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Effects of Caffeine, Cocaine and Their Combination on Fixed-Interval Behavior in Rats

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LOGAN, L., J. M. CARNEY, F. A. HOLLOWAY AND T. W. SEALE. *Effects of caffeine, cocaine and their combination on fixed-interval behavior in rats*. PHARMACOL BIOCHEM BEHAV **33**(1) 99–104, 1989.—The effects of the central nervous system stimulants, caffeine and cocaine, on schedule-controlled behavior were determined in rats trained to perform a fixed-interval (FI) 5-minute task. When given alone caffeine produced a doubling of FI response rate at a dose of 10 mg/kg and reduced responding at a dose of 32 mg/kg. Cocaine, which was also expected to increase FI responding, did not increase response rate at doses of 3.2 or 10 mg/kg and decreased the rate of responding at a dose of 32 mg/kg. Caffeine had minimal effects on quarter life and appeared to increase local rates of responding across the interval. Cocaine decreased quarter life dramatically at a dose that had no effect on overall response rate. Local rates of responding were increased early in the interval and decreased in the later segments. The effects of both drugs were found to be rate-dependent. When these compounds were given in combination the results obtained appeared to be related to the rate of responding that caffeine alone would produce.

Schedule-controlled behavior Cocaine Caffeine Drug interaction Rate dependency

CAFFEINE is a widely consumed, centrally-active compound that is found in a variety of foodstuffs and beverages. Cocaine has become a popular drug of abuse in the United States and concurrent consumption of these two compounds, perhaps by intention, appears likely. We were interested in determining what acute behavioral interactions might occur between caffeine and cocaine. Caffeine antagonizes the effects of adenosine at its receptors (3, 7, 9, 17), affects calcium mobilization (11,12), and inhibits cyclic nucleotide phosphodiesterases (1, 9, 20) and 5′-nucleotidase (6,18). Through these mechanisms both the rate of release (2, 4, 5) and the subsequent synaptic concentrations of neurotransmitters may be increased, which in turn modify postsynaptic events. Since cocaine, through inhibition of neurotransmitter reuptake (16), also increases synaptic concentrations of released neurotransmitter, the potential exists for an additive or synergistic interaction between these two stimulants.

To our knowledge there exists only one report exploring the behavioral interactions between caffeine and cocaine (15). Low doses of caffeine were found to potentiate the stimulation of locomotor activity induced by cocaine in rats. Spontaneous locomotor activity has a relatively low level behavioral complexity compared to operant or schedule-controlled behavior. Under a fixed-interval schedule both low and high rates of responding are obtained, and rate-dependent effects of drugs can be determined. In this study the effects of caffeine, cocaine and their combination on fixed-interval behavior in rats were investigated.

METHOD

Six male Sprague-Dawley rats (Sasco) weighing 250–275 g were used in this behavioral study. Following their arrival at the Animal Resource Facility they were group housed for two weeks with ad lib food (Wayne) and water. The subjects were then singly housed under a 12-hour light/dark cycle and food deprived to 80% of their free-feeding weight.

Standard two-lever operant chambers (Lafayette) were used in this study. The chambers were enclosed in sound-attenuating boxes equipped with fans for ventilation. The operant schedule was controlled by a microcomputer (C-64, Commodore), and data were stored on disk. The operating program was written in

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Promul. One 45-mg food pellet (Bio-Serv) was delivered upon completion of the schedule requirements. Single daily sessions were conducted Monday–Friday mornings.

The subjects were started on a continuous reinforcement schedule. Following the acquisition of responding, an attempt was made to concurrently train the subjects to a fixed ratio-fixed interval schedule (FIFR). Initially the FR value was 3 and the FI duration was 1 min. During the FR component a single light above the right response lever was illuminated, and a 2-min limited hold was in effect. During the FI component the house light located above the chamber was illuminated in addition to the light above the lever, and a 2-min hold was in effect. As the FI value was held constant and the FR value gradually increased, it became apparent that the subjects were not discriminating between the FR and FI components and the FR component was dropped from the schedule. The FI value was then gradually increased to a final value of 5 min with a 1-min limited hold. If the animal failed to respond within the limited hold period, the next FI cycle was begun. The final session length was 61 min to allow 10 cycles to elapse in the event of complete drug-induced disruption of responding.

