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Discriminative Stimulus Properties and Schedule Effects of Fencamfamine in Rats[1]

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RISNER, M. E., P. A. JACKSON-SMITH AND E. J. CONE. *Discriminative stimulus properties and schedule effects of fencamfamine in rats.* PHARMACOL BIOCHEM BEHAV 23(3) 449–456, 1985.—The behavioral properties of fencamfamine, a sympathomimetic central stimulant recently identified in alleged cocaine samples, were studied in two different paradigms. In Experiment I, rats were trained to discriminate between injections of saline (0.1 ml/kg, IP) and cocaine (3.0 mg/kg, IP) in a two-lever drug discrimination task on a fixed-ratio (FR) 10 schedule of water presentation. Fencamfamine (0.3–3.0 mg/kg, IP) produced cocaine-appropriate choice behavior and was slightly more potent than cocaine in producing this effect. In Experiment II, rats responded under a multiple fixed-interval (FI) 300 sec, FR 20 schedule of water presentation. Fencamfamine (0.1–10.0 mg/kg, IP) and cocaine (0.1–30.0 mg/kg, IP) produced qualitatively similar effects on responding under this schedule. With increasing doses of either drug, FI response rates first increased, then decreased; FR response rates were only decreased. Fencamfamine was approximately three times more potent than cocaine in producing these effects. The results of these two experiments indicate that fencamfamine and cocaine have similar behavioral properties.

Fencamfamine Cocaine Drug discrimination Schedule-controlled responding Rats

FENCAMFAMINE (2-ethylamino-3-phenyl-bicyclo 2.2.1 heptane; Fig. 1) is a heterocyclic beta-phenylethylamine derivative with amphetamine-like central nervous system activity. It is marketed in England for the treatment of fatigue and depression [22]. Although fencamfamine is less potent than amphetamine, both drugs have qualitatively similar anorexic, cardiovascular, locomotor and neurochemical effects [1, 3, 13, 17, 24, 26]. The effects of fencamfamine on the sleep cycle are also like those of amphetamine and another heterocyclic phenylethylamine, methylphenidate; all three drugs increase wakefulness and depress REM sleep [19,21]. Furthermore, there is evidence that fencamfamine impairs cognitive functioning, especially visual association tasks [18].

Abuse of fencamfamine has occurred among certain populations, particularly European athletes [9]. Recently, fencamfamine has appeared in the illicit drug market of the United States and is being sold as cocaine (M. Klein, Drug Enforcement Administration, personal communication, 1984). Chemical analyses of samples obtained in drug seizures have revealed the presence of fencamfamine alone and combination with other substances including ephedrine, caffeine, lidocaine and benzoic acid. Combinations of fencamfamine with a local anesthetic and benzoic acid could potentially be difficult to distinguish from cocaine.

The purpose of the present experiments was to study the behavioral properties of fencamfamine using two different paradigms. In one experiment, the ability of fencamfamine to produce cocaine-appropriate responding was assessed in rats trained to discriminate cocaine from saline in a two-lever, water-reinforced choice task. In the second experiment, the effects of fencamfamine were compared with those of cocaine in rats responding under a multiple fixed-interval (FI), fixed-ratio (FR) schedule of water presentation. The results of these two experiments provide evidence of the psychopharmacological similarities of these two drugs.

EXPERIMENT 1

METHOD

Subjects

The subjects were four experimentally naive, male Fischer-derived F344 rats (Harlan Industries, Indianapolis, IN), weighing 292 to 321 g when given free access to dry food and water. Before the experiment began, access to water was restricted until the rats reached approximately 80–85% of their control body weights. They were maintained at this weight by giving them limited water supplements after each session. Dry food was continuously available in the home cage. Between experimental sessions the rats were kept in individual home cages in a colony room that was illuminated between 6:00 a.m. and 6:00 p.m.

Apparatus

Two-lever rat test chambers (Model RTC-024, BRS/LVE,

[1]A preliminary report of these studies was presented at the 68th Annual Meeting of the Federation of American Societies for Experimental Biology, St. Louis, MO, 1984 (*Fed Proc* **43**: 573, 1984).

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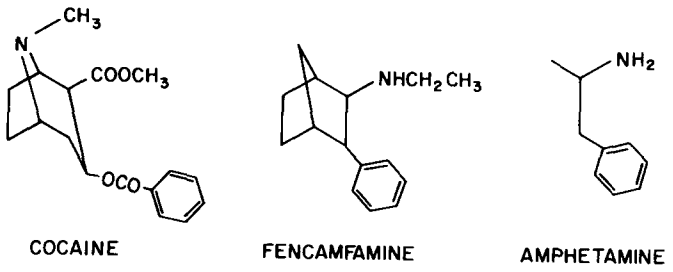

FIG. 1. Chemical structures of cocaine, fencamfamine and amphetamine. The beta-phenylethylamine linkage is evident in the latter two structures.

