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Behavioral Dependence on Caffeine and Phencyclidine in Rhesus Monkeys: Interactive Effects

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CARROLL, M. E., E. W. HAGEN, M. ASENCIO AND L. H. BRAUER. *Behavioral dependence on caffeine and phencyclidine in rhesus monkeys: Interactive effects.* PHARMACOL BIOCHEM BEHAV 31(4) 927–932, 1988.—Five rhesus monkeys were trained to self-administer orally-delivered phencyclidine (PCP) and water under concurrent fixed-ratio (FR) 8 schedules. Liquid deliveries were contingent upon lip-contact responses on solenoid-operated drinking spouts, and food pellet delivery was contingent upon responses on a centrally-located lever. Food was available during three 1-hr periods each day under an FR 64 or FR 80 schedule. The liquids were available during three 6.5-hr periods after each food component. In the first experiment caffeine (4 or 8 mg) was added to each 6-g food pellet, and after responding stabilized, noncaffeinated pellets were substituted for the caffeinated pellets for eight days. There were no differences in food-, water- or PCP-maintained behavior due to caffeine concentration (4 vs. 8 mg/pellet) although the monkeys consumed twice as much caffeine at the higher concentration. Food-maintained responding was reliably reduced by 25–50 percent the first day of caffeine removal, and there was a recovery of responding characterized by intermittent cycles of low response rates over the next 7 days. Water and PCP intake were not systematically disrupted when caffeine access was terminated. In the second experiment the monkeys were tested with caffeinated (6 mg/pellet) and noncaffeinated pellets under conditions of PCP removal (water substitution) and reinstatement. Under both food conditions, when PCP access was terminated, pellet deliveries decreased by about 50 percent and gradually recovered over the 8-day water substitution phase. However, behavioral disruptions were more severe under conditions in which monkeys received caffeinated pellets, suggesting an interactive effect due to termination of PCP access and decreased caffeine intake. These results indicate that disruptions in operant baselines are sensitive indicators of the effects of discontinuing caffeine access; however, the severity and time course of behavioral disruptions due to caffeine removal are considerably less than after termination of PCP access.

Behavioral dependence Caffeine Phencyclidine PCP Oral route Rhesus monkeys Self-administration

BEHAVIORAL dependence has been defined as disruptions in behavior that occur in the absence of physical withdrawal signs when repeated drug administration is terminated (30). Behavioral dependence is analogous to physical dependence as there is a predictable time course after frequent drug administration is terminated, and the withdrawal syndrome is immediately reversed by administration of the drug. Behavioral dependence has been demonstrated by measuring disruptions in food-reinforced operant behavior with laboratory animals after termination of chronic access to amphetamine (31), cocaine (8), phencyclidine (6,32) and THC (4). The behavioral disruptions produced by removing these drugs were substantial in intensity and duration despite the absence of severe or observable physical symptoms of drug withdrawal. These findings indicate that behavioral disruptions (in food-reinforced responding) are a sensitive measure of drug dependence.

There is additional evidence for the sensitivity of these measures from similar studies with drugs that do produce an observable withdrawal illness when their administration is terminated. When chronic administration of drugs such as morphine (16, 17, 23, 33, 35), ethanol (1) and chlordiazepoxide (25) is stopped, behavioral disruptions initially parallel physical disturbances, but full recovery of behavioral abberations if often considerably slower. These studies have consistently demonstrated behavioral dependence defined by a disruption in operant behavior maintained by food and or shock avoidance (35) across a wide range of drugs. However, the effect of removing chronic access to one drug on behavior maintained by a second drug has received little attention.

The purpose of the present study was to select two drugs, caffeine and phencyclidine (PCP), and to examine the effects of removing access to one drug on behavior maintained by the other drug. Caffeine is the most widely used behaviorally active drug; however, there have been relatively few laboratory studies of its reinforcing and dependence producing effects. In studies of human coffee drinking, headache, lethargy, fatigue, irritability, nausea and rhinorrhea were reported when caffeine administration was terminated

(14, 18–20, 24). In experiments with rats, Vitiello and Woods (37) showed that the association of a novel flavor with the removal of caffeine results in subsequent avoidance of that flavor. Carney (13) found a reduction in food-maintained responding when rats received saline after at least a week of daily injections (32 mg/kg) of caffeine, and Finn and Holtzman (15) showed decreases in spontaneous locomotor activity during the first two days a 67 mg/kg dose (but not a 36 mg/kg dose) of caffeine was removed from rats. The time course of behavioral disruptions due to termination of caffeine self-administration has not yet been examined, and that is an objective of this study.

