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CONCURRENT ACCESS TO TWO CONCENTRATIONS OF ORALLY DELIVERED PHENCYCLIDINE: EFFECTS OF FEEDING CONDITIONS

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Two experiments addressed the effects of food satiation and deprivation on oral self-administration of two concurrently available phencyclidine concentrations. In the first experiment, 8 rhesus monkeys self-administered either of two concentrations of phencyclidine ("PCP, angel dust") and water under concurrent fixed-ratio 16 schedules. One concentration was always held constant (0.25 mg/mL) while a series of other phencyclidine concentrations, ranging from 0 (water) to 1.0 mg/mL, was presented in a nonsystematic order. Initially the monkeys were tested while food satiated, and the procedure was then repeated during food deprivation. The monkeys usually selected the higher concentration within the first few minutes of the session, indicating that taste and/or other immediate postingestional effects were important factors. Contrary to a number of previous reports, there were no consistent differences across subjects in the mean number of liquid deliveries or mean drug intake (mg/kg) during food satiation and deprivation. However, for all monkeys the within-session time course of responding during food satiation consistently differed from that during deprivation. A second experiment assessed whether the failure to find consistent differences in drug intake during food satiation and deprivation had been due to the history of concurrent access to different phencyclidine concentrations or to the extended experience with phencyclidine under food-satiation conditions. Six additional monkeys (Group 2) were exposed to the phencyclidine self-administration procedure (during food satiation and deprivation) for the same length of time as the monkeys in Experiment 1 (Group 1), except they received only concurrent access to phencyclidine (0.25 mg/mL) and water. Both groups then received concurrent access to phencyclidine and water during five repeated cycles of food deprivation and satiation. There were also marked individual differences in Group 2: During food satiation, 2 of the monkeys' responding increased, 1 showed no change, and 3 decreased. Examination of a number of historical variables indicated that the greater the percentage of total sessions spent during food satiation with phencyclidine available (before these experiments began), the greater the amounts of phencyclidine consumed during food satiation and the smaller the differences in phencyclidine intake when the two feeding conditions were compared.

Key words: phencyclidine, oral drug self-administration, drug-reinforced behavior, concurrent fixed-ratio schedules, food satiation, food deprivation, drug history, taste, lip-contact response, rhesus monkeys

Effective procedures have been developed for establishing as reinforcers a variety of orally administered drugs from several major pharmacological classes of abused drugs (Meisch & Carroll, in press). Unlike the intravenous route, which is limited by short catheter life, the oral preparation allows for longer experiments. Furthermore, the oral route is the most common mode of drug use and abuse in humans, and it is important to study effects of taste and other stimuli that accompany oral ingestion. However, most studies of the reinforcing effects of orally delivered drugs (in solution) have been conducted with simple fixed-ratio (FR) schedules. In these studies total drug intake (mg/kg) in oral self-administration experiments typically increases as a negatively accelerated function of concentration while liquid deliveries increase and decrease in an inverted U-shaped fashion. The interpretation of these results may be limited by the use of simple schedules, and further understanding of the relative reinforcing efficacy of different drug concentrations as well as of different drugs may depend on the use of more complex schedules.

Concurrent schedules have been used in a limited way in the animal laboratory to assess the relative reinforcing efficacy of two different orally delivered drug concentrations. These

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have been used to assess choice between paired drinking solutions such as drug and water (Carroll, 1982) or saccharin and water (Carroll, 1985a), but not with two different drugs or drug concentrations. However, these concurrent procedures have been used in evaluating the relative reinforcing effects of different intravenously delivered drugs and drug doses (Iglauer & Woods, 1974; Johanson, 1975; Johanson & Schuster, 1975; Llewellyn, Iglauer, & Woods, 1976; Woolverton & Johanson, 1984). The general finding of these studies, that higher drug doses are more efficacious as reinforcers than lower doses, agrees with other quantitative assessments of reinforcement magnitude such as progressive-ratio schedules (Griffiths, Brady, & Snell, 1978; Yanagita, 1973) and interactions with fixed-ratio size (Lemaire & Meisch, 1984, 1985). That larger magnitudes of a substance are more efficacious as reinforcers than smaller magnitudes has also been previously demonstrated with nutritive substances (Brownstein, 1971; Catania, 1963; Nevin, 1974; Rachlin & Baum, 1969; Samson & Lindberg, 1984; Shettleworth & Nevin, 1965). A goal of the present research was to extend these findings by using concurrent schedules to assess the relative reinforcing efficacy of different concentrations of an orally delivered drug.

The use of concurrent schedules with two orally delivered drug concentrations as reinforcers offers several advantages over previous research with single schedules. For instance, with drugs as reinforcers and single schedules it should not be assumed that the commonly observed descending limb of the dose-response curve reflects changes in reinforcing effects because drug intake (mg/kg) and postingestional drug effects are increasing. The concurrent schedule provides a dependent measure of preference in addition to response rate. If clear concentration preferences emerge early in the session, before the onset of postingestional effects of the drug, this measure would be less sensitive than overall response rate to the effects of the drug's presence in the subject's body, and it would be a more direct means of quantifying reinforcing properties of different drug concentrations. In oral drug self-administration experiments, the descending portion of the concentration-response function could also be due to aversive taste properties, as well as to drug satiation and/or direct response-rate decreasing effects of the drug. An investigation of the time course of preference development for higher or lower concentrations would yield information regarding whether declining intake of higher drug concentrations is based on satiation or on immediate oral or postingestional effects. If decreased intake of a higher drug concentration is explained by liquid satiation or disruptive effects of the drug, intake of a concurrently available lower concentration would also be expected to decline. However, if aversive taste is responsible for declining intake, a lower concentration may be chosen over a higher one, and intake of the lower concentration would persist longer into the session than would intake of the higher concentration. A recent comparison of concurrent phencyclidine and saccharin intake (Carroll, 1985a) suggests that responding maintained by higher drug concentrations is not limited by disruptive effects of the drug or liquid satiation, for saccharin intake continued at high rates after intake of higher phencyclidine concentrations had declined. Hence, these results indicated that responding was limited by drug satiation, aversive taste, or both.

Another objective of the present research was to compare performance maintained by concurrently available drug concentrations during food deprivation and food satiation. Previous research with a variety of drugs using concurrent FR schedules of drug and water availability has shown that food deprivation greatly enhances drug-reinforced behavior (Carroll & Meisch, 1984). The food-deprivation effect has also been demonstrated with fixed-interval (Carroll, 1985c) and extinction (Carroll, 1985d) schedules; however, in each of these studies only a single drug concentration or dose was examined. The present experiment was an attempt to extend these findings to concurrent FR schedules across a range of concentrations, to determine whether food deprivation alters preference for drug concentrations as well as total drug intake. In Experiment 1, two phencyclidine concentrations were concurrently available under independently operating FR schedules. Experiment 2 addressed possible historical effects of concurrent access to two phencyclidine concentrations on changes in responding during food satiation and deprivation. The data from monkeys in Experiment 1 (Group 1) were compared with data from a second group (Group 2) that was

exposed to the same food satiation/deprivation history but did not have experience with concurrent phencyclidine concentrations.

