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Effects of Caffeine on Schedule-Controlled Responding in the Rat[1,2]

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MELISKA, C. J. AND R. E. BROWN. *Effects of caffeine on schedule-controlled responding in the rat.* PHARMAC. BIOCHEM. BEHAV. **16**(5) 745–750, 1982.—Six male Harlan/Wistar rats were trained to barpress under a FI300 sec schedule of food presentation until responding was stable. Caffeine (6.0 and 12.0 mg/kg, IP) increased overall response output significantly during the first half-hour after administration; 24.0 mg/kg decreased output significantly during the third and fourth half-hour. The drug also decreased quarter-life values. Rate-dependency analyses indicated that the effect was partially rate-dependent, but intermediate control rates were enhanced relatively more by caffeine than the lowest control rates.

Caffeine Schedule-controlled responding Rate-dependency Time course

DEWS [4,5] and others [11] have proposed that the behavioral actions of many psychoactive agents are "rate-dependent" in that they increase response rates when control rates are normally low, but they have less effect on (and even depress) high control rates. Rate-dependency has been demonstrated most convincingly with the amphetamines [3, 10, 15] with a wide variety of positive and negative reinforcers [12]. However, whether all CNS stimulants produce rate-dependent effects has not been established.

Despite the popularity of caffeine in various beverages throughout the world [14], controlled laboratory studies of its behavioral actions are rare. Some research [18] suggests that like the amphetamines, caffeine may enhance certain kinds of human performance (e.g., in athletics). But like the amphetamines, it has also been reported to reduce hyperactivity in children ([9,16]; see [6] for a recent review), suggesting that its effects may be similarly rate-dependent. This idea is supported by some laboratory studies [1,17], but not by all [8,13].

The present study was designed to investigate the rate-dependency of caffeine's actions on a FI300 sec schedule of food presentation in rats. A second aim was to examine the time course of the drug's actions.

METHOD

Animals

Six male Harlan/Wistar rats approximately 270 days old at the start of training were used. They were experimentally naive and were partially fasted to reduce their body weights to 80% of ad lib, after which they were maintained on Purina Lab Chow under standard laboratory conditions. Body weights ranged from 290–390 g during the experiment.

Apparatus

Two standard Skinner boxes (Scientific Prototype) with inside dimensions of 23×20×18 cm high were used. Each box occupied a separate room in which a 90 cm electric fan ran continuously to provide masking noise; overhead fluorescent lights provided illumination. The manipulandum was a 5 cm wide stainless steel lever (bar) protruding about 2 cm into the box through an end wall, about 5 cm above the grid floor. A downward force of about 12 g static weight operated the lever. A pellet dispenser delivered 37 mg Noyes food pellets. Programming and recording apparatus were located in a separate room to reduce audible relay noises. Separate printout counters printed cumulative barpress frequencies for 10 consecutive, 30 sec intervals; timing began immediately after a reinforcement and stopped after 300 sec.

Procedure

Barpressing was shaped manually and subjects were rapidly shifted to a fixed-interval 300 sec (FI300 sec) schedule in which a pellet was delivered following the first response of each session, and then following the first response which occurred 300 sec after delivery of the last food pellet. Sessions continued until 25 food pellets were delivered (about 120 min). Performance was judged to be relatively stable after about 25 days of training, at which time

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[4]The experiments were carried out by R. E. B. as part of a Senior Research Project in the Psychology Department of Monmouth College.