Phencyclidine (PCP) has been a popular drug of abuse since the late 1960's. Its reinforcing effects have also been documented in laboratory animals (3, 10, 28). Withdrawal symptoms associated with termination of PCP use in humans are characterized by depression, craving, irritability, and increased need for sleep (5). Physiological and behavioral withdrawal symptoms have been noted in rhesus monkeys after termination of high daily doses of PCP (2). Others have reported disruptions in food-reinforced behavior after removal of intravenous (32) or oral (6) PCP access. The present experiment will extend these findings by examining the effects of terminating oral PCP access on caffeine intake.

METHOD

Subjects

Five adult male rhesus monkeys (*Macaca mulatta*) served as subjects. The monkeys had self-administered PCP during daily 3-hr sessions for several years while being tested under varied feeding conditions. All of the monkeys had prior experience with oral self-administration of one or more other drugs such as amphetamine, ketamine, methohexital and N-allylnormetazocine. Three monkeys (M-C, M-M1 and M-M2) had been previously tested under repeated episodes of PCP removal. Body weights during the experiment were close to those obtained when the animals were free feeding; the average weights throughout the experiment ranged from 9.9 to 16.3 kg across the five monkeys. The monkeys were housed individually in their experimental chambers in a room maintained at 24°C under a 12-hr light/dark cycle, with the lights on at 6:00 a.m.

Apparatus

The monkeys were housed in stainless-steel primate cages (Hoeltge No. HB-108) equipped with a work panel on one wall. The panel contained two drinking spouts spaced 15 cm on either side of a centrally-located response lever. The brass drinking spouts were 2.7 cm long and 1.2 cm in diameter, and they were operated by a drinkometer circuit that was activated when the monkey put his mouth on the spout. When liquids were available, a lip contact on the drinking device operated a solenoid for about 120 msec and released 0.55 ml of liquid from the spout. Lights above each drinking device and the lever signalled experimental events. Two pairs of small lights were mounted behind a clear Plexiglas® disk supporting the spout. Two green lights were illuminated to signal lip contact responses when PCP was available, and two white lights were illuminated when water was available. A large green light above each spout indicated the availability of liquids, and the light flashed (10 times/sec) when PCP was available. Liquids were stored at room temperature in covered Nalgene containers. A large red light above the lever signalled periods of food availability. Food (Purina High Protein Monkey Chow No. 5045) delivery was contingent upon lever-press responses. Food pellets (approximately 6 g each) were delivered by a Universal Feeder (Ralph Gerbrands Co., Arlington, MA). Experimental sessions were controlled and data were recorded by microcomputers (Micro Interfaces, Inc., Minneapolis, MN) located in an adjacent room. More details of the control and recording equipment, drinking devices and experimental chambers are available elsewhere (12, 21, 37).

Drugs

Phencyclidine HCl was provided by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC). The PCP solution was prepared in tap water 20 hr before use, and the concentration refers to the salt. Caffeine was purchased from Sigma Chemical Co. (St. Louis, MO). Pilot work revealed that caffeine was not readily self-administered when it was added to the monkeys' drinking water. Thus, the drug was added to the food pellets. Similar procedures had been used by Suzuki and co-workers (34) to study physical dependence on pentobarbital in rats. Caffeine was dissolved in tap water, loaded into a syringe, and injected (1 ml/injection) into the 6 g monkey pellets in amounts of either 4, 6 or 8 mg/pellet. The pellets were stored uncovered in a refrigerator for several days to dry and then at room temperature until they were used.

