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BRIEF COMMUNICATION

Effects of Cocaine on Fixed-Interval Behavior and Schedule-Induced Alcohol Consumption in Male and Female Rats

FRANS VAN HAAREN[1] AND KAREN ANDERSON

Department of Psychology, University of Florida, Gainesville, FL 32611

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VAN HAAREN, F. AND K. ANDERSON. *Effects of cocaine on fixed-interval behavior and schedule-induced alcohol consumption in male and female rats.* PHARMACOL BIOCHEM BEHAV 47(4) 997–1002, 1994.—Three male and three female Wistar rats pressed a lever on a fixed-interval 60-s schedule of food reinforcement while they had simultaneous access to an alcohol solution. They were challenged with different doses of cocaine hydrochloride (vehicle, 1, 3, 10, and 30 mg/kg) once lever press rates and lick rates had stabilized. Low doses of cocaine (1 and 3 mg/kg) did not systematically affect lever press rates or lick rates. The administration of 10 and 30 mg/kg cocaine dose-dependently decreased lever press rates and schedule-induced licking to a greater extent in female than in male rats. Lick rates decreased even when cocaine administration did not affect the number of pellets obtained during an experimental session. Lever press rates accelerated throughout the interreinforcement interval during control sessions. Licking was mostly limited to the first 10 s (males) or 20 s (females) after pellet presentation. Cocaine administration did not affect the distribution of lever presses and licks during the interreinforcement interval. The results of the present experiment extend previous observations that cocaine's rate-dependent effects on lever press rates may be limited to situations in which changes in lever press frequency and/or distribution negatively affect reinforcement frequency and/or the physiological consequences of schedule-induced behavior.

Fixed-interval schedule Schedule-induced alcohol consumption Cocaine Sex differences Lever press Licking Male and female rats

RATS drink large amounts of water when exposed to experimental procedures in which response-dependent or response-independent food is intermittently available. The exact nature of schedule-induced water consumption is still a matter of theoretical discussion but it has been well established that intermittent food delivery consistently results in adjunctive behavior of which polydipsia is a prime example (8,15,25).

The effects of drug administration on schedule-controlled behavior differ as a function of the pharmacological properties of a drug, the baseline schedule of reinforcement, or the response rates in the absence of drug administration (2,4–6,18). The nature of the consequent event plays an important role as well as the subject's behavioral and pharmacological history (7,18).

Drug effects on schedule-induced water consumption are a function of the schedule of reinforcement and the drug's pharmacological properties (1,13). Drinking is generally facilitated by chlordiazepoxide and similar drugs, and licking and water intake are decreased by stimulants, drugs with anticholinergic properties, narcotic agonists and antagonists, ethanol and haloperidol [for review see (12)].

Drug effects on schedule-induced behavior may differ from those on schedule-controlled behavior. Small and intermediate doses of stimulant drugs, for instance, do not affect or decrease schedule-induced water consumption but increase response rates maintained by the same schedule of reinforcement (3,13,24,26). Very little is known about the behavioral effects of drug administration on schedule-controlled behavior and schedule-induced consumption of substances other than water. Such is an interesting question to pursue, how-

[1] To whom requests for reprints should be addressed.

ever, inasmuch as the literature briefly reviewed above suggests that the effects of drug administration on schedule-controlled and schedule-induced behavior are very much a function of pharmacological and environmental variables, of which the nature of the substance available for consumption could be one.

The present experiment was designed to investigate the effects of cocaine administration on response rates maintained by a FI 60-s schedule of food reinforcement and the schedule-induced consumption of an alcohol solution. Male and female rats with a long history of exposure to an FI 60-s schedule in the presence of an alcohol solution (19) served as subjects because it has previously been shown that gonadal hormones may functionally affect the behavioral outcome of pharmacological challenge (20–23).

METHOD

Subjects

Three male and three female Wistar rats who had previously participated in other experiments (16,19) served as subjects. They were housed in same-sex groups and maintained on a reversed 12 L : 12 D cycle (lights on 1900 h). They could always drink tap water in the home cage but access to food was limited to 1.5 h following the experimental session (9). The subjects weighed an average of 530 g (males) and 460 g (females) and were approximately 20 months old at the start of this experiment.