Laurel, MD), inside well-ventilated, light- and sound-attenuated cubicles (Model SEC-002, BRS/LVE, Laurel, MD), were used. One response lever was located 8.5 cm on either side of a liquid dipper that could dispense 0.1 ml water. Three colored jewel lights were positioned immediately above each lever; a houselight was mounted 21.5 cm above the water access port. White noise was continuously delivered through a loudspeaker to minimize the effects of extraneous sounds. Schedule contingencies were programmed and data recorded by a SCAT 3002/PDP 8E computer system (Grason-Stadler Co., Concord, MA/Digital Equipment Corp., Maynard, MA).

Procedure

The rats were trained to discriminate cocaine from saline using a two-lever choice task reinforced with water presentation. Experimental sessions were conducted Monday through Saturday with each rat. Sessions began with a 5-min blackout period, and ended after 20 trials (each signalled by illumination of the houselight), or 30-min, whichever occurred first. Before drug discrimination training began, a response on either lever resulted in reinforcement (0.1 ml water accompanied by illumination of the jewel lights for 6 sec) and initiated a 60-sec blackout period. Once lever-pressing behavior was acquired on a lever (approximately 3 sessions), the drug discrimination contingencies were added. Intraperitoneal injections of cocaine HCl (3.0 mg/kg) or saline (0.1 ml/kg) were given immediately before each session on a double alternation schedule (i.e., cocaine, cocaine, saline, saline, ...). Initially, trials were completed whenever the rat made a single response (i.e., fixed-ratio 1; FR 1) on the correct choice lever; the FR requirement was gradually increased to 10 over a period of 8 sessions. Thus, during the final discrimination task, 10 consecutive responses on the drug-appropriate lever produced reinforcement following cocaine injections, whereas 10 consecutive responses on the opposite lever produced reinforcement following saline injections. For two of the rats, the left lever was correct following drug; for the other two rats, the right lever was correct.

Drug discrimination training was continued until criterion performance was achieved. The rats had to complete at least 90% (i.e., 18 of 20) of the trials each session on the appropriate choice lever for eight consecutive training sessions (four cocaine and four saline) followed by two consecutive test sessions (one cocaine and one saline). During test sessions, 10 consecutive responses on either lever produced reinforcement; all other features were identical to those of the training sessions. Five doses of cocaine and fencamfamine

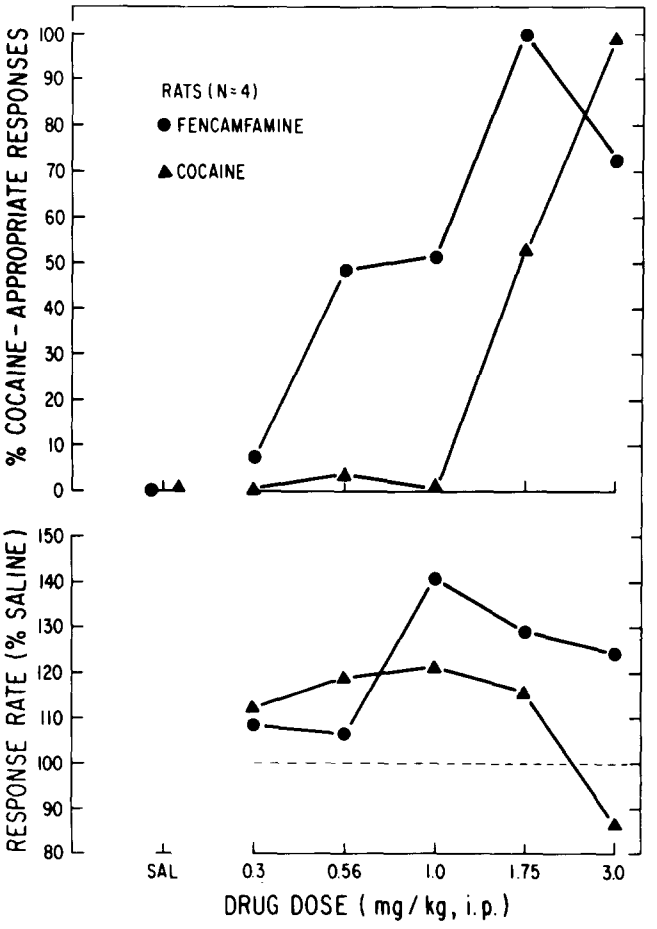

FIG. 2. Dose-response curves for fencamfamine and cocaine in rats trained to discriminate between cocaine (3.0 mg/kg, IP) and saline. Ordinates: mean percentage of total responding that occurred on the cocaine-appropriate choice lever (upper panel), overall rate of responding expressed as a percentage of the control rate following saline administration (lower panel). Abscissae: dose, log scale, SAL indicates saline. The saline data point for the cocaine dose response curve includes values from only two rats; the 3.0 mg/kg dose of cocaine was tested in only three rats; all other data points represent the mean of one observation in each of four rats.