Phencyclidine HCl was used in these experiments because it functions as a highly effective orally delivered reinforcer for rhesus monkeys, and a range of concentrations has been tested with the drug alone or concurrently with water (Carroll, 1982; Carroll & Meisch, 1980; Carroll & Stotz, 1984). Phencyclidine is a dissociative anesthetic that was developed in the 1950s by Parke-Davis, Inc. Due to occasional hallucinogenic effects and dysphoria, it was removed from clinical trials in 1965. The drug continued to be sold as a veterinary anesthetic, but due to its high rate of illicit use by young adults, its commercial manufacture was stopped in the late 1970s (Carroll, 1985b). Phencyclidine continues to be produced illegally and abused partly due to its ease of synthesis and low cost. Although the drug is used by a small percentage of the population, it was ranked fifth in 1984 on a list of drugs responsible for hospital emergency room episodes, representing a three-fold increase from 1981. The bitter-tasting drug is taken orally (in powder or tablet form); it is also used in liquid or powder form for "dipping" or "dusting" marijuana cigarettes.

METHOD

Subjects

Fourteen adult male rhesus monkeys (*Macaca mulatta*) served as subjects. Five monkeys (M-E, M-G2, M-K, M-S, and M-U) had previous experimental exposure only to oral phencyclidine self-administration. Others had previous exposure to oral self-administration of phencyclidine as well as saccharin (M-A and M-R), amphetamine (M-A1 and M-B1), etonitazene (M-B and M-R), methohexital (M-B and M-R), ketamine (M-B2, M-G1, and M-P1), quinine (M-B, M-M, and M-R) and exposure to intravenous drug self-administration procedures in another laboratory with a variety of drugs including phencyclidine (M-A1 and M-G1). In the first experiment, 8 monkeys (M-A, M-A1, M-B, M-B1, M-B2, M-E, M-G2, and M-S) served as subjects (Group 1), and in the second experiment the 8 monkeys from Experiment 1 and 6 additional (Group 2) monkeys (M-G1, M-K, M-M, M-P1, M-R, and M-U) served as subjects. During the experiments the monkeys were either food satiated by allowing them unlimited access to Purina High Protein Monkey Chow #5045, or they were food deprived by restricting their food access to maintain them at 85% of their free-feeding weights. The monkeys were housed continuously in their experimental chambers in a room maintained at 24 °C with the lights on from 6:00 a.m. to 6:00 p.m.

Apparatus

The experimental chambers were stainless steel Hoeltge (HB-108) primate cages equipped with a work panel on one wall. The panel contained two lip-operated drinking spouts positioned at about eye level for the monkey and approximately 30 cm apart. Lip-contact responses on the brass spouts (2.7 cm long and 1.2 cm O.D.) operated a solenoid for approximately 120 ms and released 0.55 mL of liquid from the spout. The spouts were mounted on clear Plexiglas® plates that had four small lights directly behind them. When a drug solution was available from a spout, two small green lights were illuminated for the duration of the lip contact, and when water was available, two small white lights were illuminated. Larger green lights on the inside of the panel above the drinking spouts were illuminated whenever liquid was available. A large green light blinked (10 Hz) on the side of the panel where a drug solution was available, but it did not blink on the side where water was available. Liquids were contained in covered Nalgene reservoirs, and there was no measurable evaporation. Experimental sessions were automatically controlled, and data were recorded and printed by microcomputers (Micro Interfaces, Inc.) located in an adjacent room. Lip-contact responses and liquid deliveries were also recorded by cumulative response recorders (Gerbrands). Complete details of the control and recording equipment, drinking devices, and experimental chambers have been described elsewhere (Carroll, Santi, & Rudell, 1981; Henningfield & Meisch, 1976; Meisch & Henningfield, 1977).

Phencyclidine HCl was provided by the National Institute on Drug Abuse. Drug solutions were prepared in tap water 20 hr before use and stored at room temperature; concentrations are expressed in terms of the salt.

General Procedure

Prior to the main experimental procedures, all 14 monkeys were trained to self-administer phencyclidine and water under concurrent FR 16 schedules during 3-hr sessions that were conducted daily, 7 days per week. Each session was preceded and followed by a 1-hr timeout for changing solutions and recording data. During the timeout, responding had no programmed consequences. In brief, the procedure involved introducing phencyclidine (0.25 mg/mL or lower concentrations) under an FR 1 schedule. The daily food allotment was available either during or after the 3-hr session. After behavior stabilized, the FR for liquid deliveries was increased to 2, 4, and then 8, allowing behavior to stabilize for at least five sessions at each value. At FR 8, water was made available concurrently under an FR 8 schedule, and side positions of drug and water were reversed daily. The FR for phencyclidine and water was then increased to 16, and food was made available only after the session. Additional details of the training procedures have been reported earlier. Monkeys M-B, M-M, and M-R were trained according to a procedure described by Carroll and Meisch (1980). Monkeys M-A, M-E, M-K, M-P1, M-S, and M-U were trained according to an abbreviated protocol (Carroll, 1982); they were food deprived when phencyclidine was introduced, and Monkeys M-A1, M-B1, M-B2, M-G1, and M-G2 received the same shortened procedure (Carroll, 1982), except that they were food satiated when phencyclidine was introduced.

EXPERIMENT 1

METHOD

At the start of this experiment all monkeys were given free access to food until three successive body weights (taken bi-weekly) showed no increasing trend. The weights stabilized in approximately 6 to 8 weeks, and the free-feeding body weights ranged from 9.6 to 17.8 kg. The monkeys initially received concurrent access to phencyclidine (0.25 mg/mL) and water (0 mg/mL) during daily 3-hr sessions until their behavior stabilized. Stability was defined as no steadily increasing or decreasing trend in the number of liquid deliveries per session and no change in the pattern of responding throughout the 3-hr session. Subsequently, other phencyclidine concentrations (1.0, 0.062, 0.5, 0.125, and 0.25 mg/mL, respectively) were substituted for water while the standard concentration (0.25 mg/mL) was always present. Side positions were reversed daily, and each pair of concentrations was available until behavior stabilized for at least five sessions. A retest condition was then conducted with concurrent phencyclidine (0.25 mg/mL) and water, and this condition remained in effect while the monkeys were reduced to 85% of their free-feeding body weights. This was accomplished by providing them with 75 g of food each day until the 85% weight was reached and then with the amounts needed to maintain that weight. After the body weights and response rates stabilized, the additional five phencyclidine concentrations were substituted for water in the same manner as they had been made available during food satiation. The phencyclidine (0.25 mg/mL) and water retest condition was also repeated at the end of this series.