Saline control sessions were conducted on Thursday. Saline injections were given 15 min before and again immediately before the session. Drug sessions were run the following day. Caffeine (Sigma Chemical Co.) was given 15 min before the session followed by a saline injection immediately before the session. The effects of cocaine hydrochloride (NIDA Psychotomimetics Committee) were evaluated by administering saline or caffeine 15 min prior to the cocaine dose. The cocaine was injected immediately before the behavioral session. Both drugs were dissolved in physiological saline and administered by intraperitoneal (IP) injection at a volume of 0.1 ml/100 g body weight.

Six rats received the 10 mg/kg doses of caffeine and cocaine, five received the 3.3 mg/kg doses and three received the 32 mg/kg doses. In the combination series four rats received the 3.2 and 10 mg/kg doses of caffeine in combination with 10 mg/kg cocaine and three received the 32 mg/kg dose of caffeine plus cocaine. The reduced numbers of animals was the consequence of subject loss.

Drug doses were chosen based upon our experience with these compounds in operant and locomotor activity investigations. The treatment times were chosen in an effort to achieve peak blood brain levels of both drugs simultaneously, based upon published pharmacokinetic data and previously obtained time courses of action.

Overall response rates and quarter lives under drug and vehicle conditions were calculated. Average control values of individual subjects were determined from saline sessions and compared to drug values by one-way analysis of variance (STAT, Matrix Software, Big Rapids, MI). Post hoc comparisons were made by Scheffe's treatment contrast and individual analysis of variances. Total segmental responses across the fixed interval were compared between saline and drug conditions by two-way analysis of variance. Responses occurring during successive 30-sec segments were also compared between drug and saline conditions by one-way analysis of variance. Local rates of responding were calculated and used to determine rate-dependent effects by least-squares regression.

RESULTS

Individual administration of either cocaine or caffeine produced significant dose-dependent effects on fixed-interval behavior (Fig. 1). Caffeine exhibited an overall dose-dependent effect on response rates, $F(3,16) = 5.02$, $p = 0.01$. FI response rates (Fig. 1A) were increased to 129% of control values at a caffeine dose of 3.2 mg/kg. Compared to the control rate of responding in saline-treated animals, response rates were approximately doubled at the 10 mg/kg dose. A further increase in the dose of caffeine to 32 mg/kg resulted in a marked inhibition of FI responding. This decrease was significant when compared to the rate of responding in rats receiving a caffeine dose of 10 mg/kg, $F(1,7) = 11.15$, $p = 0.01$. Treatment contrasts indicated that these changes were not significantly different from saline values, but when compared by single analysis of variances the 10 mg/kg dose of caffeine produced a significant increase in response rate, $F(1,10) = 16.44$, $p = 0.03$. There appeared to be a trend toward a decrease in response rate at the 32 mg/kg dose, but this change was not significant ($p = 0.13$). No significant dose-related effect on quarter-life values was observed at these caffeine doses (Fig. 1B).