Procedure

Before the start of the experiment, the monkeys responded on the two drinking spouts under concurrent fixed-ratio (FR) 16 schedules of PCP (0.25 mg/ml) and water deliveries (0.55 ml) during daily 3-hr sessions. At that time they were maintained at 85–90 percent of their free-feeding weight. Water was freely available under an FR 1 schedule during the 19-hr intersession periods. At the beginning of this experiment, the FR requirement for PCP and water was decreased to 8 to maximize drug intake. Water and PCP were concurrently available at three times each day (10:30 a.m., 6:00 p.m. and 1:30 a.m.) for 6.5 hr each time. Side positions of drug and water were reversed daily to control for side preferences. Prior to each of the three daily 6.5-hr liquid sessions, there were 1-hr food sessions beginning at 9:30 a.m., 5:00 p.m. and 12:30 a.m. Food pellet deliveries were contingent upon responses on the lever. The FR requirement was 64 for M-G2, M-M1 and M-M2 and 80 for M-A1 and M-C. These FR values allowed the monkeys to obtain enough food to maintain their free-feeding body weights, while no excess food was earned and discarded. Between 8:00 a.m. and 9:30 a.m. each day there was a time out when data were recorded and solutions were measured and changed. The monkeys' behavior was allowed to stabilize under this procedure for approximately 10 days before Experiments 1 and 2 began. Stability was defined as no steadily increasing or decreasing trend in the number of liquid and/or pellet deliveries. Thus, pellet deliveries are expressed in terms of percent of the control period defined as the last five days of stable responding before caffeine or PCP access was terminated. The number of pellets earned differed between and within monkeys over time. Also, the size of the pellets fluctuated (within 1 g) with different shipments.

Experiment 1. The Effect of Caffeine Removal on Food- and PCP-Reinforced Behavior

Caffeine (4 mg/pellet) was added to the food pellets and behavior was allowed to stabilize for at least 20 days. Caf-

feinated food pellets were then replaced by noncaffeinated pellets for 8 days, and the caffeinated pellets were reinstated for 5 days. Subsequently, the amount of caffeine added to the food was increased to 8 mg/pellet, and behavior was again allowed to stabilize for at least 20 sessions, and the withdrawal procedure was repeated.

RESULTS

Behavior rapidly stabilized under the 6-component liquid (19.5-hr) and food (3-hr) sessions. The 5 monkeys (M-A1, M-C, M-G2, M-M1 and M-M2) consumed a mean of 49.2, 82.8, 71.9, 66.5 and 56.5 pellets of food per day, respectively, over the last 5 days before caffeine was added to the food. The mean number of pellets (±S.E.) earned by the 5 monkeys over this 5-day period was 65.4 (±5.9). They quickly gained weight to equal or slightly exceed weights that were recorded while they were free-feeding. Most responding for food, drug and water was distributed between the first two food and liquid components, and very little responding occurred during the third component which was late in the dark cycle. When caffeinated pellets (4 mg/pellet) were introduced, there was no systematic change in the number of pellets earned. The mean (±S.E.) number of caffeinated (4 mg/pellets) pellets obtained by the 5 monkeys over the last 5 days before noncaffeinated pellets were substituted was 57.2 (±3.9). The mean (±S.E.) number of pellets earned at the higher caffeine concentration (8 mg/pellet) was 57.7 (±4.2). The data are presented as 24-hr totals, and the day was defined as beginning with a liquid component (10:30 a.m.–5:00 p.m.) and ending with a food component (9:30–10:30 a.m.). When noncaffeinated pellets were substituted for caffeinated pellets, the monkeys had been without caffeine for at least 9 hr. At the lower caffeine concentration (4 mg/pellet) the mean amount of caffeine consumed daily during the 5-day control period was 228.8 mg/monkey or 19.2 mg/kg, while the mean amount consumed at the higher concentration (8 mg/pellet) was 461.6 mg/monkey or 36.2 mg/kg.

Figure 1 shows the results of caffeine withdrawal on pellet deliveries as a function of caffeine concentration. Pellet deliveries were reduced when caffeine access was terminated with respect to the mean deliveries during the control period and the last 5 days when caffeinated pellets were reinstated. The most consistent finding across monkeys was that the first day caffeine was removed there was a 25–50 percent reduction in pellet deliveries. In some of the monkeys (e.g., M-A1 and M-C at 4 mg/pellet) pellet deliveries returned to control rates by the second day of caffeine withdrawal followed by alternating days of high and low pellet deliveries, while in M-M2 (4 mg/pellet) pellet deliveries did not return to baseline rates until caffeine was reinstated. When caffeine was reinstated, the daily variability in pellet deliveries was reduced in some monkeys (e.g., M-M1, and M-M2 at 8 mg/pellet). In other monkeys pellet deliveries were less variable during caffeine withdrawal, (e.g., M-G2 and M-M2 at 4 mg and M-C at 8 mg/pellet). There were no consistent differences in pellet deliveries as a function of caffeine concentration (4 or 8 mg/pellet), although almost twice as much drug was consumed at the higher concentration. Under both the 4 and 8 mg/pellet conditions, caffeine intake (mg/kg) was nearly the same before and after caffeine withdrawal.

