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BRIEF COMMUNICATION

Potentiation of Cocaine's Discriminative Effects by Caffeine: A Time-Effect Analysis[1]

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GAUVIN, D. V., J. R. CRIADO, K. R. MOORE AND F. A. HOLLOWAY. *Potentiation of cocaine's discriminative effects by caffeine: A time-effect analysis.* PHARMACOL BIOCHEM BEHAV 36(1) 195–197, 1990.—The effects of caffeine upon the discriminative and rate-altering effects of cocaine were examined in rats. Using a food-reinforced two-lever operant procedure, 12 male Sprague-Dawley rats were trained to discriminate between 10 mg/kg cocaine and saline. Time-effect analysis of the training dose resulted in a median effective time interval (the duration of the discriminable effects of cocaine in producing 50% cocaine-appropriate responding), of 60.5 minutes postinjection. Caffeine partially generalized to the cocaine stimulus and, when administered with cocaine, produced a dose- and time-dependent increase in the percentage of drug-appropriate responding. Data are discussed with reference to our previous results with cocaine-caffeine interactions.

Cocaine Caffeine Drug discrimination

WE have recently reported the results of experiments that were designed to assess the interactive effects of caffeine on the discriminative stimulus properties of cocaine (10 mg/kg) in rats (1). Caffeine generalization tests resulted in intermediate levels of cocaine-appropriate responding at high doses. Dose-effect curves were generated for cocaine in combination with various doses of caffeine and for caffeine in combination with various doses of cocaine. Isobolographic analysis of the dose-additive effects of drug combinations categorized the interaction as simple additivity.

The present study was designed to further characterize the interaction between cocaine and caffeine. By using the same drug discrimination procedure as in our previous study, we trained a separate group of rats to discriminate between 10 mg/kg cocaine versus saline. We now report a time-effect analysis of the interaction between caffeine and the cocaine discriminative cue.

METHOD

Animals and Apparatus

Twelve male Sprague-Dawley rats (Sasco, Inc., Omaha, NE), reduced to 85% of their free-feeding weights were used as subjects. The drug discrimination procedure used in the present experiment has been described in greater detail elsewhere (1). Briefly, animals were trained in standard operant chambers equipped with two response levers, stimulus lamps, houselight, and automated pellet dispenser. Behavioral contingencies and data collection were achieved by Commodore-64 microcomputer systems interfaced with the operant chambers (Rayfield Electronics, Waitsfield, VT). Animals were trained to press a lever for food reinforcement on either of the two levers in 10-minute experimental sessions. The correct lever to obtain food was determined by which of the two interoceptive stimuli was administered (intraperitoneally) 15 minutes prior to the session. The number of responses required for reinforcement was gradually increased to a Variable Ratio 10 (VR-10) schedule (min, 5, max 15). Rats were trained seven days per week. Once per week the training sessions were extended to 11 minutes in duration. The first minute was an extinction period followed by the normal 10-minute training session. These latter sessions were categorized as "test/train" sessions and served as an index of discriminative accuracy. Test sessions commenced once each animal met the criteria of: 1) stable

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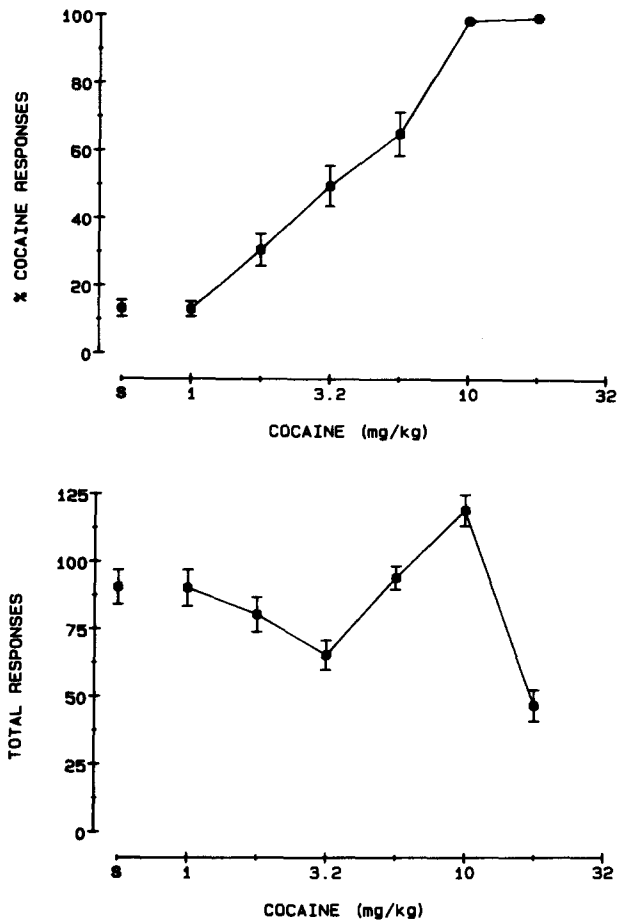

FIG. 1. Dose-effect function for cocaine administered 15 minutes prior to test sessions. Top panel: Percentage of total session responses emitted on the cocaine-appropriate lever. Bottom panel: Total number of responses emitted on either lever during the two-minute extinction periods are expressed as a function of dose. The points about the "S" on the abscissa represent data from saline test sessions (n = 11).