RESULTS

Figure 1 shows the mean number of liquid deliveries for each monkey during both food satiation and deprivation for each pair of drug concentrations. The intrasubject variability was generally very low. Side preferences were minimal except when the 0.25 mg/mL concentration was presented on both sides. Note that in Figure 1 the concurrent 0.25 mg/mL concentrations are presented separately for the left and right sides, and for the other concentration pairs data are pooled for the left and right sides. The intersubject variability was considerable, especially during food satiation. Two of the monkeys (M-A and M-B2) increased their phencyclidine deliveries (by at least two-fold) during food deprivation, 3 monkeys (M-A1, M-B, and M-S) showed no systematic change, and 3 (M-B1, M-E, and M-G2) showed about 50% fewer phencyclidine deliveries during food deprivation than they did during satiation. Intake of the standard (0.25 mg/mL) concentration was a generally decreasing function of the phencyclidine concentration that was presented concurrently with the standard concentration. For most monkeys, intake of the variable concentration increased and decreased in an inverted U-shaped function within a narrow range of concentrations; however, this concentration-response function

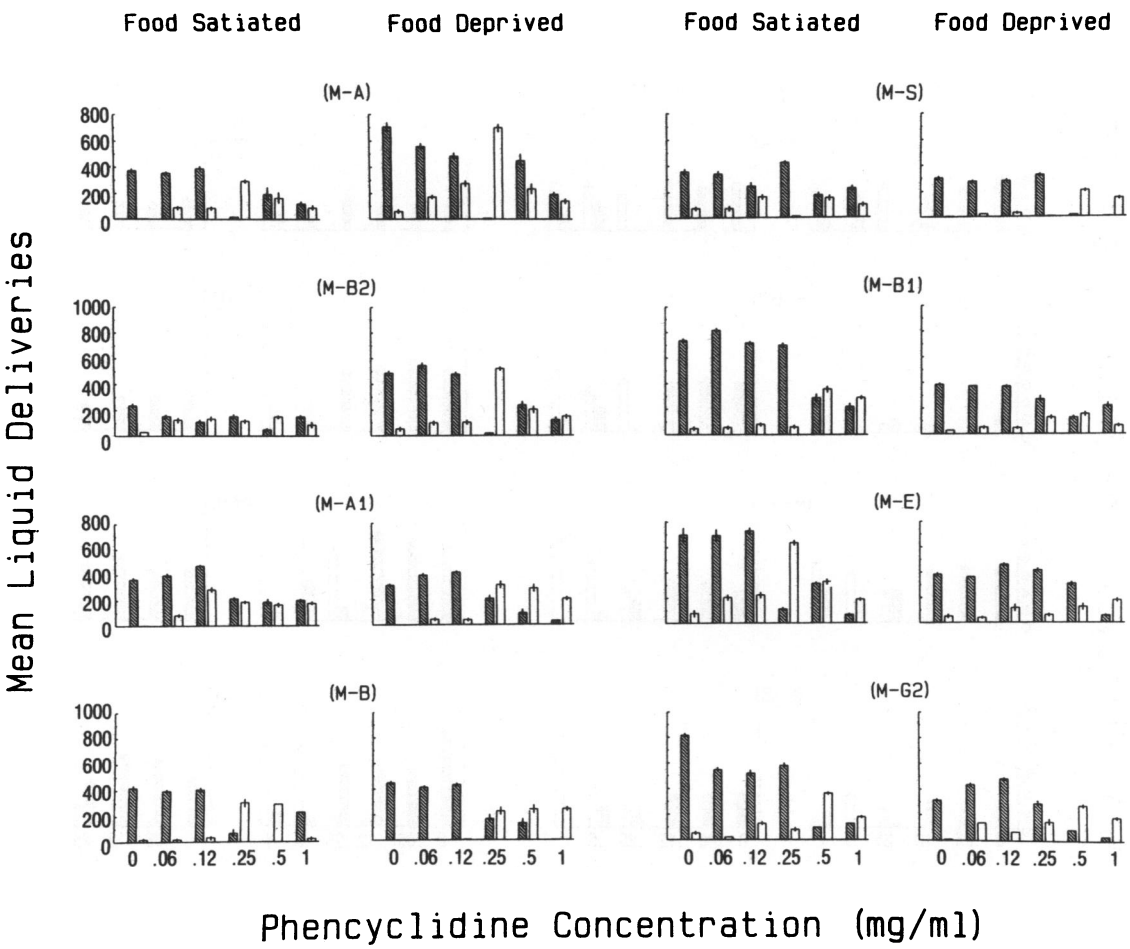

Fig. 1. Mean (±*SE*) number of liquid deliveries per 3-hr session as a function of the feeding condition (food satiation or deprivation) and concentration (mg/mL) of phencyclidine solutions or water (0) that were concurrently available. Shaded bars correspond to the standard phencyclidine concentration (0.25 mg/mL), and open bars represent the phencyclidine concentration that was varied. For the condition in which 0.25 mg/mL phencyclidine was available from both spouts, the shaded bars refer to deliveries received at the left spout and the open bars represent deliveries on the right spout. Each bar represents the mean of the last five sessions on a given condition. Letters in parentheses identify individual monkeys.

was not always consistently present during both food satiation and deprivation. Results of the retests with concurrent 0.25 mg/mL and water (0) were very close to the original values reported in Figure 1.

During both satiation and food deprivation, nearly every monkey (except M-B2, food satiated, 0.125 mg/mL) selected the 0.25 mg/mL phencyclidine over water and over 0.062 and 0.125 mg/mL phencyclidine. When the same concentration (0.25 mg/mL) was concurrently available from both drinking devices, most monkeys (except M-A1 and M-B) sampled the liquid from both spouts and then selected one spout exclusively. Five of the 8 monkeys selected the 0.5 mg/mL concentration over the 0.25 mg/mL concentration regardless of the feeding condition. Six of the 8 monkeys preferred the 1.0 mg/mL concentration over the 0.25 mg/mL concentration while food deprived, but only 3 preferred the 1.0 mg/mL concentration while food satiated. In addition, there were approximately 20 concentration pairs (across 8 monkeys) at which a nearly exclusive choice for the higher concentration occurred. Fifteen of these 20 nearly exclusive choices occurred during food deprivation. Thus, there was some evidence that food deprivation