Figure 2 shows the number of PCP and water deliveries before and during the caffeine removal period and after caffeine was reinstated. The number of PCP and water deliveries was not consistently altered by caffeine removal, and there was little relationship between the degree of disruption of pellet deliveries and the number of PCP or water deliveries. In 2 of the monkeys (M-M1 and M-M2), PCP deliveries were suppressed on alternating days while water deliveries increased on those days. Thus, total liquid deliveries were relatively unchanged, but the preference for PCP was reduced. Precaffeine liquid deliveries are not presented, as they were nearly identical to those shown during the 5-day control period and they were similar to those recently reported in a similar experiment (6). Mean PCP intake over the 5-day control period ranged from 13.9 to 25 mg/kg across the 5 monkeys. Other monkeys showed disruptions in PCP deliveries on the first day (M-C) and/or later during the caffeine withdrawal phase (M-C, M-G2). One monkey (M-A1) did not show any consistent change in PCP or water deliveries as a

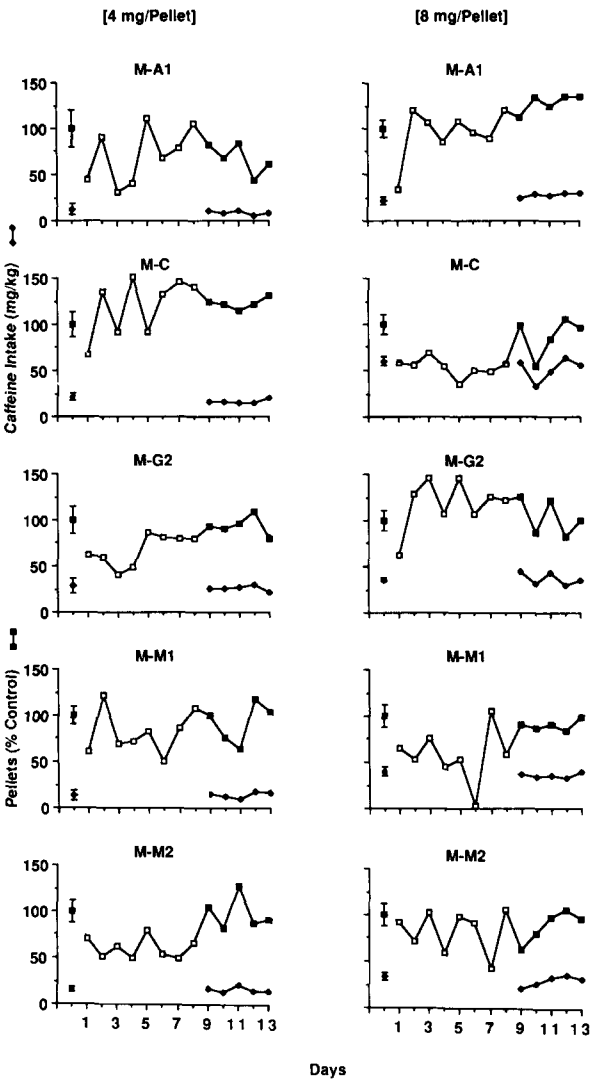

FIG. 1. Caffeine intake (mg/kg) and pellet deliveries (expressed as a percent of control) are presented for each of five monkeys as a function of drug concentration (4 or 8 mg/pellet). *Filled squares* indicate that caffeine was present in the food pellets, and *open squares* refer to noncaffeinated pellets. *Diamonds* represent the amount of caffeine consumed. The first square (100%) serves as a control and represents a mean (±S.D.) of the last five days of stable behavior before caffeine removal. The first diamond represents the mean (±S.D.) caffeine intake (mg/kg) over those five days. Connected points refer to individual daily totals.