Apparatus

Experiments were run in two identical Coulbourn Instruments rodent operant conditioning chambers that were 24 cm deep, 30 cm wide, and 29 cm high. The walls of the chamber were made of translucent Plexiglas except for the aluminum intelligence panel. The floor consisted of 16 rods, spaced 2 cm apart (center to center). The houselight was located 2 cm from the ceiling in the middle of the intelligence panel. A nonretractable rodent lever was located immediately to the left of the pellet tray, 7 cm from the floor of the chamber. The lever protruded 1.75 cm into the chamber from the intelligence panel and required a force in excess of 0.20 N to be operated. Three stimulus lights were located immediately above the lever. A lever press produced a click from a clicker located directly behind the intelligence panel immediately underneath the pellet trough. A sipper tube (Coulbourn Instruments) was available through an aperture to the right of the pellet tray. Individual licks were detected whenever the subject interrupted an infrared light source with the tip of its tongue. Each experimental chamber was housed in a sound-attenuating cabinet and connected to a PDP 11-23 microcomputer (Digital Equipment Corporation, Maynard, MA) located in the experimental room itself. Experimental contingencies and data acquisition procedures were programmed in SKED-11 (14).

Procedure

All subjects had been trained to press a lever on a FI 60-s schedule of food reinforcement with access to an alcohol solution in a preceding experiment (alcohol mixed in distilled water, v/v). The alcohol concentration to yield the highest alcohol intake during an experimental session (in g ETOH/kg) had been individually determined in that study (19). This alcohol concentration was maintained in the present experiment such that male subjects had access to solutions containing 24% (#601), 16% (#602), and 24% (#603) alcohol and female subjects to solutions containing 8% (#301), 12% (302), and 4% (#306) alcohol. Sessions were run 5 days per week (Monday through Friday) and were terminated after 36 pellets had been presented or after 45 min, whichever came first.

Drug Administration

Once response rates and lick rates had stabilized subjects were intraperitoneally (IP) injected with different doses of cocaine hydrochloride (saline, 1, 3, 10, and 30 mg/kg) 10 min before the start of the session. The different doses of cocaine were administered at least three times (range 3–6) on Tuesdays and Fridays of each week when lever press rates and lick rates during the preceding sessions did not exceed the control range. Vaginal smears were obtained at the time of drug administration to determine the stage of the estrous cycle in intact female subjects.

Blood alcohol levels (BAL) were measured on two occasions following the completion of the experiment. Blood was drawn from the tail immediately after the experimental session and BALs were determined using a commercially available kit (Sigma).

RESULTS

Absolute individual response rates (lever presses per minute) and lick rates (licks per minute) are shown as a function of the dose of cocaine in the first and third row panels of Fig. 1. These same data are expressed as a function of their respective control rates in the second and fourth row panels of the figure. The filled symbols represent the average of the three sets of individual data presented in each panel.

Male rats pressed the lever at higher rates than female rats during control sessions and after administration of cocaine's vehicle; females licked at higher rates than males. Low doses of cocaine (1 and 3 mg/kg) did not systematically affect the males' lever press rates and increased lever press rates for only one of the female rats (306). The higher doses of cocaine (10 and 30 mg/kg) resulted in a dose-dependent decrease in lever press rates. The decrease was greater in female than in male rats after 10 mg/kg cocaine. The 30 mg/kg cocaine dose completely eliminated lever pressing in all three female rats and virtually eliminated lever pressing in two of the three male rats (except 603). Administration of 1 and 3 mg/kg cocaine decreased lick rates with few exceptions (306 and 602 after 3 mg/kg). The higher doses of cocaine dose-dependently decreased lick rates in all subjects except 602 after 10 mg/kg cocaine.

Most subjects obtained nearly all of the scheduled reinforcers after the administration of the lower and intermediate doses (1, 3, and 10 mg/kg) of cocaine. Only subject 302 obtained just 17% of the scheduled reinforcers after 10 mg/kg. The 30 mg/kg cocaine dose reduced the percentage of obtained reinforcers to near zero for all female rats, and it greatly reduced this percentage for two of the three male rats (601, 59%; 602, 15%).

An analysis of the lick rate data shown in Fig. 1 in conjunction with the data presented supra reveals that lick rates decreased considerably after 10 mg/kg cocaine even though most subjects still obtained nearly all of the scheduled reinforcers. The administration of 30 mg/kg cocaine reduced the percentage of obtained reinforcers to zero in female rats and abol-