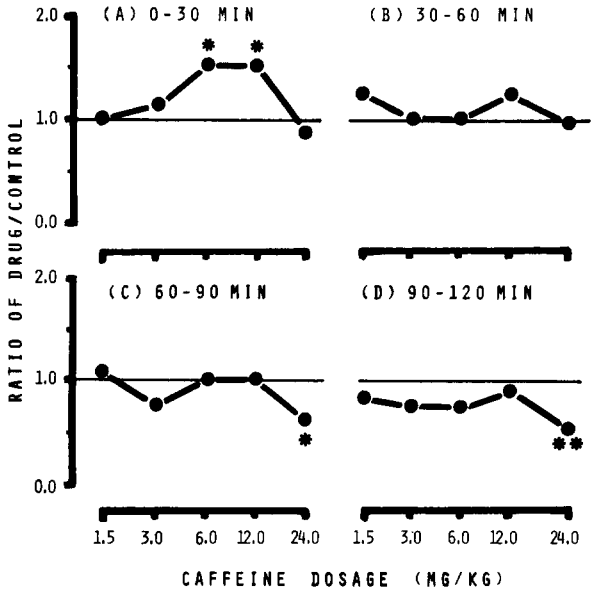

FIG. 1. Effects of caffeine on mean response output of FI300 sec. A–D represent successive half-hour intervals after drug administration. Ordinate is ratio of drug mean to previous day's control mean. Means are based on N=6 rats. Asterisks denote significance of differences between control and drug response rates; $*p<0.05$, $**p<0.01$.

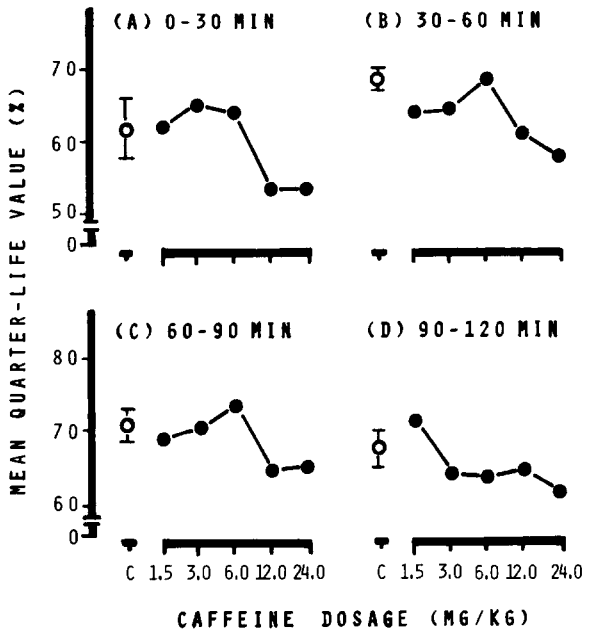

FIG. 2. Effects of caffeine on mean quarter-life values as percent of FI300 sec (see Method section). A–D represent successive half-hour intervals after drug administration. Data points represent means of N=6 rats. Control points (C) are means of five separate determinations made on the day before each drug test. Vertical lines indicate ±2 SEM.

daily baseline response rates varied on the average by 15.54% for days 23–25. Rats were tested seven days a week between 0800 and 2100 hr, each animal being tested at about the same time each day. Rats were fasted for about 22 hr between tests.

Drug tests were begun after responding had stabilized. Saline injections were given routinely on all non-drug test days and performance on the day immediately preceding each drug day served as the control for that test. Each animal received five doses of caffeine—1.5, 3.0, 6.0, 12.0, and 24.0 mg/kg. A balanced, Latin Square order of administration was created by adding an "extra" dose of saline following the 24.0 mg/kg dose. Drug tests were separated by 72 hr except for the 1.5 mg/kg dose which was separated from the preceding dose (24.0 mg/kg) by 144 hr in order to minimize possible drug carryover from the higher dose. Intraperitoneal (IP) injections of caffeine alkaloid (Merck) in saline, in volumes of 1.0 ml/kg of body weight, were given immediately before placing animals into the test chamber. Equal volumes of saline were injected on control days.

Data Analyses

Separate repeated measures analyses of variance (ANOVAs) were performed on grouped data (N=6) using the Geisser-Greenhouse [7] correction for repeated measures on the same subjects. Post hoc analyses of statisically significant main effects and/or interactions ($p<0.05$ or beyond) were performed using analyses of simple effects and appropriate t-tests. Quarter-life and rate-dependency analyses were carried out by dividing the FI300 sec interval into 10 equal 30 sec segments. Total number of responses within each segment were used to estimate the average time required to make 25% of the total number of responses within the FI300 sec interval. The percentage of the interval elapsed when 25% of the responses occurred was estimated by linear extrapolation. (A quarter-life value of 25% occurs when responses are equally distributed throughout the interval.) For the rate-dependency analysis, the mean number of responses made in each segment was determined for each drug dosage. Corresponding means for the previous saline day served as control for each drug administration. Linear regression analyses were performed on log (mean drug rate/mean control rate) as a function of log (mean control rate) and regression lines were plotted using the least-squares method.