(0.3–3.0 mg/kg) were then tested for their ability to produce drug-appropriate choice responding; saline was also included in the series. For two of the rats, the order of testing was: 3.0, 0.3, 0.56, 1.0 and 1.75 mg/kg fencamfamine, 0.1 mg/kg saline, and 1.75, 1.0, 0.56, 0.3 and 3.0 mg/kg cocaine; the other two rats were tested in the reverse order. The rats were also tested with saline at the completion of the entire series. The double alternation training protocol was continued throughout the drug testing phase. Test sessions were interspersed every third day (e.g., cocaine, saline, test, saline, cocaine, test, ...), provided the rats completed at least 90% of the trials each session on the appropriate choice lever.

RESULTS

A mean of 74 (range, 68 to 82) training sessions was required for the rats to learn the cocaine-saline discrimination. When criterion performance was achieved, the rats were making 99.75% of the total responses on the cocaine-

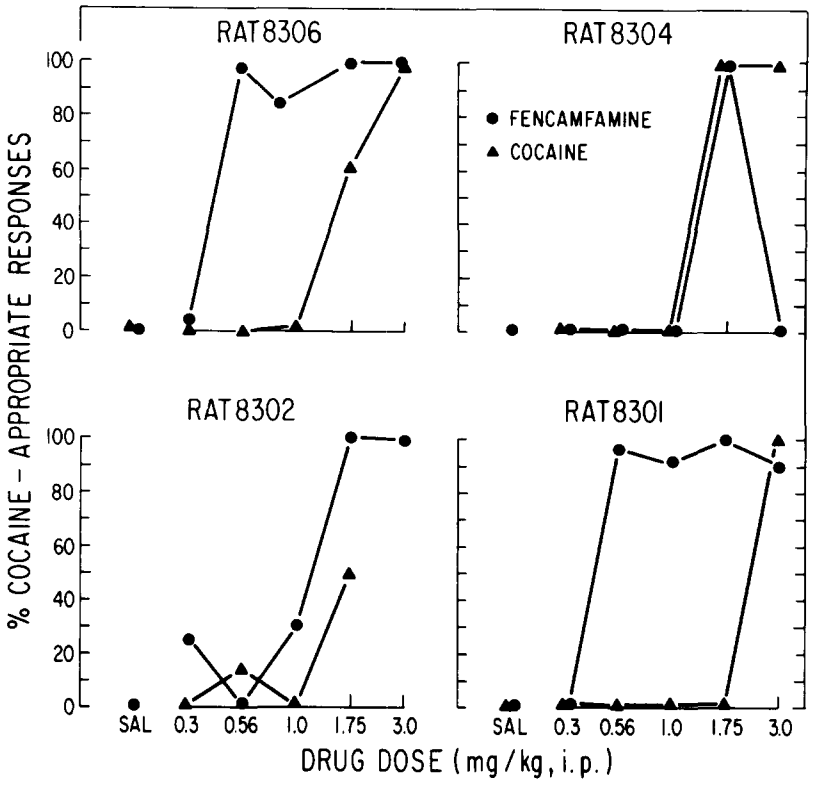

FIG. 3. Dose-response curves for fencamfamine and cocaine in each of four rats trained to discriminate between cocaine (3.0 mg/kg, IP) and saline. Ordinates: percentage of total responding that occurred on the cocaine-appropriate choice lever. Abscissae: dose, log scale, SAL indicates saline. Each data point represents one observation; rat 8302 died before the cocaine dose-response test was completed.

appropriate lever following the administration of cocaine, but only 0.13% following saline. The average response rate during saline sessions was 1.37 responses/second for all four rats (range, 0.88 to 1.89).

When the rats were tested with a wide range of cocaine doses, the amount of responding on the drug-appropriate lever increased from 0.25% of total responding at a dose of 0.3 mg/kg to 99.50% at a dose of 3.0 mg/kg (Fig. 2). Response rates were moderately increased above saline levels by all except the highest dose of cocaine (i.e., 3.0 mg/kg) whe rates were decreased to 86.00% of control. When fencamfamine was administered to the rats, the amount of responding on the cocaine-appropriate lever increased from 7.33% of total responding at a dose of 0.3 mg/kg to 100.00% at a dose of 1.75 mg/kg. When tested with 3.0 mg/kg, the amount of responding on the cocaine-appropriate lever was 90% or greater for three of the rats, while the fourth rat responded entirely on the saline-appropriate lever; thus, the average was 72.39%. Response rates were increased above saline levels by all doses of fencamfamine, especially when the three highest doses were tested.