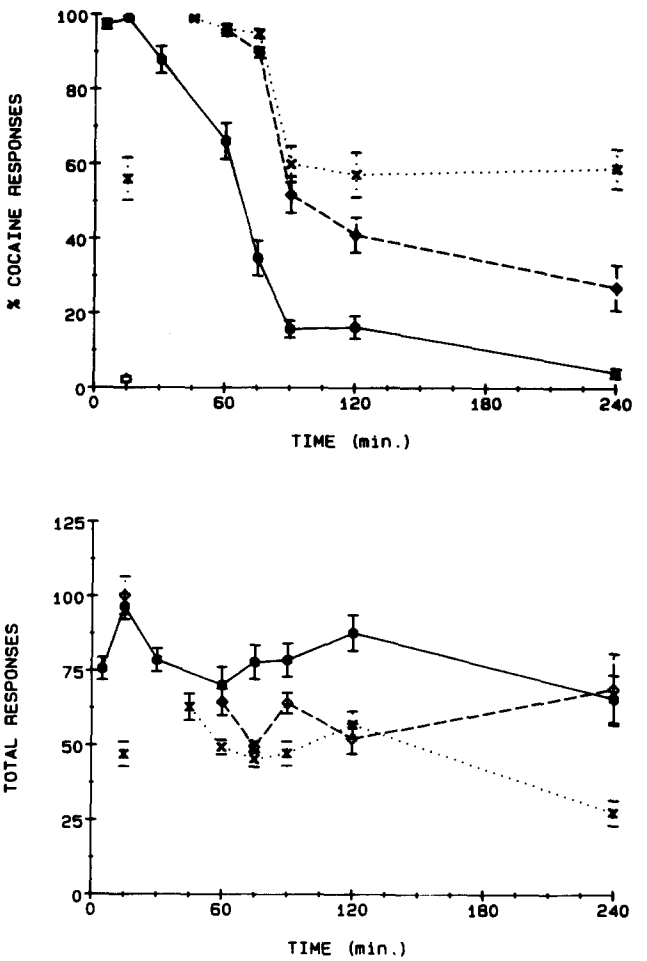

FIG. 2. Time-effect function for cocaine administered with saline (closed circles), 10 mg/kg caffeine (open diamonds) or 32 mg/kg caffeine (×'s). Top panel: Percentage of total session responses emitted on the cocaine-appropriate lever. Bottom panel: Total number of responses emitted on either lever during two-minute extinction periods are expressed as a function of pretreatment time of the cocaine stimulus. Data from test sessions conducted after 10 or 32 mg/kg caffeine in combination with saline are represented by the appropriate symbols above the 15-minute mark on the abscissa (n = 11).

rates of responding (± 10% session to session variability) for four sessions; 2) greater than 80% discriminative accuracy for four consecutive training sessions; and 3) greater than 80% discriminative accuracy for four consecutive test/train extinction periods. Test sessions were two-minute extinction sessions and were conducted once per week.

The order of tests were: dose- and time-related effects of cocaine in combination with saline, caffeine dose-effect functions, caffeine (administered 15 minutes prior to the test session) in combination with 10 mg/kg cocaine administered from 5 to 240 minutes prior to the test sessions.

Drugs and Dosages

Cocaine hydrochloride and caffeine (in free form anhydrous) were purchased from Sigma Chemical Company (St. Louis, MO) and dissolved in 0.9% sterile saline. In all instances, caffeine was administered intraperitoneally 15 minutes before the session. Cocaine hydrochloride was administered at various time intervals between 5 and 240 minutes prior to test sessions as indicated in the Results section. The cocaine pretreatment time for training and for the initial dose-effect function test sessions was 15 minutes.

Data Analysis

A test drug and dose was considered to generalize to the 10 mg/kg cocaine training stimulus if greater than 80% of the total sessions responses were emitted on the cocaine-appropriate lever. Test session discriminative performance is expressed as the percentage of total session responses emitted on the cocaine-appropriate lever. Rates of responding are expressed as the total number of responses emitted on either lever throughout the two-minute extinction test sessions. Data were analyzed by one-way (Subject × Treatment) ANOVA for dose-related effects using the General Linear Model (SAS Institute, Cary, NC) which is designed to handle unequal cell size; individual dose comparisons were made with Duncan's New Multiple Range Test. The median effective time interval was defined as the postinjection time interval for the training dose of cocaine (10 mg/kg) required to elicit 50% drug-appropriate responding. The group median effective time interval was estimated from linear regression equation determined by the method of least squares.