RESULTS

The dose- and time-dependency of caffeine's effects on mean response output are illustrated in Fig. 1. The drug increased barpress rates in a dose-dependent fashion during the first half-hour after administration except at the highest dose (24.0 mg/kg), which depressed responding somewhat (Fig. 1A). During the second half-hour, mean response rates remained slightly elevated with all doses except 24.0 mg/kg (Fig. 1B); rates became increasingly depressed, especially with 24.0 mg/kg, at 60–90 and at 90–120 min after injection (Fig. 1C, 1D).

Under control conditions responding within the FI300 sec intervals was essentially positively accelerated, with a tendency for the function to be slightly "J"-shaped because the lowest response rates tended to occur during the second or third $^1/_{10}$th of the interval, rather than the first. The greatest effect on quarter-life values was obtained with 12.0 and 24.0 mg/kg (Fig. 2). The effect was also time-dependent, and less clearly dose-dependent from 30–90 min post-injection. The dissociation between quarter-life values and magnitude of

TABLE 1

PEARSON rs RELATING INDIVIDUAL CONTROL RATES TO RATIOS OF DRUG/CONTROL

Time (min)	Successive Tenths of FI300 sec									
	1	2	3	4	5	6	7	8	9	10
0– 30	−.33	−.83*	−.95†	−.92†	−.96†	−.58	−.04	−.48	.05	−.06
30– 60	−.41	−.47	−.44	−.75	−.78	−.88*	−.66	−.30	−.67	−.62
60– 90	−.31	−.41	−.55	−.53	−.55	−.58	−.44	−.46	−.67	−.53
90–120	−.36	−.37	−.27	.26	−.22	.24	.16	.58	−.01	.14

*$p<0.05$, †$p<0.01$ (Two-tailed test).

drug effect is noteworthy; e.g., while 6.0 mg/kg elevated responding significantly during the first half-hour after injection, it produced little change in quarter-life; and while 12.0 mg/kg elevated output to about the same extent, it reduced quarter-life considerably.

In Fig. 3 barpress rates were averaged across all drug doses and mean changes in response rates, relative to means for the previous day's saline control, were plotted. Response rates were mostly unchanged by the drug during the first three post-reinforcement $^1/_{10}$ths of the FI. For the first hour after injection, caffeine enhanced response rates significantly during the "late-middle" segments of the FI—i.e., 150–210 sec after reinforcements. During the second hour there was no appreciable rate enhancement, and significant decreases in rates occurred during the last three $^1/_{10}$ths of the interval (210–300 sec).

In order to assess the contribution of individual differences in response rates, scores were averaged across drug doses and across control days for each animal, then Pearson r's relating individual rat's pre-drug control response rates to ratios of drug/control were calculated for each $^1/_{10}$th of the FI (Table 1). Most of the correlations (29 of 30) were negative during the first 90 min after injection (Chi Square=26.1, $p<0.001$), indicating that response rates on drug days tended to be inversely proportional to rates on control days; lower control rates were associated with higher ratios of drug/control, higher control rates with lower ratios. The highest correlations—some of which were statistically significant despite the small number of subjects (N=6)—tended to occur during the "middle" segments of the FI. Correlations became smaller and more positive during the last half-hour of testing.

Rate-dependency analyses for the 6.0, 12.0, and 24.0 mg/kg doses are shown in Fig. 4, with data on slopes and y-intercepts of the regression lines for all doses given in Table 2. Logs of ratios of drug/control are plotted as a function of the previous day's control rates, with the first four consecutive post-reinforcement $^1/_{10}$ths of the interval identified. Rate dependency was evident with 12.0 and 24.0 mg/kg, especially between 30 and 90 min after drug injection. However, the drug effect appears to be only partially rate-dependent since ratios of drug/control were less consistently related to control response rates during the first three $^1/_{10}$ths of the interval than during the fourth through tenth. A comparison of the slopes of the regression lines for all 10 data points vs the last seven data points, only, confirms this interpretation (Table 2).

