.

TABLE 5

EFFECTS OF *d*-CYCLAZOCINE* ON CONDITIONAL PROBABILITY OF SWITCHING

Subject	Dose		Run Length 5	10	15	20	25	30
R46	saline	high	0.27	0.39	0.6	0.88	0.93	1
	saline	low	0.25	0.34	0.5	0.74	0.81	0.5
	10 mg/kg		*0.37*	*0.5*	*0.7*	0.82	*0.66*	0.57
R47	saline	high	0.25	0.35	0.55	0.82	0.95	1
	saline	low	0.23	0.3	0.43	0.65	0.74	0.5
	5.6 mg/kg		*0.27*	*0.38*	*0.58*	*0.83*	0.93	*0.4*
R52	saline	high	0.24	0.23	0.25	0.31	0.4	0.56
	saline	low	0.16	0.16	0.21	0.27	0.35	0.52
	10 mg/kg		*0.26*	*0.25*	*0.26*	*0.32*	0.38	*0.57*

*Each value is the mean of two determinations in each subject. Values in italics are outside saline range.

agonists (NANM and *d*-cyclazocine) all produced dose-dependent increases in premature switching (i.e., switching to the right lever before 20 responses had been completed on the left lever). Morphine produced a substantial decrease in those run lengths which would have been reinforced, i.e., run lengths of 20 or greater. In contrast, the sigma agonists tended to either increase or have no effect on run lengths of 20 or more. The differential effects of the opioids on the conditional probability of switching is in striking contrast to their more uniform effects on response rate and accuracy obtained in the present and previous studies [12]. Thus, a more molecular analysis of responding may reveal differential effects of various drugs upon discriminative performance that are not readily evident when a more molar analysis of the data is made.

The various opioids also differed in terms of their effects on the within-session patterning of responding. While both morphine and buprenorphine decreased the overall response rate, morphine did so by decreasing the local rate of responding and by producing sporadic pauses. Buprenorphine, on the other hand, decreased rate by producing long within-session pauses in responding. While *d*-cyclazocine and NANM also produced short and sporadic pausing within the session, the primary effect of NANM was to produce a dose-dependent decrease in the local rate of responding early in the session. EKC also produced dose-dependent pauses at the beginning of the session, but it differed from NANM and *d*-cyclazocine in that when responding was restored, it was similar to responding under saline conditions.

In summary, each of the opioid agonists under consideration produced a decrease in the overall rate of responding. In addition, morphine, NANM and *d*-cyclazocine all produced a decrease in the percent of reinforced runs, while buprenorphine and EKC generally had no effect. It was possible, however, to distinguish between mu and sigma agonists on the basis of their effects on conditional probability and also according to their within-session pattern of responding. Thus, it appears that the FCN may be a useful procedure for distinguishing among the behavioral effects of different opioid agonists in the rat.

REFERENCES

1. Andrews, J. S. and S. G. Holtzman. Effects of amphetamine, morphine and naloxone on visual-discrimination in rats. *Fed Proc* **45:** 561, 1986.
2. Balster, R. L. and S. E. Lukas. Review of self-administration. *Drug Alcohol Depend* **14:** 249–261, 1985.
3. Bronson, M. and J. M. Moerschbaecher. Effects of amphetamine and opioids on rats responding under a fixed consecutive number schedule. *Pharmacologist* **27:** 793, 1985.
4. Goldberg, S. R., R. D. Spealman and H. E. Shannon. Psychotropic effects of opioids and opioid antagonists. In: *Psychotropic Agents. Part III: Alcohol and Psychotomimetics, Psychotropic Effects of Central Acting Drugs,* edited by F. Hoffmeister and G. Stille. New York: Springer-Verlag, 1982, pp. 269–304.
5. Herling, S. and J. H. Woods. Discriminative stimulus effects of narcotics: Evidence for multiple receptor-mediated actions. *Life Sci* **28:** 1571–1584, 1981.
6. Holtzman, S. G. Discriminative stimulus properties of opioids that interact with mu, kappa and PCP/sigma receptors. In: *Behavioral Pharmacology: The Current Status,* edited by L. S. Seiden and R. L. Balster. New York: A. R. Liss, 1985.
7. Laties, V. G. The modification of drug effects on behavior by external discriminative stimuli. *J Pharmacol Exp Ther* **183:** 1–13, 1972.
8. Laties, V. G., R. W. Wood and D. C. Rees. Stimulus control and the effects of *d*-amphetamine in the rat. *Psychopharmacology (Berlin)* **75:** 277–282, 1981.
9. Martin, W. R., C. G. Eades, J. A. Thompson, R. E. Huppler and P. E. Gilbert. The effects of morphine and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J Pharmacol Exp Ther* **197:** 517–532, 1976.
10. Mechner, F. Probability relations within response sequences under ratio reinforcement. *J Exp Anal Behav* **1:** 109–121, 1958.
11. Mechner, F. and M. Latranyi. Behavioral effects of caffeine, methamphetamine, and methylphenidate in the rat. *J Exp Anal Behav* **6:** 331–342, 1963.

12. Moerschbaecher, J. M., J. Mastropaolo, P. J. Winsauer and D. M. Thompson. Effects of opioids on accuracy of a fixed-ratio discrimination in monkeys and rats. *J Pharmacol Exp Ther* **230:** 541–549, 1984.
13. Moerschbaecher, J. M. and D. M. Thompson. Differential effects of prototype opioid agonists on the acquisition of conditional discriminations in monkeys. *J Pharmacol Exp Ther* **226:** 738–748, 1983.
14. Paule, M. G. and D. E. McMillan. Incremental repeated acquisition in the rat: Acute effects of drugs. *Pharmacol Biochem Behav* **21:** 431–439, 1984.
15. Picker, M., L. Leibold, B. Endsley and A. Poling. Modulations of the behavioral effects of anticonvulsant drugs by an external discriminative stimulus in the pigeon. *J Pharmacol Exp Ther* **238:** 529–535, 1986.
16. Rees, D. C., R. W. Wood and V. G. Laties. The roles of stimulus control and reinforcement frequency in modulating the behavioral effects of *d*-amphetamine in the rat. *J Exp Anal Behav* **43:** 243–255, 1985.
17. Slifer, B. L. and R. L. Balster. Reinforcing properties of stereoisomers of the putative sigma agonists N-allynormetazocine and cyclazocine in rhesus monkeys. *J Pharmacol Exp Ther* **225:** 522–528, 1983.
18. Szostak, C. and T. N. Tombaugh. Use of a fixed consecutive number schedule of reinforcement to investigate the effects of pimozide on behavior controlled by internal and external stimuli. *Pharmacol Biochem Behav* **15:** 609–617, 1981.
19. Woods, J. H., A. M. Young and S. Herling. Classification of narcotics on the basis of their reinforcing, discriminative and antagonist effects in rhesus monkeys. *Fed Proc* **41:** 221–227, 1982.
20. Woolverton, W. L. and C. R. Schuster. Behavioral and pharmacological aspects of opioid dependence: Mixed agonist-antagonists. *Pharmacol Rev* **35:** 33–52, 1983.