Cocaine and fencamfamine generalization test data for individual rats are depicted in Fig. 3. Typically, the dose-response curves resembled all-or-none functions; there were only a few instances when the amount of responding on the drug-appropriate lever was intermediate. Two notable examples occurred when cocaine was tested at a dose of 1.75 mg/kg; rat 8306 made 61.72% of total responses on the drug-appropriate lever, and rat 8302, 49.75%. Response rates for individual rats were not unlike those presented as the group average in Fig. 2.

EXPERIMENT II

METHOD

Subjects

The subjects were four male Fischer-derived F344 rats (Harlan Industries, Indianapolis, IN), weighing 345 to 431 g when given free access to dry food and water. The rats had been previously trained to lever press under a multiple schedule of water presentation, and had received drug injections, most recently amphetamine and beta-phenylethylamine. All had been drug-free for at least one month before the present experiment began. Access to water was restricted until the rats reached approximately 80–85% of their control body weights; they were maintained at this value by giving them limited water supplements after each session. Other features were as in Experiment I.

Apparatus

The two-lever rat test chambers used in Experiment I were also used in this experiment. Only the left lever was operational; responses on the right lever were neither counted nor had programmed consequences. Schedule con-

TABLE 1

MEAN (±S.D.) OVERALL RATES OF RESPONDING AND QUARTER-LIFE VALUES DURING THE FI COMPONENTS, AND MEAN (±S.D.) OVERALL AND LOCAL RATES OF RESPONDING AND PAUSE DURATIONS DURING THE FR COMPONENTS, FOR INDIVIDUAL RATS DURING SALINE SESSIONS

	Fixed-Interval		Fixed-Ratio		
	Overall Rate	Quarter-Life	Overall Rate	Local Rate	
Subject	Responses/ Sec	Percent of Interval	Responses/ Sec		Pause Sec
8162	0.082 ± 0.032	83.44 ± 3.10	2.64 ± 0.66	6.81 ± 1.65	5.24 ± 1.98
8164	0.028 ± 0.008	69.25 ± 11.27	0.55 ± 0.10	0.86 ± 0.17	13.24 ± 5.91
8147	0.056 ± 0.034	66.10 ± 22.03	0.69 ± 0.22	1.17 ± 0.34	16.73 ± 4.84
82-120	0.038 ± 0.011	69.72 ± 17.62	0.92 ± 0.29	2.08 ± 0.57	12.29 ± 7.26

tingencies were programmed and data recorded by the same computer system used in Experiment 1. The temporal pattern of responding was obtained with cumulative response recorders.

Procedure

The rats responded under a multiple fixed-interval (FI) 300 sec, fixed-ratio (FR) 20 schedule of water presentation. Experimental sessions were conducted daily, Monday through Friday, with each rat. Each session began with a 5-min blackout period, and was followed by 10 FI components (signalled by illumination of the jewel lights) alternating with 10 FR components (signalled by illumination of the houselight). During the FI components, the first response after 300 sec had elapsed resulted in reinforcement (two successive operations of the liquid dipper, each delivering 0.1 ml water accompanied by illumination of the jewel lights for 6 sec); during the FR components, the 20th response resulted in reinforcement (two successive operations of the liquid dipper, each delivering 0.1 ml water accompanied by illumination of the houselight for 6 sec). The FI component terminated without reinforcement if a response did not occur within 60 sec after the 300 sec interval had elapsed, and the FR components terminated without reinforcement if 20 responses were not completed within 180 sec. Successive components were separated by 60-sec blackout periods, during which responses were counted but had no programmed consequences.

Drug testing began when response rates varied less than 20% from day-to-day, and patterns of responding were stable as determined by visual inspection of the cumulative response records. Five doses of fencamfamine (0.1–10.0 mg/kg, IP) and six doses of cocaine (0.1–30.0 mg/kg, IP) were tested. Drugs were typically administered on Tuesdays and Fridays; saline control injections (0.1 ml/kg, IP) were given on Thursdays. Each dose was tested twice in each rat; two of the rats were tested with the fencamfamine doses, then the cocaine doses, in an ascending order, followed by fencamfamine then cocaine in a descending order. The other two rats were tested with cocaine first, followed by fencamfamine.

Data Analysis

For each rat, the average *overall* rates of responding in the FI and FR components of the multiple schedule were calculated separately by dividing the total number of responses in each component by the total amount of time the component was in effect. For analysis of the temporal pattern of FI responding, the FI component was divided into 10 successive 30-sec segments. Responses in corresponding segments were accumulated over the entire session, and the percentage of the interval taken to complete the first one-fourth of responses (i.e., the quarter-life value) was obtained by the method of linear interpolation. For analysis of the temporal pattern of FR responding, the average pause durations from the beginning of the FR components to the first response, and the average *local* rates of responding from the first to the last response in the component were calculated over the entire session. Overall and local rates of responding, quarter-life values and pause durations during each session with drug treatment were expressed as a percentage of average values during saline-injection control sessions.