RESULTS

Figure 1 is the dose-effect function for cocaine. Increasing

doses of cocaine resulted in a dose-related increase in the percentage of total session responses emitted on the cocaine-appropriate lever, $F(6,54)=5.52$, p's<0.05. The training dose of cocaine (closed circle above 10 on the abscissa) resulted in a significant response rate increase above saline control rates ($p<0.05$). Figure 2 is the kinetics function for the training dose of 10 mg/kg cocaine. This dose of cocaine was administered at varying intervals prior to the test session with additional administration of either saline (closed circles), 10 mg/kg caffeine (open diamonds), or 32 mg/kg caffeine ($\times$'s) injected 15 minutes prior to the test session. Data from test sessions of caffeine in combination with saline are displayed as single data points above the 15-minute mark on the abscissa. The 5-minute pretreatment test was conducted after a simultaneous injection of cocaine and saline. The median effective time interval for the discriminative stimulus properties of the training dose was 60.5 minutes. Fifteen-minute pretreatments with 10 and 32 mg/kg caffeine, respectively, produced 57% and 4% cocaine-appropriate responding.

Both doses of caffeine potentiated the discriminative effects of cocaine at the 60- and 75-minute pretreatment times (p's<0.05 compared to cocaine plus saline). The potentiation of the discriminative stimulus properties of cocaine by the additional administration of 32 mg/kg caffeine demonstrated at the early time course points (45, 60, 75 min) returned to baseline caffeine levels at 90 minute (10 mg/kg cocaine plus 32 mg/kg caffeine compared to 32 mg/kg caffeine plus saline, $p>0.05$). The addition of 10 mg/kg caffeine to the cocaine stimulus resulted in significant increases in the percentage of total session responses emitted on the drug-appropriate lever above cocaine and caffeine baseline levels (all time points of 10 mg/kg cocaine and 10 mg/kg caffeine compared to 10 mg/kg caffeine plus saline and 10 mg/kg cocaine plus saline, p's<0.05).

Response rates were relatively stable across the full time interval when cocaine was coadministered with saline. The addition of caffeine reduced most response rate measures, with the greatest response rate suppression elicited by 32 mg/kg caffeine administered at the 240-minute mark of the cocaine stimulus. The rate reductions resulting from the addition of 32 mg/kg caffeine to the 10 mg/kg cocaine stimulus were not statistically significant from those seen after administration of 32 mg/kg caffeine when administered alone (Duncan's p's>0.05) except for the 240-min pretreatment interval. The addition of 10 mg/kg caffeine to the cocaine training stimulus resulted in greater than additive effects on the rate reduction measure at the 75-, 90-, and 120-min intervals when compared to 10 mg/kg cocaine or 10 mg/kg caffeine administered with saline (Duncan's p's<0.05).

DISCUSSION

We have recently reported the interaction between cocaine and caffeine administered simultaneously in a similar drug discrimination procedure (1) using a cocaine training stimulus. An isobolographic analysis of the interaction categorized it as "simple additivity." The results of the present study support these conclusions using a time-effect analysis. The median effective time interval for the 10 mg/kg cocaine stimulus in the present study is similar to that previously reported by McKenna and Ho (4). Interestingly, these data are similar to those reported by Jarbe (2) for a 4 mg/kg cocaine stimulus (57.9 minutes). The estimated effective dose corresponding to the median effective time interval of 60.5 min, using a biological half-life of 34.2 min (3), was 3.08 mg/kg. This dose was similar to the group mean of the individual response choice ED_{50} values for the 15-min training pretreatment interval of 3.44 mg/kg (S.E. = 0.45 mg/kg).

Combining caffeine (15 minutes prior to the test session) with a time-dependent cocaine stimulus engendered significant increases in the effective stimulus time for the training cues. These increases appear dependent on the degree to which the caffeine dose engenders cocaine-like responding when administered with saline. The partial generalization of the 32 mg/kg caffeine dose adds to the 10 mg/kg cocaine stimulus in a simple additive fashion. However, the 10 mg/kg caffeine dose potentiated the cocaine stimulus at the 4-hour postinjection time interval (240 minutes) which was greater than would be predicted when either drug was administered singly ($p>0.05$). However, this potentiation did *not* raise the group mean of drug appropriate responding above 40%. These data are of interest because of the high probability that illicit cocaine would be administered concomitantly with caffeine "on-board" from common foodstuffs. Further research seems appropriate to investigate the effects of such combinations.

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