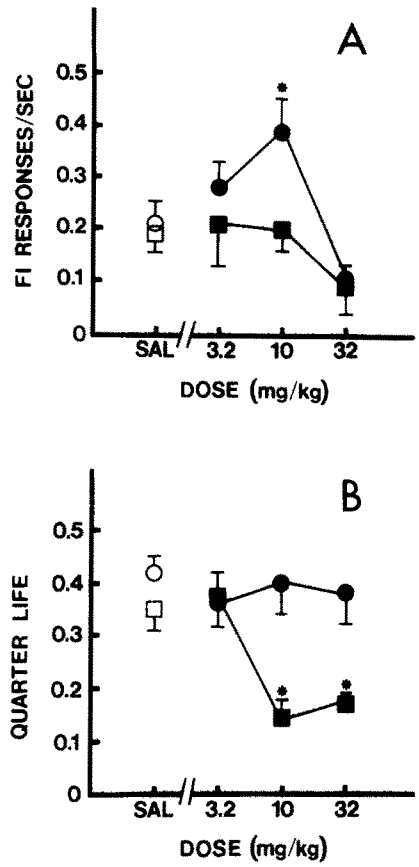

FIG. 1. Dose-response curves for the effects of caffeine (●) and cocaine (■) on fixed-interval response rate (A) and quarter life (B). Data points for the drug conditions are the mean values of 3 to 6 subjects. Open symbols to the left indicate control values for each drug. Vertical lines represent standard error of the mean (SEM). Asterisks denote $p<0.05$ when compared to respective controls by one-way ANOVA.

The effects of cocaine were somewhat different compared to those of caffeine. At low to intermediate doses (3.2 and 10 mg/kg), cocaine had no significant effect on response rates. When the cocaine dose was increased to 32 mg/kg, response rates were reduced to about half of control values. There was no overall significant dose-related effect of cocaine on response rates, although the 32 mg/kg dose tended towards significant reduction ($p = 0.07$). Quarter-life values following cocaine administration (Fig. 1B) were reduced markedly at the 10 and 32 mg/kg doses. These decrements were significantly dose-related, $F(3,16) = 4.01$, $p = 0.03$. Each quarter-life value differed significantly from con-

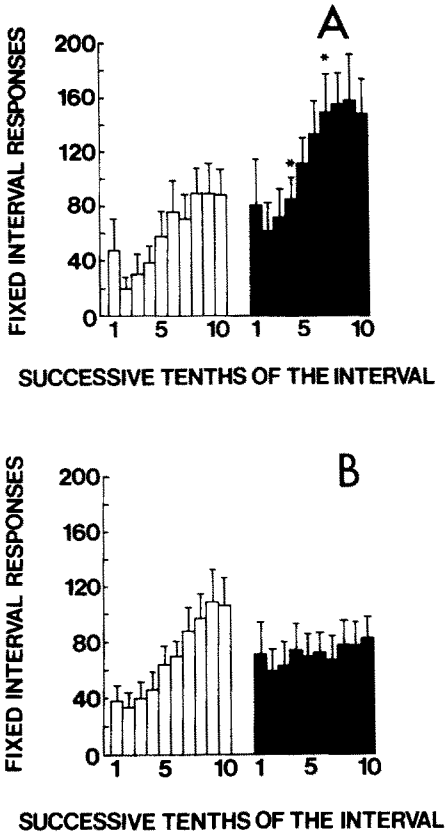

FIG. 2. Effects of caffeine, 10 mg/kg (A), and cocaine, 10 mg/kg (B), on fixed-interval responding. Saline responding (open bars) is shown on the left and drug responding (filled bars) is shown on the right. Vertical bars represent the mean (n=6) accumulated number of responses occurring in successive 30-second segments of the fixed interval. Vertical lines indicate SEM. Asterisks denote $p<0.05$ when compared by one-way ANOVA to corresponding control segment.