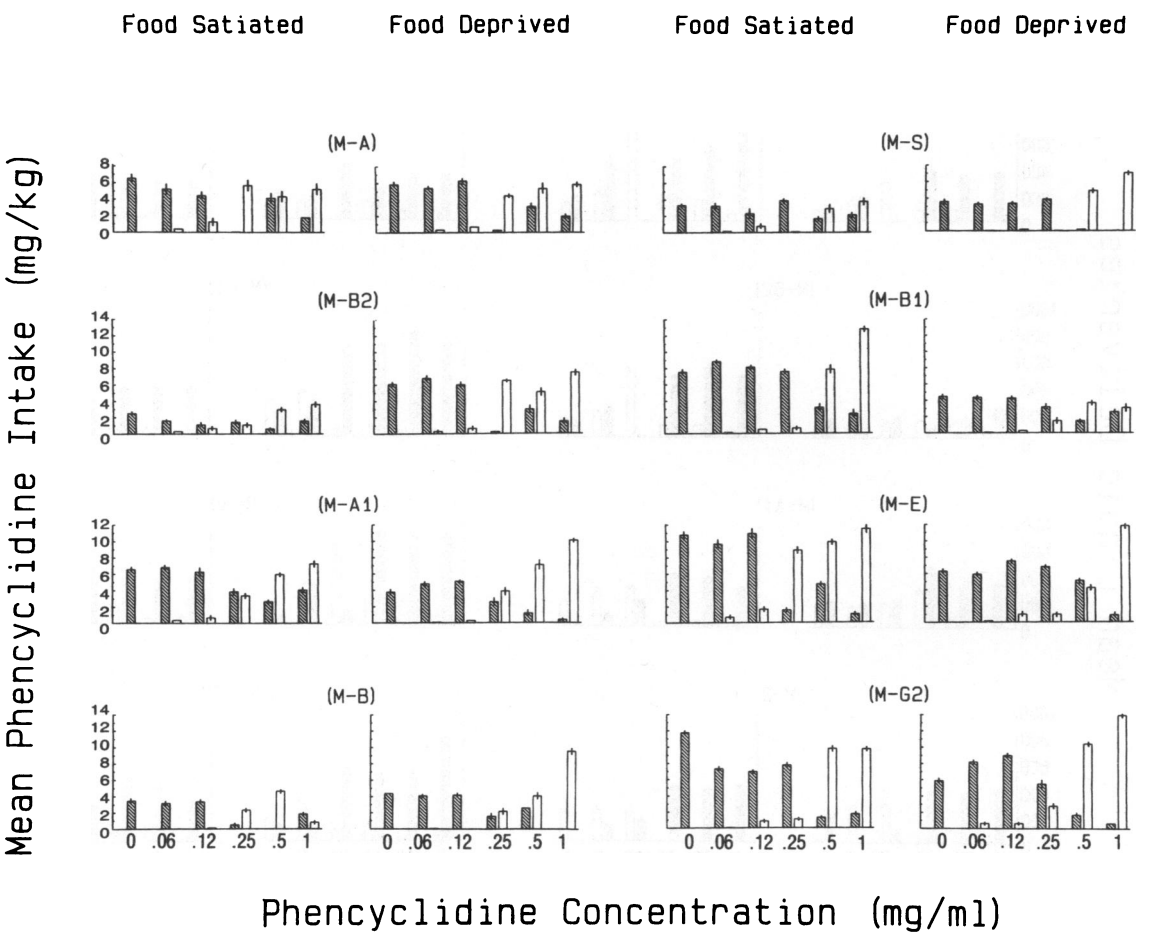

Fig. 2. The details of this figure are identical to those described for Figure 1 except that each bar represents the mean (±*SE*) phencyclidine intake (mg/kg).

increased the preference for higher drug concentrations.

The differential rates of responding on a given pair of drug concentrations were always present on the first day of a concentration change, indicating that the monkeys' choices of the higher concentration were controlled by taste or other immediate postingestional effects, and that control developed within the first 10 min of the session. With each concentration change, behavior typically stabilized within 6 to 10 sessions. Observations made at the end of the sessions indicated that some of the monkeys had become noticeably intoxicated by the higher drug concentrations. Characteristic signs were blank stare, ataxia, salivation, and vertical and horizontal nystagmus. These observations did not differ substantially as a function of feeding condition.

Figure 2 shows the mean phencyclidine intake (mg/kg) for each monkey during both food satiation and deprivation for each pair of concentrations. Total phencyclidine intake (mg/kg) most frequently increased as the variable phencyclidine concentrations increased, with the highest intake occurring when the 1.0 mg/mL concentration was concurrently available with the 0.25 mg/mL concentration. For the monkeys whose liquid deliveries were substantially higher during food satiation than during food deprivation (M-B1, M-E, M-G2) there were much smaller differences in drug intake when it was calculated on a per kg basis.

Figure 3 shows the time course of phencyclidine deliveries for four phencyclidine combinations over the 3-hr sessions for 3 individual monkeys during food satiation and deprivation. These monkeys represent those whose