RESULTS

Control Performance

During saline-injection control sessions, the multiple FI FR schedule of water presentation maintained rates and patterns of responding characteristic of this schedule [14]. The mean overall rates of responding in each component, the quarter-life values, and the local rates of responding and pause durations in the FR components are shown in Table 1, for individual rats. Under control conditions, responding during the FI components followed a long initial pause and increased at a positively accelerated rate until a response produced water; responding druing the FR components was preceded by a short pause and occurred at a high, steady rate until water was delivered (Fig. 4, No Injection, Saline). During the timeout periods that separated successive components, the rate of responding seldom exceeded 0.005 responses/sec, and was usually less than 0.002 responses/sec.

Effects of Fencamfamine and Cocaine

Fencamfamine and cocaine produced qualitatively similar effects on performance under the multiple FI FR schedule of water presentation. During the FI components, overall rates of responding first increased, then decreased with increasing doses of either drug (Fig. 5, upper panel). Peak increases, to 270 percent and 174 percent of control values, were produced by 3.0 mg/kg fencamfamine and 10.0 mg/kg cocaine, respectively. The temporal patterning of responding

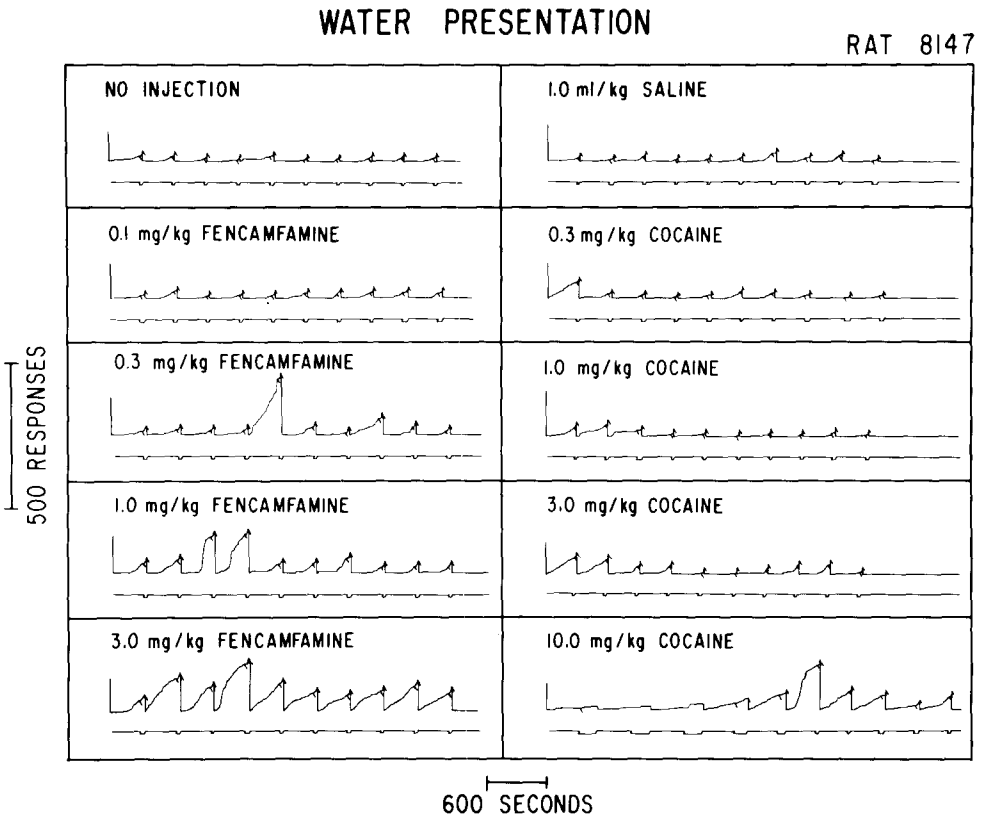

FIG. 4. Representative cumulative response records from rat 8147 depicting behavior under the multiple FI 300 sec FR 20 schedule of water presentation. Ordinates: cumulative lever-pressing responses. Abscissae: time. Diagonal marks of the response pen indicate water delivery; downward deflections of the event pen represent FR components. The response pen was reset at the end of each FR component. The recorder did not operate during timeout periods. Each record shows a complete session.

within the fixed intervals was also affected similarly by the two drugs. Both fencamfamine and cocaine decreased the FI quarter-life values, and these decreases were dose-dependent and quantitatively alike (Fig. 6, upper panel). In general, the doses that produced the peak increases in overall FI response rates increased the low rates of responding that occurred during the early portions of the intervals, while the relatively high rates of responding characteristic of the later portions of the intervals were moderately, if at all, decreased (Fig. 7). Lower doses of either drug had quantitatively similar, but less pronounced effects.

During the FR components, overall rates of responding were not appreciably different from saline until the highest dose of each drug was tested, at which time responding was almost completely suppressed (Fig. 5, lower panel). These changes were the result of decreased local rates of responding (Fig. 6, middle panel) and increased pause durations (Fig. 6, lower panel), both of which occurred when the highest dose of each drug was administered to the rats.