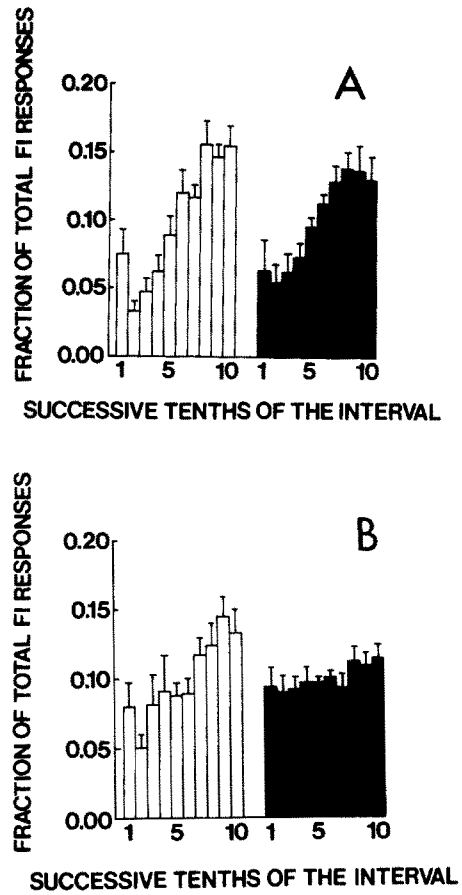

FIG. 3. Effects of caffeine, 10 mg/kg (A), and cocaine, 10 mg/kg (B), on the temporal pattern of responding. Saline responding (open bars) is shown on the left and drug responding (filled bars) is shown on the right. Vertical bars represent the mean (n=6) percentage of total responses occurring in successive 30-second segments of the fixed interval. Vertical lines indicate SEM.

trol values, $F(1,10)=4.94$, $p=0.05$, and $F(1,7)=7.74$, $p=0.03$. Thus, the behavioral effects elicited by cocaine and caffeine were demonstrably different in these rats.

The effects of 10 mg/kg doses of caffeine and cocaine on the temporal pattern of responding are shown in Fig. 2. Response rates increased as the fixed interval progressed in saline-treated rats. After a 10 mg/kg dose of caffeine, total responding was doubled (Fig. 2A). This increase occurred during all segments of the fixed interval and was reflected in the similarity of quarter lives between the saline and caffeine conditions. When compared by two-way ANOVA, this effect of caffeine (10 mg/kg) was significantly different from saline values, $F(1,100)=30.24$, $p=3\times10^{-7}$. Again, the action of cocaine was distinctly different. While the 10 mg/kg dose of cocaine did not affect the overall response rate, the pattern of responding appeared to be affected. The low level of responding in the early segments of the fixed interval was increased by cocaine while the late segment responding was decreased. Statistical analysis by two-way ANOVA did not support the visual impression that the overall pattern of responding was different, $F(1,100)=0.64$, $p=0.43$. However, when responses in each half of the interval were compared by one-way ANOVA, cocaine significantly increased responding during the first half of the interval compared to saline-treated animals, $F(1,58)=6.77$, $p=0.01$.

When the segmental data are represented as a percentage of total responding to normalize for rate differences, the effects of these compounds on the temporal pattern can be better assessed (Fig. 3). Although the 10 mg/kg dose of caffeine doubled response rates (Fig. 1A), the pattern of responding relative to the vehicle control was maintained (Fig. 3A). The segmental patterns for saline and for caffeine were not significantly different, $F(1,100)=1.00$, $p=0.32$, when compared by two-way ANOVA. Cocaine (Fig. 3B) appeared to have a flattening effect on the temporal pattern of responding. The early responding was slightly increased while the responding in the later segments was decreased to produce a fairly constant level of responding throughout the fixed interval. This effect of cocaine was not significant, $F(1,100)=7\times10^{-5}$, $p=0.99$, when compared to saline by two-way ANOVA. When the percentages obtained for cocaine and saline during each half of the interval were compared by one-way ANOVA, cocaine marginally increased percent responding, $F(1,58)=3.09$, $p=0.08$, during the first half of the interval and decreased percent responding, $F(1,58)=3.87$, $p=0.05$, during the last half of the interval.

Response rates for each segment of the fixed interval were determined and rate-dependency plots were constructed by graphing the logarithm of the drug-induced rate of responding divided