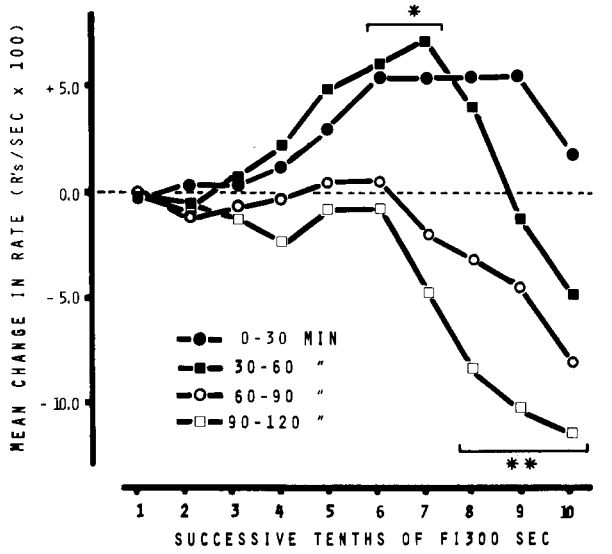

FIG. 3. Mean change in response rate at successive tenths of FI300 sec, at half-hour intervals after administration of caffeine. Individual rates were summed across all five doses before calculating means. Asterisks indicate significance of differences between control and first hour (0–60 min), and control and second hour (60–120 min); *$p<0.05$, **$p<0.01$. Brackets enclose differences with the same p-values.

DISCUSSION

Our results are consistent with earlier reports of enhancement of FI output by caffeine in monkeys [1] and pigeons [13]. Depression of FI responding in rats has also been reported [8,17] but with higher doses (56–100 mg/kg) than those used in the present work. We also noted a small reduction in response output during the first 30 min after injection with 24.0 mg/kg, our highest dose.

As expected, caffeine either enhanced or depressed response rates depending on dosage and time-since-administration. We observed a biphasic effect, with the initial enhancement followed by a substantial response rate depression, especially of high-rate responding in the late $^1/_{10}$ths of the FI (Figs. 3, 4). Whether this depression represents a delayed pharmacological action of the drug or simply a be-