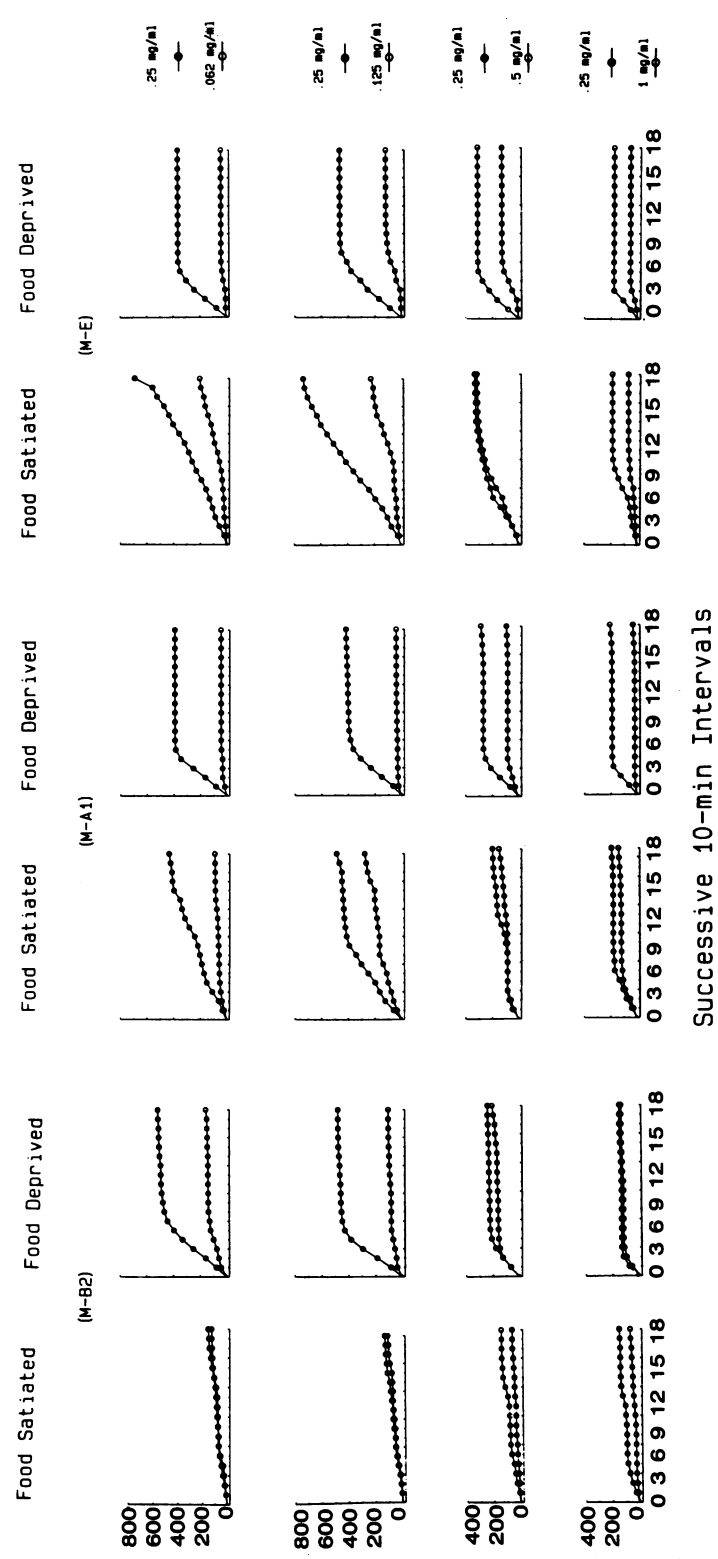

Fig. 3. Mean numbers of liquid deliveries cumulated at 10-min intervals over 3-hr sessions for 3 monkeys at four concentration pairs (0.062 + 0.25, 0.125 + 0.25, 0.5 + 0.25, and 1.0 + 0.25 mg/mL) during food satiation (left frames) and food deprivation (right frames). The 3 monkeys (M-B2, M-A1, and M-E) represent groups that showed decreases, no change, or increases, respectively, in the number of liquid deliveries during food satiation. Filled circles represent the standard concentration (0.25 mg/mL), and open circles refer to the phencyclidine concentration that was varied. Each point refers to a mean of the last five sessions of stable behavior under each condition. Letters in parentheses identify individual monkeys.

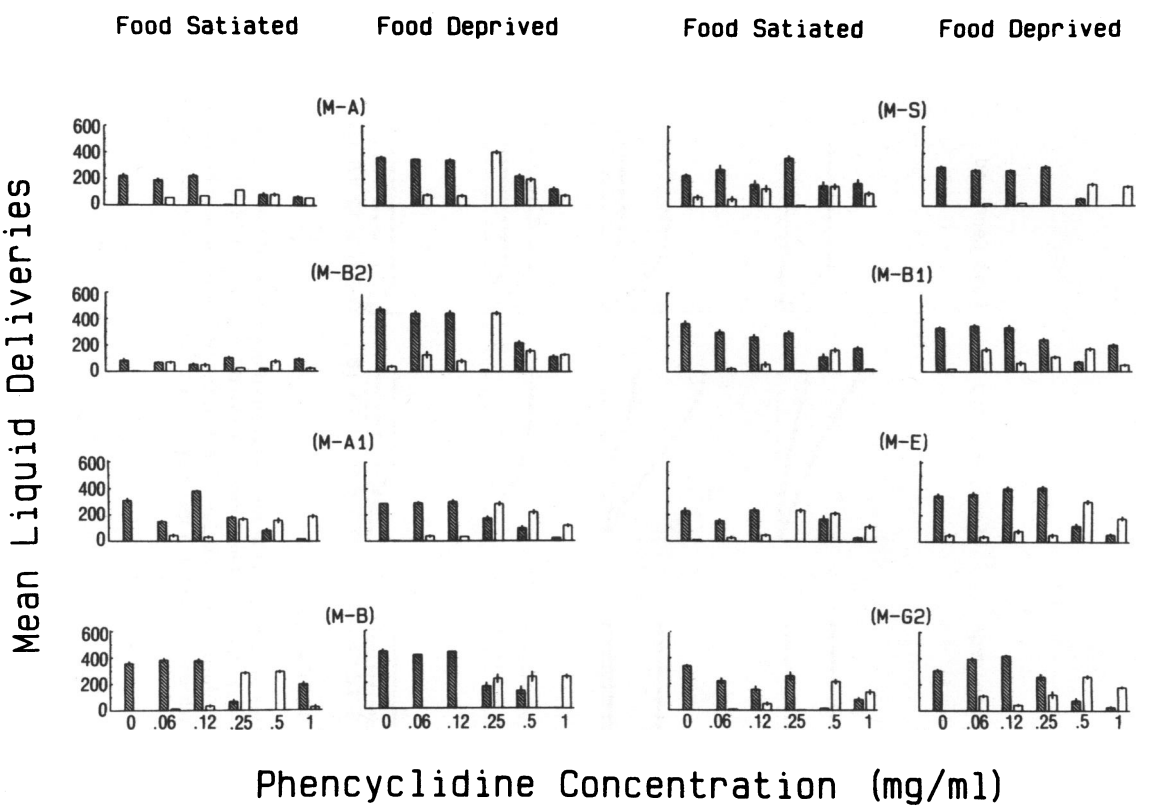

Fig. 4. Mean (±*SE*) number of liquid deliveries during the 1st hr of 3-hr sessions as a function of the feeding condition (food satiation or deprivation) and concentration (mg/mL) of phencyclidine solutions or water (0) that were concurrently available. Shaded bars correspond to the standard phencyclidine concentration (0.25 mg/mL), and open bars represent the phencyclidine concentration that was varied. For the condition in which 0.25 mg/mL phencyclidine was available from both spouts, the shaded bars refer to deliveries received at the left spout and the open bars represent deliveries on the right spout. Each bar represents the mean of the last five sessions on a given condition. Letters in parentheses identify individual monkeys.

phencyclidine-maintained responding either decreased (M-B2), remained the same (M-A1), or increased (M-E) during food satiation. During food satiation there was occasionally a preference for the higher concentration by the first 30 min of the session, but often the maximum separation did not occur until at least half way through the session. During food deprivation the preference for the higher concentration often emerged within the first 10 min, and the maximum separation was apparent within 30 to 60 min. The time course of liquid deliveries for the 0.25 + 0 (water) and 0.25 (left) + 0.25 (right) conditions (not shown) was similar to the 0.25 + 0.062 mg/mL condition (shown in Figure 3) and to data previously reported for concurrent phencyclidine (0.25 mg/mL) and water access (Carroll, 1982).

Drinking patterns were markedly different during food satiation and food deprivation regardless of the total number of liquid deliveries obtained, and the patterns changed immediately when the feeding conditions were changed. During the first session that the monkeys were food deprived, their patterns were considerably different than the previous day, although in some cases (e.g., M-A1, 0.25 vs. 0.062 mg/mL, Figure 3) total deliveries and the available solutions had not changed. Differences in individual cumulative response records are not shown because they were nearly identical to those that have been published previously (Carroll, 1982). As reported previously (Carroll, 1982), during food satiation smaller drinking bouts were often separated by long pauses, and occasionally drinking did not begin until 10 to 30 min after session onset. In contrast, during food deprivation, drinking always commenced immediately at session onset, and

most of the drinking was completed within the 1st hr of the 3-hr session.