The time course of drug effect was also similar for fencamfamine and cocaine (Fig. 8). These effects were especially apparent during the FI components. Both drugs had relatively rapid onsets of action; the response rate was significantly elevated above saline levels by the second fixed interval. The maximal increase in FI responding typically occurred by the fourth fixed interval, after which the rates slowly declined over the remainder of the session.

DISCUSSION

Fencamfamine produced cocaine-appropriate choice behavior, and had effects similar to those of cocaine on schedule-controlled responding. In both paradigms, fencamfamine was slightly more potent than cocaine. These results, combined with previous findings, indicate fencamfamine and cocaine share many psychopharmacological effects.

In the first experiment, rats were trained to discriminate between intraperitoneal injections of cocaine (3.0 mg/kg) and saline using a two-lever, water-reinforced choice task. Approximately 75 training sessions were needed for the rats to achieve criterion discrimination behavior. The acquisition period was not appreciably unlike previous studies using rodents, especially when the training dose of cocaine was low. For example, using a less stringent discrimination criterion, about 60 sessions were required for rats to discriminate between cocaine (1.25 mg/kg or 2.5 mg/kg) and saline ([12] and [5], respectively). With higher training doses (e.g., 10 mg/kg), acquisition periods between 40 and 50 days have been reported [11,20], but the pharmacological specificity of the discrimination may be diminished (see [5]).

During generalization testing, there was a positive relationship between the dose of fencamfamine and the number of responses made on the cocaine-appropriate choice lever, suggesting that fencamfamine produced cocaine-like discriminative stimuli. Fencamfamine was slightly more potent

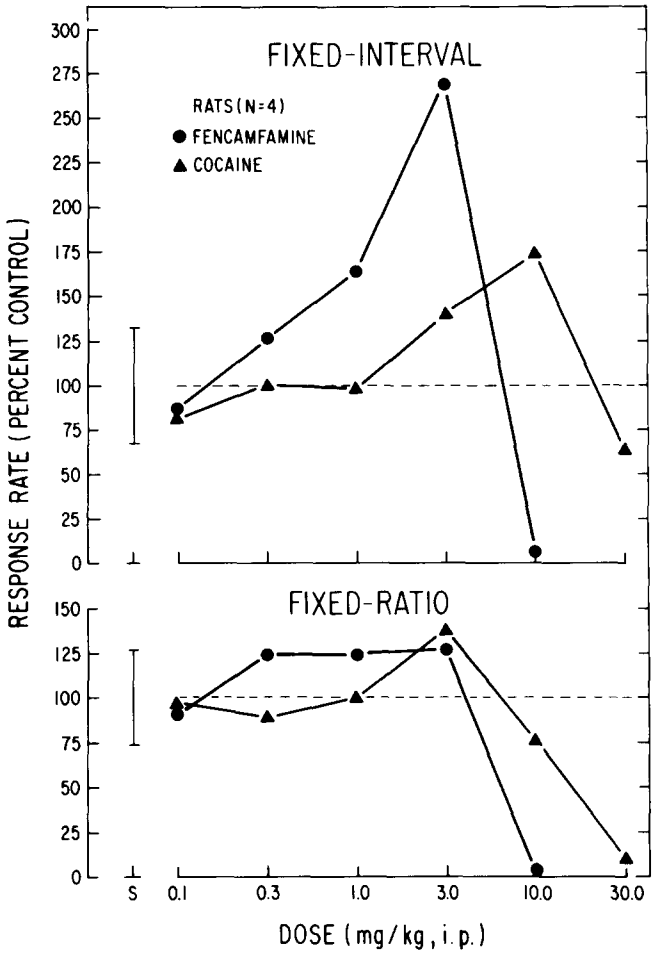

FIG. 5. Effects of fencamfamine and cocaine on responding by rats under the multiple FI 300 sec FR 20 schedule of water presentation. Ordinates: overall response rate during FI components (upper panel) and FR components (lower panel) expressed as a percentage of the mean saline-injection control rates. Abscissae: dose, log scale, S indicates saline. The dashed horizontal lines show the mean saline-injection control values, 100%; brackets at S represent ±S.D. Each point represents the mean of two observations obtained in each of four rats. Control rates of responding for individual rats are shown in Table 1.