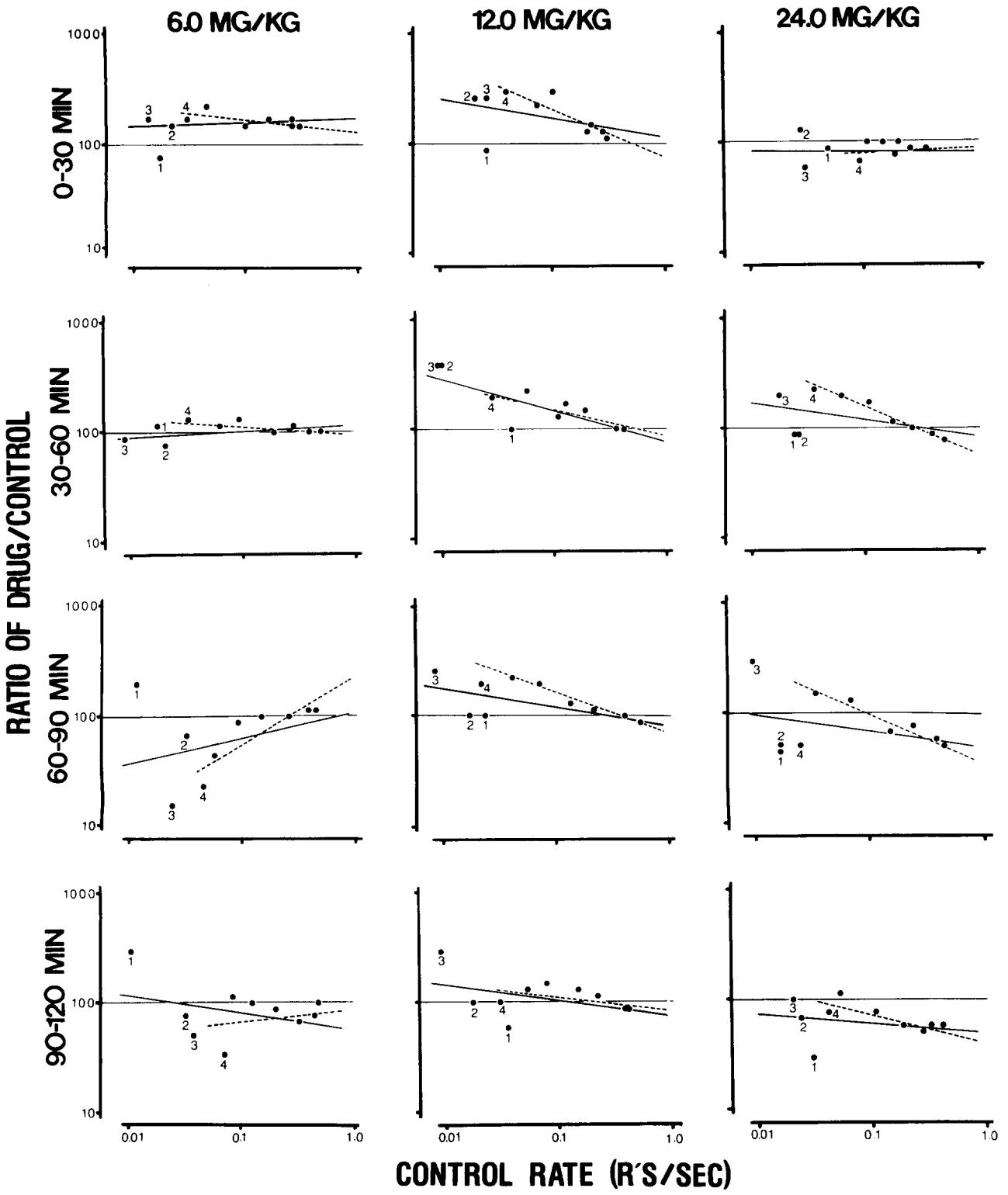

FIG. 4. Rate-dependency analyses: Mean control response rates in 30 sec intervals are plotted on a log scale on the abscissae. Ordinates represent ratios of mean response rate after caffeine vs mean control rate on non-drug days. The first four successive tenths of FI300 sec after each reinforcement are labeled. Solid line represents regression line based on all 10 data points; dashed line represents the regression line based on the 7 data points preceding each reinforcement, only. Regression lines were drawn by the least squares method.

TABLE 2
RATE-DEPENDENCY ANALYSES

Data Points	Time (min)	Dose (mg/kg)	Slope	y-intercept (%)	r
1–10	0– 30	6.0	.05	172	.22
		12.0	−.18	114	−.44
		24.0	−.01	80	−.03
	30– 60	6.0	.05	114	.37
		12.0	−.30	75	−.80
		24.0	−.16	80	−.47
	60– 90	6.0	.25	117	.38
		12.0	−.17	83	−.62
		24.0	−.15	49	−.33
	90–120	6.0	−.15	56	−.34
		12.0	−.15	73	−.46
		24.0	−.08	49	−.24
4–10	0– 30	6.0	−.11	133	−.68
		12.0	−.45	75	−.93
		24.0	−.04	85	.14
	30– 60	6.0	−.08	94	−.70
		12.0	−.25	85	−.84
		24.0	−.44	54	−.99
	60– 90	6.0	.60	209	.86
		12.0	−.70	70	−.93
		24.0	−.44	36	−.98
	90–120	6.0	.12	85	.21
		12.0	−.13	80	−.58
		24.0	−.26	40	−.86

Slopes of the regression lines and y-intercepts as percentage of control when control rate is 1 response/sec are presented, along with Pearson correlations coefficients (r). Data are presented for all 10 successive $^1/_{10}$ths of the FI300 sec (1–10) as well as for the last 7 successive $^1/_{10}$ths (4–10) only. Data are based on means for 6 rats.

havioral "rebound" following the initial rate enhancement bears further study. Delaying behavioral tests until 60–90 min after administration could clarify this point. (It is noteworthy that most studies of human performance report no improvement with caffeine until at least one to two hours after oral administration [18]. This delayed onset probably reflects the slower rate of absorption via the oral route of administration, used most often in human studies.)

Whether caffeine produces rate-dependent effects in a manner analogous to amphetamine is a matter of some theoretical interest [14]. In general, studies have inferred rate-dependency mainly from two phenomena: (1) Schedule-dependency—i.e., enhancement of the low response rates generated by certain schedules (e.g., FI, DRL) at doses of the drug which either diminish or do not affect high response rates generated by other schedules (e.g., FR, VI) [4,15]; and (2) within FI schedules, enhancement of the normally-low response rates at the start of the interval, and depression of (or no effect on) the normally-high rates at the end of the interval [5,11].