Figure 3 shows that the time course of drinking appeared to be a more sensitive indicator than total liquid deliveries of the effects of changing feeding conditions. Because during food deprivation almost all of the drinking occurred within the 1st hr of the session, and during food satiation drinking was distributed throughout the session, a food-deprivation effect (increased liquid deliveries) described in previous research (Carroll & Meisch, 1984) might have been evident in more monkeys if liquid deliveries under food satiation and deprivation conditions had been compared during only the 1st hr of the session.

Figure 4 shows the mean liquid deliveries for each monkey during both food satiation and deprivation, at each pair of concentrations for only the 1st hr of the session. Five (M-A, M-B2, M-A1, M-E, and M-G2) of the 8 monkeys showed increased liquid deliveries during food deprivation at most (four or more) concentration pairs, whereas 3 monkeys (M-A1, M-E, and M-S) showed about equal numbers of increases and decreases in liquid deliveries (due to food deprivation) across the six concentration pairs. There were no consistent increases in phencyclidine deliveries due to food satiation as reported in Figure 1 for Monkeys M-B1, M-E, and M-G2. When Figure 4 is compared with Figure 1, it is apparent (especially for M-B1, M-E, and M-G2) that during food satiation the number of phencyclidine deliveries was much higher at the end of the 3-hr session (Figure 1) than after the 1st hr of the session (Figure 4), but during food deprivation the number of deliveries was nearly identical after 1 and 3 hr.

EXPERIMENT 2

The results from 6 of 8 monkeys in Experiment 1 were in direct contrast to previous results that showed at least a two-fold increase in response-produced phencyclidine deliveries during food deprivation as compared with food satiation (Carroll, 1982; Carroll & Meisch, 1980). Results of a recent study indicated that initial training with phencyclidine during food satiation increased the amount of (food satiated) phencyclidine-reinforced responding when the monkeys were tested under both feeding conditions (Carroll & Stotz, 1984). Consequently, the unexpected results of Experiment 1 may have been due to the history of concurrent access to different phencyclidine concentrations or to extended experience with oral phencyclidine under food-satiation conditions. The purpose of Experiment 2 was to examine these possibilities by adding a group of 6 monkeys that, for the same length of time as the monkeys in Experiment 1, received the same exposures to food satiation and deprivation and the same access to phencyclidine, except they did not receive concurrent access to two phencyclidine concentrations. Instead, the 6 monkeys were exposed to 3-hr sessions of concurrent access to phencyclidine (0.25 mg/mL) and water. Then all 14 monkeys were tested with concurrent phencyclidine (0.25 mg/mL) and water during repeated cycles of food deprivation and satiation. An additional purpose of this experiment was to assess whether differences in phencyclidine-reinforced responding due to feeding conditions would change with repeated testing under the different feeding conditions.

METHOD

Subjects

The 6 new monkeys in this experiment (Group 2) as well as the 8 from Experiment 1 (Group 1) had similar drug histories before the start of Experiment 1. Groups 1 and 2 had been exposed to a mean of 1,364.9 and 1,466.0 phencyclidine sessions, respectively; they had been food satiated for a mean total of 252.3 and 185.0 sessions, respectively; and they had been exposed to a mean of 2.9 and 3.0 cycles of food satiation and deprivation, respectively.

Procedure

All subjects were first given unlimited access to food until their weights stabilized (approximately 6–8 weeks), as in Experiment 1. The initial free-feeding body weights of the 6 monkeys in Group 2 ranged from 10.1 to 13.2 kg. Group 1 began Experiment 2 upon completion of Experiment 1. While Group 1 was finishing Experiment 1, Group 2 was exposed to the same satiation and deprivation conditions, for approximately the same lengths of time, as Group 1, but with concurrent phencyclidine and water available. Thus, the repeated testing of food deprivation and food satiation as described for Experiment 2 was conducted later in Group 2 than in Group 1. Also, individual monkeys in each group were exposed to the experimental conditions at slightly different

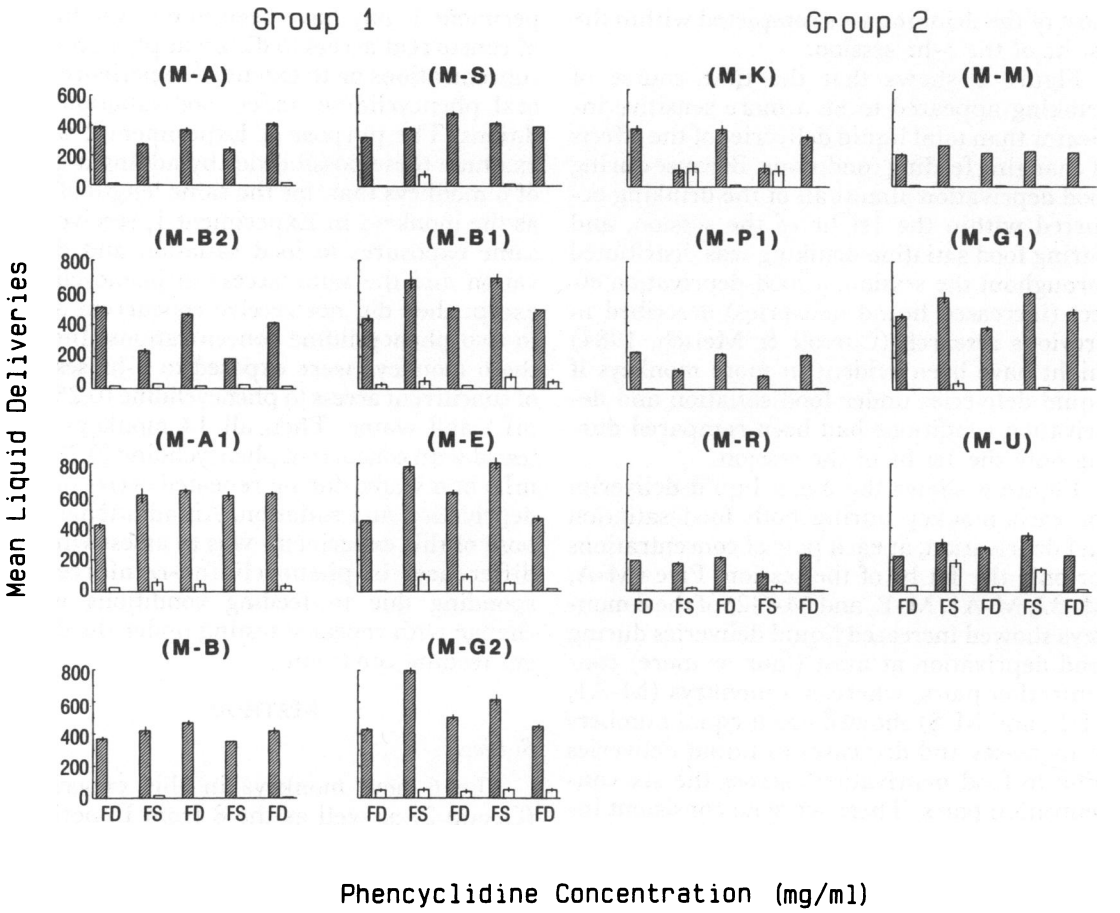

Fig. 5. Mean (±*SE*) liquid deliveries per 3-hr session as a function of successive feeding conditions, food satiation (FS) and food deprivation (FD), as they occurred in the following sequence: FD, FS, FD, FS, and FD for the 8 monkeys in Group 1 and the 6 monkeys in Group 2. The left, center, and right-hand bars are from FD conditions, the others from FS. Shaded bars refer to the standard phencyclidine concentration (0.25 mg/mL), and open bars represent concurrently available water (0 mg/mL). Each bar represents the mean of the last five sessions on each condition. Letters in parentheses identify individual monkeys.