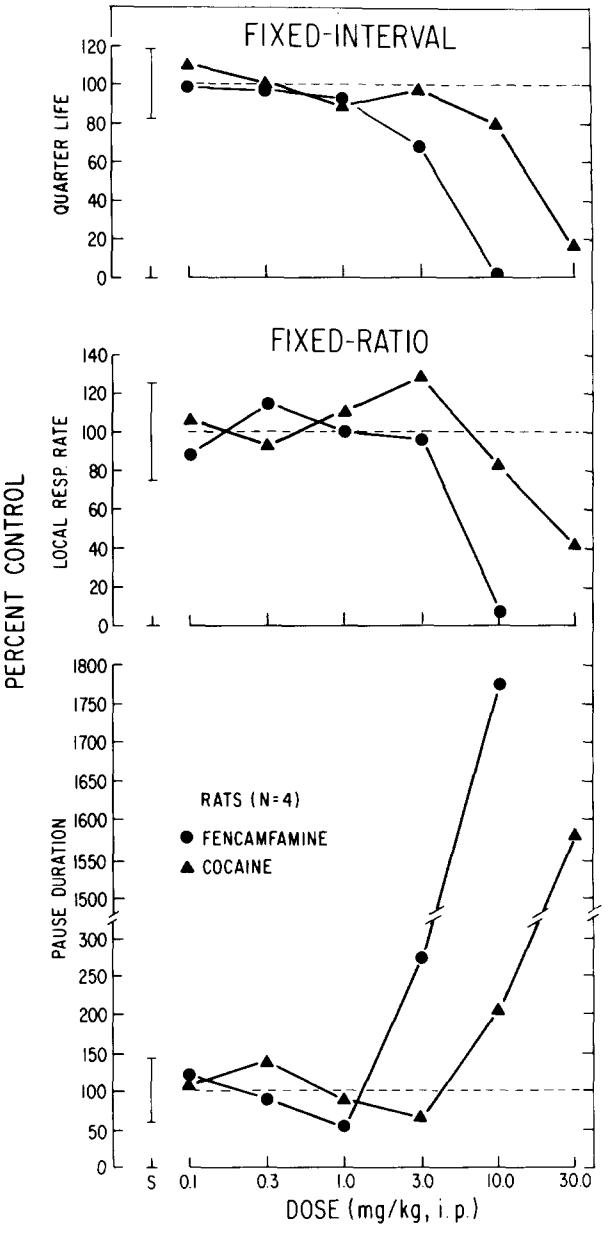

FIG. 6. Effects of fencamfamine and cocaine on performance by rats under the multiple FI 300 sec FR 20 schedule of water presentation. Ordinates: quarter-life values in the FI components (upper panel), local response rates (middle panel) and pause durations (lower panel) in the FR components, expressed as a percentage of the mean saline-injection control values. Abscissae: dose, log scale, S indicates saline. The dashed horizontal lines show the mean saline-injection control values, 100%; brackets at S represent ±S.D. Each point represents the mean of two observations obtained from each of four rats. Control values for these three measures for individual rats are shown in Table 1.

than cocaine; the dose-response curve for fencamfamine was approximately one-quarter log unit to the left of the cocaine curve. The results of this experiment may have implications regarding the abuse potential of fencamfamine since drugs that have overlapping discriminative stimuli in animals commonly have similar subjective effects in humans [4,16]. Several psychomotor stimulant drugs, known to be abused, fully substitute for cocaine in a discrimination paradigm; these include *d*-amphetamine, methylphenidate and *l*-cathinone [2, 6, 8, 11, 12]. In contrast, only partial, if any,

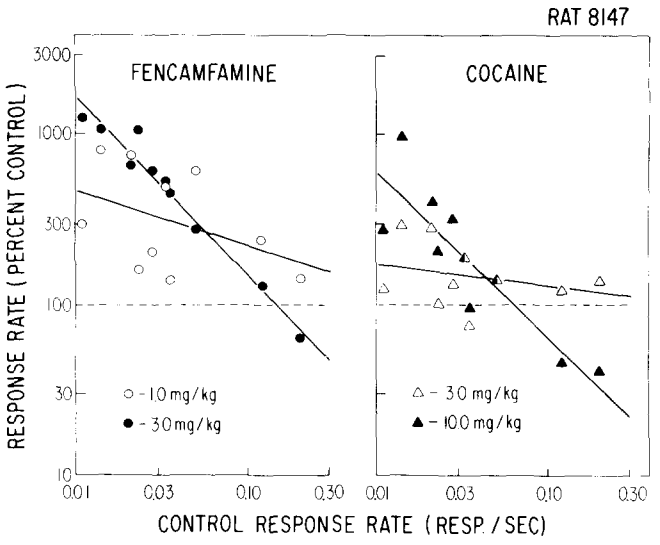

FIG. 7. Effects of selected doses of fencamfamine and cocaine on responding within the FI components plotted as a percentage of the saline-injection control rates in rat 8147. Abscissae: mean control rate of responding in successive 30-sec segments of the FI components during the saline-injection control sessions, log scale. Ordinates: rate of responding during drug sessions in corresponding segments expressed as a percentage of the control rate, log scale. The dashed horizontal lines show the mean saline-injection control values, 100%. The solid regression lines were mathematically fitted by the method of least squares. Each data point represents a single determination.

cocaine-appropriate choice behavior is engendered by several other abused psychoactive drugs such as pentobarbital, morphine and nicotine [2,8].