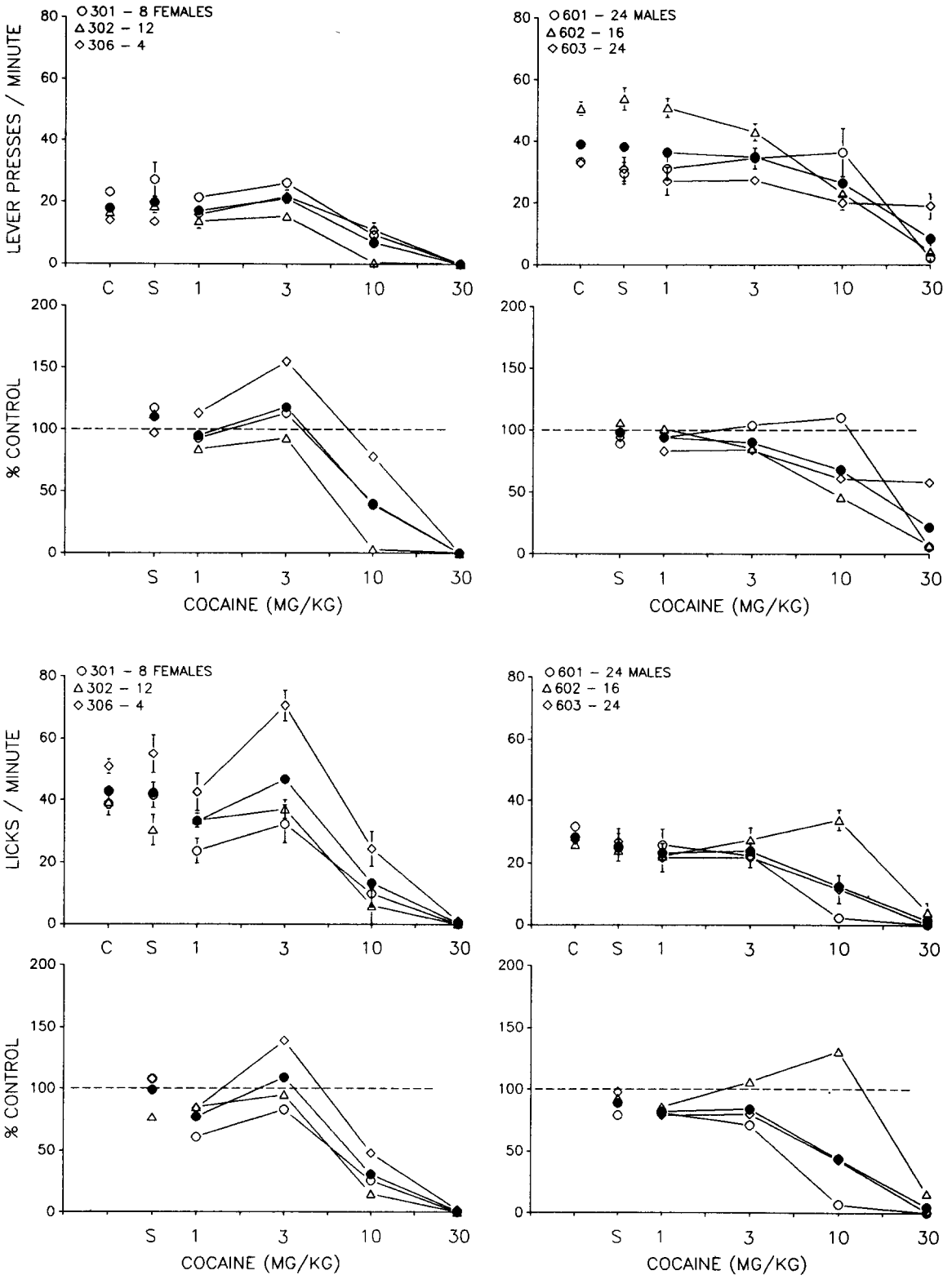

FIG. 1. Lever presses per minute (mean ± 1 SEM) for individual female and male Wistar rats as a function of the different doses of cocaine (first row). The second row shows the the same data expressed as a percentage of lever press rates during control sessions. Licks per minute (mean ± 1 SEM) are presented as a function of the different doses of cocaine in the third row. The fourth row shows the same data expressed as a percentage of lick rates during control sessions. The data points above C and S are from control observations during sessions preceding those in which cocaine was administered (C) and observations after saline administration (S). Filled symbols represent the average of the data points presented in each panel.

ished licking altogether. Cocaine at 30 mg/kg greatly reduced lick rates in all three male rats, but only reduced the percentage of obtained reinforcers to almost zero in one of the three (602) subjects.

Figure 2 shows lever presses per minute (filled symbols) and licks per minute (open symbols) as a function of the different doses of cocaine and postfood time (s) for individual male (dashed lines) and female (solid lines) rats.

Lever press rates during control sessions and after saline administration accelerated throughout the interval for all subjects. During control and saline sessions licking was mostly limited to the first 20 s after pellet presentation in female rats and to the first 10 s after pellet presentation in male rats.