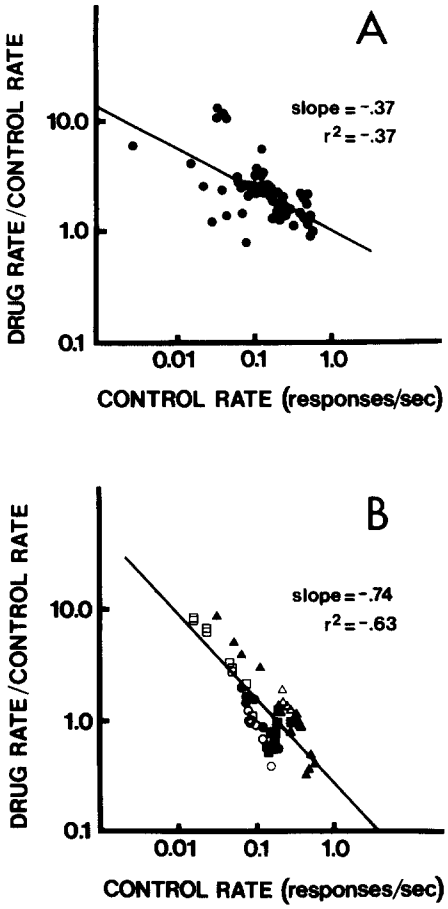

FIG. 4. Rate-dependency plots for the effects of 10 mg/kg doses of caffeine (A) and cocaine (B). Control response rates derived from 30-second segments of the fixed interval are plotted on the abscissa and the ratios of the drug rate/control rate are plotted on the ordinate. For cocaine individual subjects are indicated by different symbols. Least squares linear regression was performed on the pooled data.

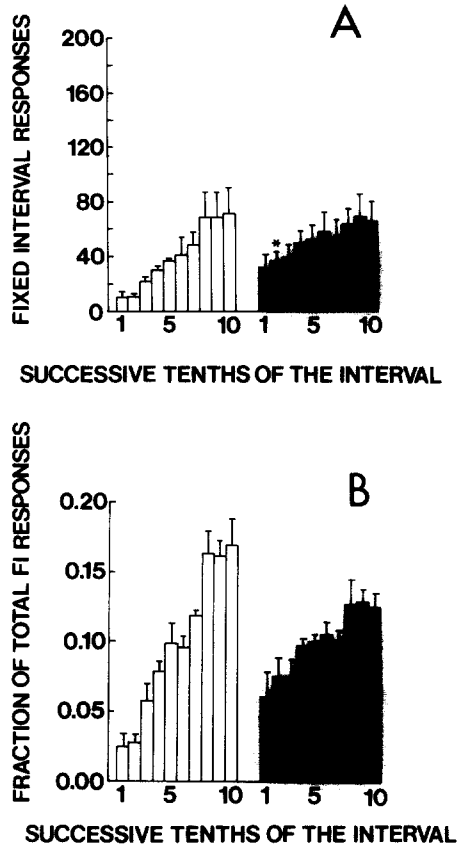

FIG. 5. Effects of the combination of caffeine, 10 mg/kg, and cocaine, 10 mg/kg, on the temporal pattern of responding. Control responding is shown on the left (open bars) and drug responding (filled bars) is shown on the right. (A) Vertical bars represent the mean (N=3) accumulated number of responses occurring in successive 30-second segments of the fixed interval. B represents the percentage of total responses occurring in each segment. Vertical lines indicate SEM. Asterisk denotes $p<0.05$ when compared to control values by one-way ANOVA.

by the control rate of responding as a function of the logarithm of the control rate of responding. Plotting the data for the 10 mg/kg doses of caffeine and cocaine resulted in the regression lines shown in Fig. 4. The influence of basal response rates on effects of the two drug treatments can be compared by the slopes of the lines (Fig. 4A versus Fig. 4B). The slope of the caffeine regression line was less negative than that of cocaine, and the scatter of the caffeine points was greater than that of cocaine. With the exception of a few data points, the caffeine points were above the drug rate/control rate ratio of 1.0. This indicated that caffeine generally increased response rates. Cocaine generally increased low response rates and decreased higher response rates. From the regression line in Fig. 4B, response rates of 0.2 resp/sec would be unaffected by this dose of cocaine.