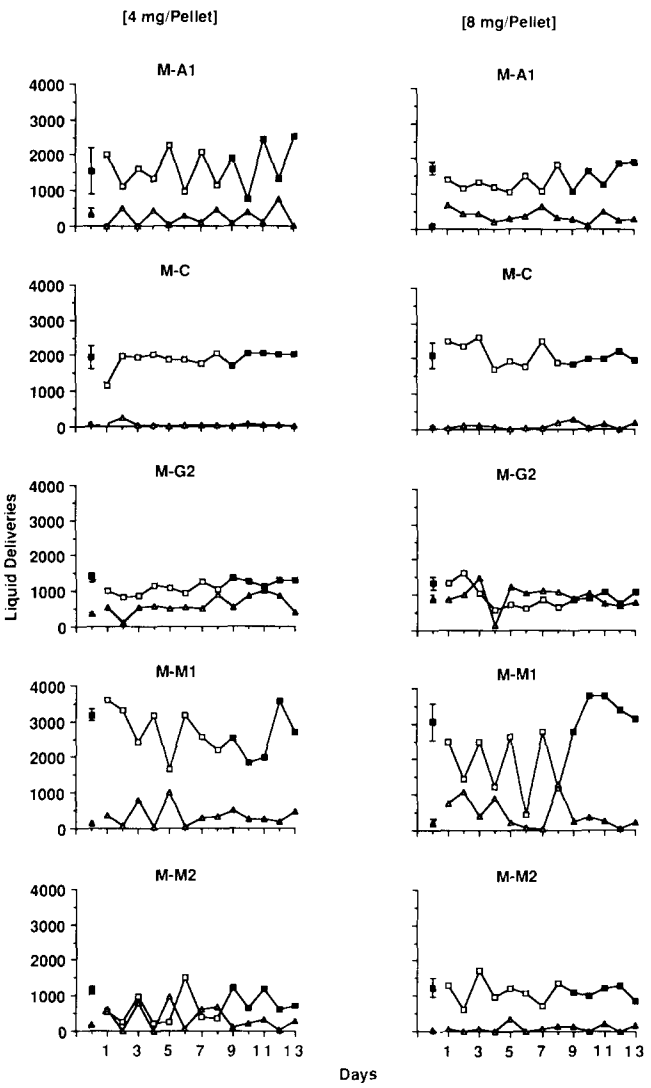

FIG. 2. Liquid deliveries are presented for each of five monkeys as a function of drug concentration (4 or 8 mg/pellet). *Squares* represent PCP deliveries and *triangles* refer to concurrent water deliveries. *Filled symbols* indicate that caffeine was present in the food pellets, and *open* symbols refer to days when noncaffeinated pellets were available. The first points serve as controls and represent means (±S.D.) of the last five days of stable behavior before caffeine removal. Connected points are the individual daily totals.

result of caffeine withdrawal. In Fig. 1 it can be seen that this monkey's caffeine intake was the lowest of the 5 monkeys. The caffeine withdrawal signs (yawning, lethargy, rhinorrhea and irritability) reported by human volunteers (20,24) were not systematically monitored but were occasionally noted during the first 2 days that caffeine had been absent in the monkey's food. These signs were not observed during pre-caffeine or control periods.

Experiment 2. The Effect of PCP Removal on Behavior Maintained by Caffeinated and Noncaffeinated Food

The amount of caffeine added to the pellets was reduced to 6 mg/pellet, and behavior was allowed to stabilize for at least 10 sessions. Subsequently, PCP was replaced by water for 8 days. Water was concurrently available from the 2 drinking devices. After the water substitution phase, PCP replaced water for at least 5 days. Noncaffeinated pellets then replaced the caffeinated pellets, and behavior was again allowed to stabilize for at least 10 sessions. The PCP removal experiment was then replicated with noncaffeinated food pellets. Three of the monkeys (M-C, M-M1 and M-M2) received the noncaffeinated food condition first.