Figure 2 also convincingly shows that drug administration, while decreasing lever press rates and lick rates, did not systematically change the distribution of lever presses and licks throughout the interreinforcement interval (except for subject 603 after 30 mg/kg cocaine).

Table 1 shows that BALs obtained at the conclusion of the experiment sometimes approached levels usually considered physiologically significant (100 mg/dl). The between-sample variability in BALs was greater for female rats than for males.

It should be noted that an obvious correlation between the estrous cycle and the behavioral effects of cocaine was not observed.

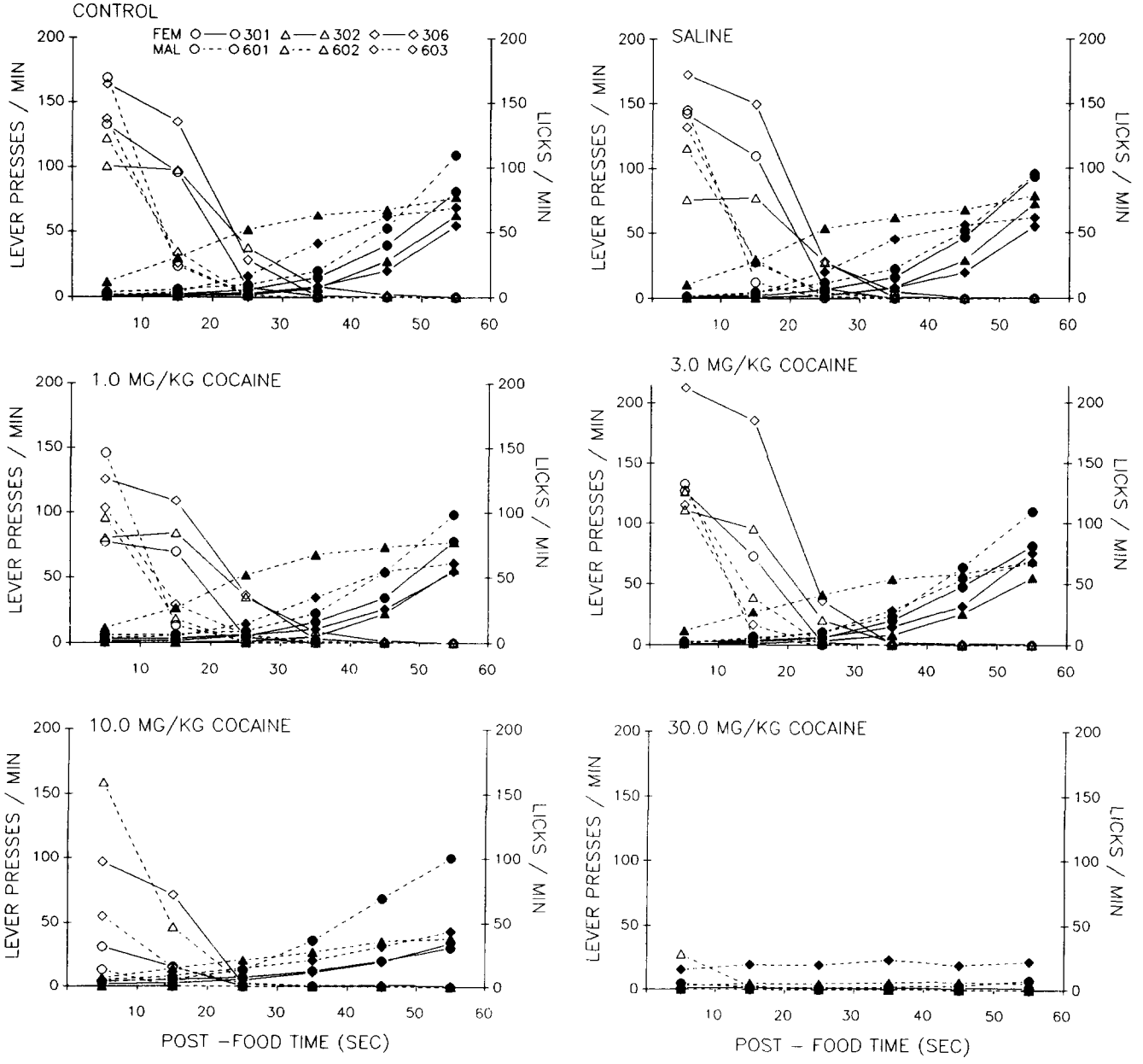

FIG. 2. Lever presses per minute (filled symbols) and licks per minute (open symbols) as a function of the different doses of cocaine and postfood time (s) for individual male and female rats.