Having established the separate effects of caffeine and cocaine on FI behavior, we next investigated the interaction of these two stimulants. Since the 10 mg/kg dose of cocaine exhibited temporal effects without markedly affecting response rate, this dose was chosen to examine the interacting effects of caffeine and cocaine. The effects of varying doses of caffeine in combination with this fixed dose of cocaine on response rate and quarter life are shown in Fig. 5. In contrast to the action of caffeine administered alone the combination of 10 mg/kg cocaine with caffeine did not produce significant dose-related changes in response rates. Combining the caffeine dose of 3.2 mg/kg with the 10 mg/kg dose of cocaine increased responding 30% while caffeine alone produced a 29% increase. The combination of 10 mg/kg caffeine and cocaine increased responding by 20% compared to a 92% increase induced by caffeine when administered alone. The stimulation of responding produced by this combination was significantly less than that observed with caffeine alone, $F(1,8)=7.86$, $p=0.02$. The 32 mg/kg dose of caffeine alone decreased responding to 62% of control. The combination had no effect on response rate compared to saline-treated rats ($p=0.61$). The quarter-life values seen with the caffeine-cocaine combinations were less than those seen with caffeine alone but were not reduced to those seen with cocaine alone. These values were significantly less than those seen in saline-treated animals [$F(3,11)=7.11$, $p=0.006$; $p<0.02$ at each combination by single comparisons]. The quarter-life values of the caffeine-cocaine combinations were not significantly different from the quarter lives of either caffeine- or cocaine-treated rats, although the combination with 3.2 mg/kg caffeine had a trend towards a significant difference from both 3.2 mg/kg caffeine ($p=0.08$) and 10 mg/kg cocaine ($p=0.07$).

The effects of the combination of 10 mg/kg caffeine and 10 mg/kg cocaine on the temporal pattern of responding are shown in Fig. 6. Responses in the early segments of the interval were increased in a manner similar to that observed when caffeine or

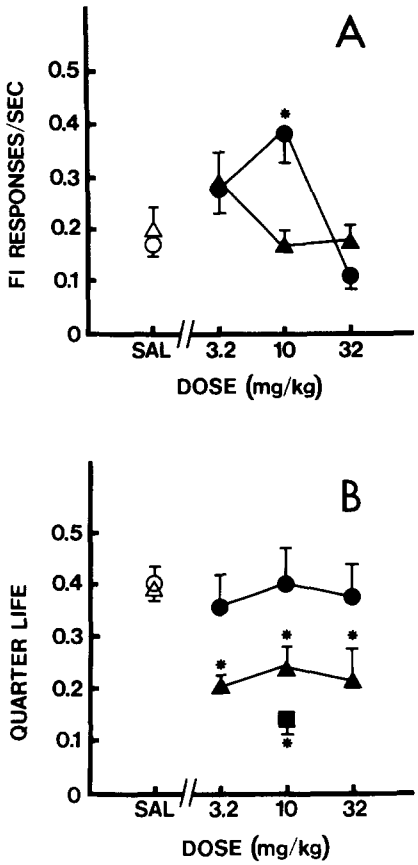

FIG. 6. Dose-effect curves for the combination of various doses of caffeine alone (●) and with 10 mg/kg cocaine (▲) on fixed-interval response rate (A) and quarter life (B). Open symbols to the left indicate control values for each condition. The filled square at the 10 mg/kg dose in B represents the effect of 10 mg/kg cocaine alone. Vertical lines denote SEM. Asterisks indicate $p<0.05$ when compared to corresponding control values by one-way ANOVA.

cocaine were administered alone. Responses in the later segments of the interval were similar to those in the control condition. The stimulation of responding in these later segments observed with caffeine alone is absent. In the combined drug condition, responding in the early segments of the interval was low and increased as the interval progressed. This is in contrast to the effects of cocaine administered alone in which responding throughout the interval was fairly constant.

DISCUSSION

The first portion of our study focused upon the actions of caffeine or cocaine on FI responding when each drug was administered singly. We found that a 10 mg/kg dose of caffeine produced an approximate doubling of FI5-min behavior. Caffeine increased responding throughout each 30-second segment of the 5-minute interval rather than causing a selective increase in the earlier segments. At a comparable caffeine dose, Meliska and Brown (14) observed an increase in FI5-min responding similar to that which we found. This increase occurred only during the first 30 min of their test session. At the highest caffeine dose (32 mg/kg) we found a 50% decrease in FI responding compared to vehicle-treated animals. This disruption of responding is in agreement with other reports describing the actions of similarly high doses of caffeine on FI behavior in rodents (8, 10, 13, 14). Therefore, the dose-dependent effects of caffeine on FI behavior observed in our study confirm the observations of other investigators.