times, depending upon their body-weight changes. All 14 monkeys were tested with concurrent phencyclidine (0.25 mg/mL) and water during repeated periods of food satiation (FS) and food deprivation (FD) as follows: FD, FS, FD, FS, and FD. Each condition was held constant until body weights returned to previous levels under that feeding condition. Each condition lasted approximately 4 to 6 weeks.

Results

Figure 5 shows the mean liquid deliveries for the 8 monkeys in Group 1 (left) and the 6 monkeys in Group 2 (right) during food satiation and deprivation. The effects of food satiation and deprivation for individual monkeys in Group 1 were the same as in Experiment 1, indicating that stable patterns emerged regardless of whether two phencyclidine concentrations or drug and water were the concurrently available alternatives. Although the monkeys with concurrent drug experience produced greater numbers of phencyclidine deliveries, both groups displayed the same range of effects resulting from changes in the feeding conditions. In Group 2, food deprivation increased the phencyclidine-maintained responding of 3 monkeys (M-K, M-P1, and M-R), decreased that responding in 2 (M-G1 and M-U), and produced no change in 1 monkey's responding (M-M). Considered across all subjects, there was no systematic trend in the number of liquid deliveries over repeated food-satiation or deprivation cycles.

Figure 6 shows the mean phencyclidine intake (mg/kg) for each monkey across the re-

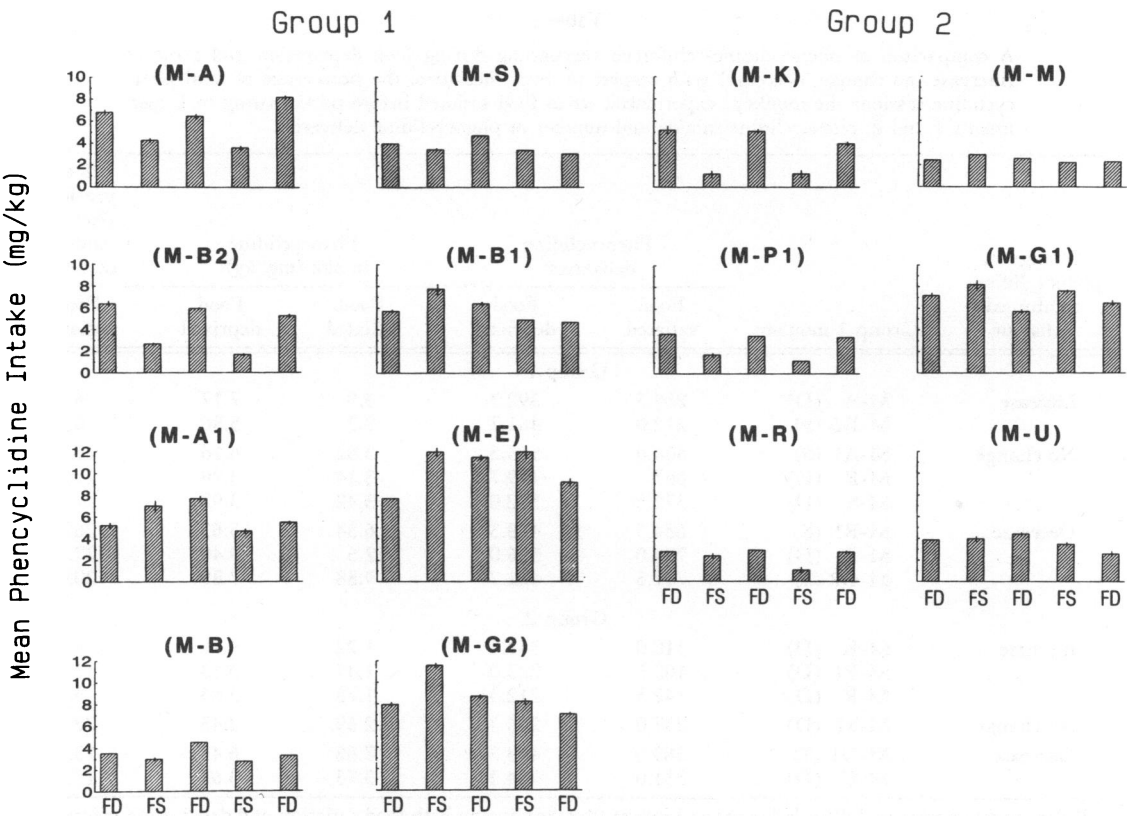

Fig. 6. Mean (±*SE*) phencyclidine intake (mg/kg) per 3-hr session, as a function of successive feeding conditions, food satiation (FS) and food deprivation (FD), for the 8 monkeys in Group 1 and the 6 monkeys in Group 2. Each bar represents the mean of the last five sessions on each condition. Letters in parentheses identify individual monkeys.

peated food-deprivation and satiation conditions. Generally, Group 1 consumed more drug than Group 2. For the monkeys that produced more phencyclidine deliveries during food satiation than during food deprivation (M-B1, M-E, M-G2, M-G1, and M-U), when body weight was taken into account, drug intake (mg/kg) was about the same under both feeding conditions.

For a post hoc analysis of the results, the monkeys in both groups ($n = 14$) were divided into three subgroups or outcome categories based upon whether food deprivation produced increases ($n = 5$), no change ($n = 4$), or decreases ($n = 5$) in phencyclidine-reinforced responding with respect to the food-satiation condition. These three groups were compared according to the following measures, to determine whether historical variables (conditions occurring prior to these experiments) were related to the three experimental outcomes: initial training condition (whether the monkeys had been food satiated or deprived when they were initially introduced to phencyclidine), free-feeding weight, total number of cycles of food satiation and deprivation, total 3-hr sessions of exposure to phencyclidine, total sessions food satiated, percentage of total phencyclidine sessions while food satiated, and exposure to drugs other than phencyclidine. One of these variables, percentage of total phencyclidine sessions while food satiated (prior to the beginning of Experiments 1 and 2), varied most consistently with the present results. Monkeys that consumed more phencyclidine during food satiation than during food deprivation in the present study typically had spent a greater percentage of their total previous training with phencyclidine in the food-satiation condition. A second variable, training condition, also seemed to be somewhat reliably related to the experimental outcome. Four of the 5 monkeys that responded more during food deprivation than during food satiation had received their initial phencyclidine self-administration training while food deprived. In con-

Table 1

A comparison of phencyclidine-reinforced responding during food deprivation and satiation (increase, no change, decrease) with respect to three measures: the percentage of total phencyclidine sessions the monkeys experienced when food satiated before participating in Experiments 1 and 2; phencyclidine intake; and number of phencyclidine deliveries.