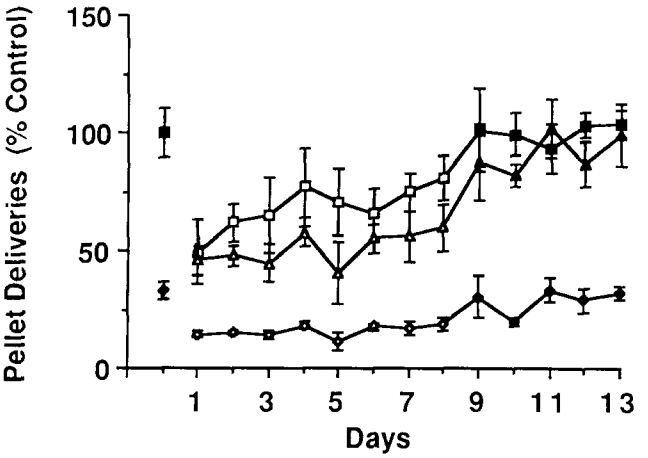

FIG. 3. Pellet deliveries (expressed as a percent of control) are presented as a mean (±S.E.) for five monkeys. *Squares* indicate that no caffeine was added to the pellets, and *triangles* indicate that caffeine (6 mg) was added to the pellets. *Filled symbols* indicate that PCP (0.25 mg/ml) was available concurrently with water, and *open symbols* refer to days when water was available from both drinking spouts. The first point (100%) serves as a control and represents a mean (±S.E.) of the last five days of stable behavior before water substitution. Connected points are the number of pellet deliveries (as a percent of control) during water substitution and PCP reinstatement. Diamonds refer to the mean (±S.E.) caffeine intake (mg/kg) when caffeinated pellets were available throughout the experiment.

RESULTS

Figure 3 shows the number of pellet deliveries (as a percent of control) during PCP removal and reinstatement under both caffeinated and noncaffeinated food conditions. The mean (±S.E.) pellet deliveries over the 5-day control period was 63.6 (±6.2) for the caffeinated (6 mg/pellet) condition and 57.2 (±5.5) for the noncaffeinated condition. Under both conditions pellet deliveries decreased by about 50 percent on the first day water was substituted for PCP. When noncaffeinated food was available, there was a gradual recovery to near baseline rates, over the next 7 days; however, when caffeinated pellets were available, responding remained suppressed at about 50 percent of control values until PCP was reinstated. Thus, caffeine intake was also reduced by about half during water substitution. Liquid deliveries are not presented, as PCP and water deliveries did not differ across caffeinated and noncaffeinated food conditions, and PCP and water deliveries were similar to those presented in an earlier report (6). Thus, the presence of

caffeine in the food did not appear to have any rate increasing or decreasing effect on liquid-maintained behavior. As shown in earlier work using the same experimental design (6), when water was substituted for PCP, the total number of liquid deliveries decreased to amounts that were lower than when drug had been available, and they did not increase as pellet deliveries began to return to baseline. There was no consistent change in the number of water deliveries throughout the 8-day water substitution phase. Mean PCP intake over the 5-day control period ranged from 9.5 to 29.8 and from 8.8 to 33.4 mg/kg across the 5 monkeys in the caffeinated and noncaffeinated pellet condition, respectively.

DISCUSSION

Phencyclidine (0.25 mg/ml) was reliably self-administered, and PCP deliveries far exceeded water deliveries indicating that the drug was functioning as a reinforcer. The reinforcing effects of PCP have been demonstrated previously (6,10) under similar conditions. The amount of orally-delivered PCP consumed in the present study was nearly twice as high as that consumed during 3-hr sessions (10). Caffeine was also self-administered when it was added to the food pellets; however, the number of pellets consumed was similar whether 0, 4, 6 or 8 mg of caffeine were added. The means for daily pellet deliveries over the last 5 days at each dose level (e.g., 0, 4, 6 or 8 mg/kg) for the 5 monkeys and 2 experiments were 60.4, 57.2, 63.6, and 57.7, respectively; thus, food intake was not controlled by the presence of caffeine. The amount of caffeine consumed ranged from 188 to 276 mg/monkey/day at the 4 mg/pellet concentration and from 389 to 554 mg at the 8 mg/pellet concentration. The amounts of caffeine consumed by these monkeys (ranging from 12.5–47.4 mg/kg in both experiments) equal or exceed mean amounts consumed by heavy coffee drinkers (e.g., 8.8 and 15.2 mg/kg or 615.7 to 1250 mg/per day, respectively) who report withdrawal headaches (19,20).