In our study we observed no increase in total FI5-min responding at any of the cocaine doses (3.2–32 mg/kg) evaluated. This lack of stimulation by cocaine is in agreement with earlier studies in the rat under a FR30FI2-min schedule (10) and in the mouse under a FI1-min schedule (8). The onset of cocaine effects on mouse locomotor activity is rapid (<10 minutes) and duration of effect is about 30 minutes (our unpublished observations). Response rates may be increased early in the session and offset by later decreases. Although overall rates of responding were not increased by cocaine, low rates of responding in the early segments of the interval were increased and high rates of responding later in the interval were decreased in a manner similar to that observed in the mouse (8). Apparently these differential effects of cocaine on basal rates of responding cancel each other out when summated across the entire interval. Determination of the overall rate of responding leads to an apparent lack of effect because of the opposing changes in different segments of the fixed interval.

The effects of caffeine on FI responding have been shown to be rate-dependent (13,14) as have those of cocaine (10). In the present study, we also observed rate-dependent effects for both caffeine and cocaine. Caffeine increased both low and high response rates with lower response rates being increased to a larger extent. The slope of the regression line for the 10 mg/kg dose of cocaine was steeper than that of caffeine. This suggests that cocaine has a greater effect on low rates of responding than does caffeine. From the rate-dependency regression data, a response rate of 0.2 responses/sec is expected to be unaffected by 10 mg/kg cocaine. This closely approximated the control rates of responding of our animals and may explain why our animals failed to exhibit increased response rates with cocaine.

Having evaluated the effects of caffeine and cocaine administered singly, we then evaluated their effects upon concurrent injection. Several different effects of coadministration might be expected: 1) the effects on FI5-min responding could be additive; 2) the effects could be synergistic; 3) the drugs might interact negatively so that the effect of their coadministration was less than the effect produced by either alone. Misra *et al.* (15), using locomotor activity as a behavioral assay, found that low doses of caffeine potentiated the stimulant effects of intravenous cocaine. Higher doses of caffeine did not potentiate the effects of cocaine. We observed a complex interaction between the effects of caffeine and cocaine. The behavioral effects of a low dose of caffeine (3.2 mg/kg) were not affected by concomitant administration of a 10 mg/kg dose of cocaine. At a caffeine dose which markedly stimulated responding (10 mg/kg), cocaine reduced the overall response rate to control values. Cocaine (10 mg/kg) coadministered with an inhibitory dose of caffeine (32 mg/kg) increased responding to control values.

Understanding of the rate-dependent effects of cocaine appears to be useful in interpreting the effects observed after administration of the drug combination. A 10 mg/kg dose of caffeine alone resulted in a doubling of response rate. From the rate-dependency data, cocaine would be expected to decrease this higher rate of responding by about 60% and to result in values that were near control response rates. Conversely, at 32 mg/kg, caffeine alone decreased response rates by about 50% and the effect of cocaine would be to increase these lower rates by about 70%. The actual results obtained are similar to those expected from the rate-dependency effects.

The results of this investigation indicate that the interacting effects of caffeine and cocaine on behavior are not simple. Cocaine does not induce a left-shift of the caffeine dose-response

curve (increased potency) nor does cocaine potentiate the efficacy of the stimulant effects of caffeine. Cocaine has an opposing effect on the dose-dependent modification of FI behavior elicited by caffeine. If caffeine increases FI responding, cocaine reduces this effect to control levels. When caffeine decreases these responses, cocaine increases responding to control levels. The outcome of the interaction of cocaine and caffeine appears to be dependent upon the rate of responding achieved after caffeine administration.

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