In the second experiment, rats responded under a multiple FI FR schedule of water reinforcement. The rates and temporal patterns of responding on non-drug control sessions were characteristic of performances under this schedule [14]. When the rats were administered graded doses of either fencamfamine or cocaine, qualitatively similar effects on responding were seen, and these effects depended on the type of schedule component (FI or FR) controlling behavior. Both drugs caused dose-related decreases in the high overall rates of responding during the FR components, whereas intermediate doses of each drug increased the lower rates of responding during FI components. Although fencamfamine was slightly more potent than cocaine in producing these effects, the drugs had similar time courses, especially during the FI components. The rate-dependency of the effects [10] was also especially evident during the FI components; doses of fencamfamine and cocaine that increased overall FI rates preferentially increased the low rates that occurred early in the intervals more than the higher rates later in the intervals. Similar effects on FI and FR responding have been previously reported for cocaine when tested in animals responding under schedules of food presentation [15,25] or stimulus-shock termination [27]; the effects of fencamfamine on multiple FI FR schedule-controlled responding have not been previously reported.

The results of the present study indicate fencamfamine and cocaine have many common actions; their discriminative stimulus properties overlap, they produce qualitatively similar effects on schedule-controlled responding, and their time courses of action are alike. That fencamfamine has reinforcing properties has been previously demonstrated; in beagle dogs, fencamfamine and cocaine were approximately equipotent in maintaining intravenous self-administration behavior [7]. Combined with the present results, the psychopharmacological profiles of fencamfamine and cocaine appear to be similar in many respects. There is good concordance between the discriminative stimulus properties of drugs as measured in animals and their subjective effects in humans; furthermore, drugs that are self-administered by laboratory animals are frequently those that are abused by humans [23,28]. Thus, fencamfamine, or fencamfamine in combination with other compounds, may be abused for its cocaine-like effects.

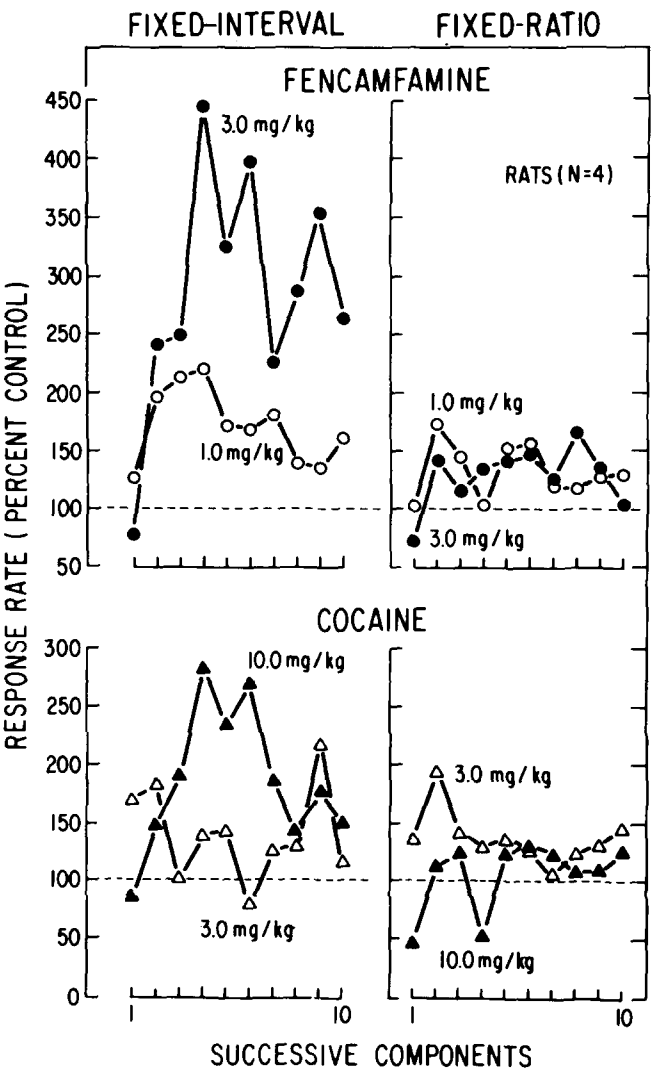

FIG. 8. Time course of effect of fencamfamine (1.0 and 3.0 mg/kg, IP) and cocaine (3.0 and 10.0 mg/kg, IP) on responding by rats under the multiple FI 300 sec FR 20 schedule of water presentation. Ordinates: response rate during individual components expressed as a percentage of saline-injection control rates during corresponding components. Abscissae: ordinal position of individual FI (left panels) or FR (right panels) components within the session. The dashed horizontal lines show the mean saline-injection control values, 100%. Each point represents the mean of two observations obtained in each of four rats.

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