Earlier tests of the rate-dependency of caffeine's effects have produced both positive and negative outcomes. For example, one study [17] tested caffeine under a FI60 sec schedule of food presentation in rats, under two conditions: Food satiation, which generated low response rates, and food deprivation, which generated higher response rates. At 3.0 mg/kg, IP, caffeine enhanced response output significantly in the low-response-rate (food-satiated) condition, without affecting it in the high-response-rate (food-deprived) condition. Another study tested squirrel monkeys [1] under a multiple FI-FR schedule of food presentation. Small but statistically significant increases in response rates occurred during the first (low-rate) half of FI180 sec with 1.0 to 10.0 mg/kg caffeine, IP; no change, or small decreases in output occurred during the FR30 component with comparable doses. In contrast, a study with rats [8] reported that caffeine decreased output on both FI120 sec and FR30 schedules of food presentation with 30 to 100 mg/kg, IP; separate rate-dependency analyses of the FI performance showed clear evidence of rate-dependency with amphetamine, but not with caffeine. And in another comparison of the effects of amphetamine and caffeine on a multiple FI-FR schedule of food presentation in pigeons [13], amphetamine stimulated FI300 sec output while decreasing FR30 output in a classic rate-dependent fashion, over a broad dose range. But caffeine enhanced FI output only at 3.0 mg/kg, IM, and without a discernible effect on FR output; 30.0 mg/kg decreased FI output without affecting FR—the opposite of what is ordinarily found with amphetamine.

In the present study, caffeine's effects on FI were similar to those reported for amphetamine, but with notable differences. For example, for about an hour after administration, caffeine tended to increase overall output (Fig. 1) while reducing quarter-life values (Fig. 2)—an amphetamine-like action. The rate-dependency analyses (Figs. 3, 4) also show that the drug tended to decrease or have no effect on the normally high-rate responding toward the end of the interval. Also, with caffeine individual animals' response rates tended to be inversely proportional to control rates (Table 1). But the drug did not substantially enhance low-rate responding at the start of the interval; no change, or a decrease in response rates occurred during the first minutes after reinforcements—a time when amphetamine exerts maximal rate-enhancing effects [2]. Maximal rate enhancement did not occur until control rates were intermediate—i.e., during the middle segments of the FI. At this time control rates were most negatively correlated with ratios of drug/control; also, slopes of the regression lines based on the last seven $^1/_{10}$ths of the FI were steeper than those based on all ten. Rate depression characterized the second hour of testing, especially during the normally high-rate ("late") portions of the FI, but also during the normally low-rate ("early") portions; intermediate-rate responding was essentially unaffected by the drug.

Exceptions to the rate-dependency effect with CNS stimulants have been noted previously. For example, amphetamine has sometimes failed to enhance responding in situations where the control rate was very low [15]. While mean control rates were sometimes very low at the start of the FI in the present study ($\bar{X}$=0.012/sec), they were zero in only two of the six subjects, and not in all pre-drug control sessions. Furthermore, examination of individual records showed that animals making the lowest control rates responded to caffeine with substantial rate enhancements during the early $^1/_{10}$ths of the FI.

Our data imply that caffeine's effects are rate-dependent, but not to the same degree that amphetamine's are. The

simplest interpretation of our results is that caffeine enhances low-rate responding less than amphetamine does. This hypothesis could be tested by comparing the effects of the two drugs on schedules which generate low response rates, e.g., DRL, CRF, or responding suppressed by extinction, punishment, or discrimination training. An alternative hypothesis would be that the two drugs differ primarily in their effects on post-reinforcement "pauses"; i.e., amphetamine may selectively reduce or eliminate the delay in resumption of responding after a reinforcement [2] while caffeine may not. This notion could be tested by determining whether amphetamine enhances post-reinforcement responding relatively more than caffeine under various schedules (e.g., FI, FR, DRL). These two alternative hypotheses might be tested in a single experimental design using multiple or mixed schedules of reinforcement.

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