TABLE 1

BLOOD ALCOHOL LEVELS (mg/dl) AND ALCOHOL SOLUTION (ml) CONSUMED BY INDIVIDUAL SUBJECTS DETERMINED AT THE COMPLETION OF THE EXPERIMENT

Subject	Alcohol Concentration	Sample 1 mg/dl (ml)	Sample 2 mg/dl (ml)
301	8%	20.00 (2)	62.35 (10)
302	12%	10.59 (6)	69.41 (7)
306	4%	64.71 (16)	29.41 (9)
601	24%	64.71 (4)	76.47 (10)
602	16%	55.29 (9)	88.24 (9)
603	24%	100.00 (9)	76.47 (4)

DISCUSSION

Cocaine administration dose-dependently affected schedule-controlled behavior and schedule-induced alcohol consumption. Low doses of cocaine hydrochloride (1 and 3 mg/kg) did not functionally affect FI lever press rates or schedule-induced licking of an alcohol solution in male and female rats. Higher doses of cocaine (10 and 30 mg/kg), however, dose-dependently decreased lever press rates and lick rates, which were reduced to a greater extent in female rats than in males. Interestingly, cocaine administration did not affect the distribution of lever presses and licks throughout the interreinforcement interval; lever press rates continued to accelerate as the interval progressed and licking remained limited to the first 10 s (males) or 20 s (females) after pellet presentation.

Our observations support those of others who showed that the behavior of female rats may be more easily disrupted than that of male rats by administration of psychomotor stimulant drugs including cocaine (20–23). However, our observations are not in agreement with those of other experiments in which it was shown that stimulant drugs that do not alter or decrease the frequency of schedule-induced behavior increase response rates maintained by FI schedules of reinforcement, much as they do when subjects do not have an opportunity to engage in adjunctive behavior (3,5,13,24,26). One of the major differences between those studies and our experiment concerned the substance available from the drinking tube: water when lever press rates increased and alcohol when lever press rates did not increase. It would, of course, have been interesting to directly compare the effects of cocaine on lever press rates and water consumption in our subjects as well. This comparison, however, was deemed impossible because other experiments had shown that a change in fluid alone (from alcohol to water) greatly increased lick rates (19).

To our knowledge, only one other paper has reported the effects of cocaine administration on voluntary alcohol consumption. McMillan and Snodgrass (10) exposed subjects to four daily, equally spaced experimental sessions in which they pressed a lever on a fixed-ratio (FR) 40 of food reinforcement while access to water and an alcohol solution was simultaneously available. Acute cocaine administration (up to 30 mg/kg) had little effect on alcohol intake, which increased, however, after chronic administration of 30 mg/kg cocaine. The results of this study are not easy to interpret because cocaine administration was preceded by acute and chronic administration of Δ^9-tetrahydrocannabinol.

Our results also provide for interesting comparisons with those of other studies that have reported the effects of psychomotor stimulant drugs on behavior maintained by FI schedules of food reinforcement. In these experiments, low to moderate doses of cocaine and *d*-amphetamine increased low response rates and decreased high response rates during different parts of the FI interval. These observations have been the cornerstone of the rate-dependency [e.g. (6)] and rate-constancy [e.g. (4)] hypotheses that have long provided a parsimonious description for a multitude of drug effects on schedule-controlled behavior [see (2)]. The present data, which do not show any rate-dependent effects or tendencies towards rate-constancy after low doses of cocaine, provide an interesting exception to these notions. To account for these observations it has recently been proposed that drug administration may only affect schedule-controlled behavior to the extent that direct schedule variables allow for behavioral variability to occur without negatively affecting important behavioral outcomes (17,18,27). For instance, FI response rates may vary over a wide range without seriously endangering the reinforcement frequency that the schedule used to provide in the absence of drug administration. Thus, when conditions were arranged to facilitate schedule-induced water consumption on FI schedules in other experiments, the administration of low to moderate doses of cocaine or amphetamine increased low rates of lever pressing and decreased schedule-induced polydipsia (3,5,24). To account for this redistribution of behavior it has been suggested that an increase in response rates did not affect reinforcement frequency and a decrease in water intake did not threaten any important behavioral or physiological homeostasis (11,12). In other words, drug-induced changes in schedule-controlled and schedule-induced behavior did not negatively affect behavioral outcomes. The data of the present experiment suggest that the disruption of schedule-controlled behavior by drug administration in a schedule-induction environment may also be a function of the nature of the schedule-induced activity simultaneously available to the subject. Other studies will have to be conducted to further evaluate the nature of these interactions.

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