A comparison of food intake as a function of caffeine dose (0, 4, 6 or 8 mg/pellet) indicated that caffeine was not demonstrated to be functioning as a reinforcer in the present study. However, the monkeys in the present experiment were not food deprived, and earlier work has shown that food deprivation is often necessary to demonstrate that orally-delivered drugs are functioning as reinforcers (9). Other studies with human (20) and animal (22,36) subjects have demonstrated limited evidence for the reinforcing effects of caffeine. For example, coffee drinkers that had consumed caffeinated coffee for a week or more reliably chose caffeinated over decaffeinated coffee, while those that had been exposed to decaffeinated coffee did not reliably choose caffeinated coffee (20). Similar results had been reported in a free-choice drinking experiment with rats; forced caffeine consumption resulted in a subsequent preference for a caffeine solution over a flavor associated with caffeine; however, a group of rats that received lower concentrations of caffeine during the forced consumption period did not prefer caffeine (36). Recently, Heppner and co-workers (22) found that caffeine was preferred over water in a two-bottle preference test at a limited range of concentrations and only in female rats. They found that food deprivation greatly enhanced caffeine intake in both male and female rats. These results suggest that caffeine is a somewhat weak reinforcer, but its reinforcing effects can be enhanced by chronic exposure and food deprivation. The present results show that caffeine deprivation had no subsequent effects on caffeine intake or the reinforcing effects of caffeine.

When caffeine was removed from the food pellets, there was a reliable reduction in the number of pellet deliveries during the first 24 hr followed by subsequent disruptions that varied among individual monkeys over the next seven days when noncaffeinated pellets were available. The time course of behavioral disruptions paralleled the onset (3 hr) and duration (18–24 hr) of withdrawal manifestations (e.g., headache) reported by human coffee drinkers (14, 18, 19), as well as changes in cerebral blood flow that have been reported after termination of caffeine use in heavy coffee drinkers (26). The disruptions in pellet deliveries were not as severe, long-lasting or orderly as when access to THC (4) or PCP (6,32) was removed; however, the patterns of behavior in the present study were very similar to those reported by Griffiths and colleagues (20) in a study of human coffee drinking. In their study, when decaffeinated coffee replaced caffeinated coffee for approximately 2 weeks, they found significant decreases in the number of cigarettes smoked on the first day of substitution. This decrease in the rate of behavior maintained by an alternative substance may be analogous to the results shown here and in previous reports of decreased food-maintained responding (4, 6, 32). They also found small, nonsignificant decreases in the number of cups consumed and disruptions in performance on a psychomotor task.

In Experiment 2 a comparison of food intake under caffeinated and noncaffeinated food conditions revealed that food, water and PCP intake were not affected by caffeine. Increases in nicotine self-administration but not food-maintained responding have been reported after caffeine pretreatment (29). The effect of removing PCP on behavior maintained by caffeinated pellets was more severe than it was on that maintained by noncaffeinated food delivery. The greater disruption in caffeinated vs. decaffeinated food intake during PCP removal may have been due to the combined effects of PCP and caffeine removal, as caffeine intake was decreased by about half while pellet deliveries were reduced due to termination of PCP access. Further work is needed with animal models of behavioral dependence to determine whether these apparently additive effects were specific to the two drugs tested.

The present results emphasize the importance of considering the reinforcing and dependence-producing properties of drugs within the context of other drug and nondrug reinforcers. Recent work in this laboratory has demonstrated that removal of a nondrug reinforcer leads to increased PCP- (7) and cocaine-reinforced behavior (11). However, removal of a drug that is functioning as a reinforcer can result in increases or decreases in responding maintained by a nondrug reinforcer depending on whether the animal is in the acquisition or maintenance phase of drug self-administration (11). Results of the present study show that caffeine removal had little effect on PCP self-administration, but termination of PCP access had an interactive effect on food and caffeine self-administration.

In summary, termination of caffeine access resulted in a brief disruption in food-maintained responding. The time course paralleled reports of caffeine withdrawal symptoms in human coffee drinkers. Caffeine removal had little effect on behavior reinforced by orally-delivered PCP. Substitution of water for PCP resulted in a protracted decrease in behavior maintained by caffeinated and noncaffeinated food. However, the disruption in caffeinated food intake was more

pronounced. These behavioral disturbances and the additive effect of PCP and caffeine removal on food-maintained behavior suggest that caffeine dependence may enhance disruptive effects resulting from withdrawal of other drugs.

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