Change in phencyclidine-reinforced behavior	Group 1 monkey	Phencyclidine deliveries[a]		Phencyclidine intake (mg/kg)[a]		% of previous phencyclidine sessions[b]
		Food satiated	Food deprived	Food satiated	Food deprived	Food satiated
			Group 1			
Increase	M-A (D)[c]	258.5	392.3	3.9	7.17	4.4
	M-B2 (S)	212.0	461.7	2.2	5.86	16.4
No change	M-A1 (S)	604.0	555.3	3.52	6.16	19.3
	M-B (D)	387.5	419.7	3.14	3.78	21.9
	M-S (D)	372.5	372.0	3.42	3.92	17.5
Decrease	M-B1 (S)	684.5	478.3	6.34	5.63	26.7
	M-E (D)	794.0	506.0	12.5	9.48	27.4
	M-G2 (S)	717.5	461.7	9.88	7.89	20.6
			Group 2			
Increase	M-K (D)	110.0	341.7	1.22	4.76	4.8
	M-P1 (D)	102.5	223.0	1.49	3.53	11.7
	M-R (D)	142.5	212.3	1.75	2.83	5.3
No change	M-M (D)	237.0	206.7	2.59	2.45	22.3
Decrease	M-G1 (S)	589.0	443.3	7.88	6.45	15.9
	M-U (D)	331.0	244.3	3.73	3.63	17.5

[a] Refers to mean phencyclidine deliveries and intake (mg/kg) during both food satiation and deprivation components of present experiment.

[b] Refers to the percentage of total phencyclidine sessions the monkeys were food satiated before the present experiments began.

[c] Food satiated (S) or deprived (D) during initial phencyclidine self-administration training.

trast, 3 of the 5 monkeys that showed the opposite effect (greater phencyclidine-maintained responding during food satiation) had initially been trained while food satiated.

In addition to historical variables, the numbers of liquid deliveries and mg/kg intakes during both food satiation and deprivation in Experiment 2 were compared across the three outcome categories. Table 1 shows a relationship between the number of phencyclidine deliveries and amount of drug consumed (mg/kg) during food satiation and the experimental outcome. Drug intake during food satiation was generally higher in monkeys that showed either no change or a decrease in drug-maintained responding during food deprivation with respect to food satiation. Table 1 shows that the greater proportion of total phencyclidine sessions spent in the food-satiation condition prior to the onset of the present experiments, the greater the amount of phencyclidine-maintained responding during food satiation in the present experiment.

GENERAL DISCUSSION

Concurrent access to two phencyclidine concentrations resulted in consistent preferences for the 0.25 mg/mL drug concentration over lower concentrations, and in a number of cases the 0.5 and 1.0 mg/mL concentrations were preferred over the 0.25 mg/mL concentration. These findings are consistent with previous results from studies that compared differing reinforcer magnitudes under concurrent schedules of intravenously delivered drug (Johanson & Schuster, 1975), food presentation (Brownstein, 1971; Catania, 1963; Herrnstein, 1970; Rachlin & Baum, 1969), and sucrose delivery (Collier & Bolles, 1968; Samson & Lindberg, 1984; Schrier, 1963). The present findings are also in agreement with studies that

used other methods of comparing reinforcing efficacy of different drug doses (Griffiths et al., 1978), concentrations (Lemaire & Meisch, 1984), or amounts (Lemaire & Meisch, 1985). Studies with other drugs involving choice of different doses of orally delivered diazepam by humans (Griffiths, Bigelow, Liebson, & Kaliszak, 1980; Healey & Pickens, 1983; Johanson & Uhlenhuth, 1980) or pentobarbital (Pickens, Cunningham, Heston, Eckert, & Gustafson, 1977) have not shown clear preferences for higher doses, although Griffiths et al. (1980) found preferences for higher doses of pentobarbital.

The present results demonstrate the feasibility of presenting a range of orally delivered drug solutions, including some pairs that were very similar, in a concurrent-schedule paradigm. The rapid selection of the higher concentration indicated that the monkeys' discrimination of the higher drug concentration was based on taste or other immediate postingestional effects. Also, the rapid change from no side preference to an exclusive daily side preference when identical drug concentrations (0.25 mg/mL) were available suggests that the lack of difference readily controlled performance (via taste or immediate postingestional effects). Inasmuch as a preference for the higher concentration emerged at almost every concentration pair during both feeding conditions, food deprivation did not appear to produce a clear shift in the preference curve. However, there was some evidence that food deprivation enhanced the reinforcing efficacy of higher drug concentrations. When the monkeys were food deprived, twice as many monkeys (6 vs. 3) preferred the higher concentration at the highest concentration pair (0.25 vs. 1.0 mg/mL). Furthermore, in the few cases in which exclusive preferences for higher concentrations occurred, they were three times as likely to appear during food deprivation.

When the present results are compared with concentration-response functions obtained from earlier studies in which a range of phencyclidine concentrations were presented individually with concurrent access to water (Carroll & Stotz, 1984), one finds a number of differences. In the present experiment the greatest numbers of liquid-reinforced responses occurred when 0.125 and/or 0.25 mg/mL phencyclidine was available (concurrently with the standard concentration of 0.25 mg/mL), whereas in the earlier study the peak of the inverted U-shaped concentration-response function ranged from 0.062 to 0.125 mg/mL across monkeys. In the present study, when behavior maintained by phencyclidine was compared to that maintained by the vehicle, water, as an indicator of the ability of the drug to function as a reinforcer, the lower concentrations (e.g., 0.062 and 0.125 mg/mL) did not appear to be functioning as potent reinforcers when a higher concentration (0.25 mg/mL) was concurrently available (i.e., intake of these concentrations usually did not exceed that of water when it was concurrently available with 0.25 mg/mL phencyclidine). In previous work, responding maintained by these concentrations exceeded that maintained by water (Carroll & Stotz, 1984). Earlier work has also shown that concurrent access to sweet solutions of sucrose (Lester & Greenberg, 1952; Samson & Falk, 1974; Samson, Roehrs, & Tolliver, 1982) or saccharin (Carroll, 1985a) greatly diminished behavior maintained by ethanol or lower phencyclidine concentrations, respectively. Thus, the reinforcing effects of a given drug concentration are highly dependent upon the type and strength of a concurrently available substance.

The results of the food satiation/deprivation comparison were equivocal in both Experiments 1 and 2. In Experiment 2, during food deprivation the differences in mean phencyclidine deliveries among the 14 monkeys were small, ranging from 206.7 to 555.3 compared to a range of 102.5 to 794.0 phencyclidine deliveries during food satiation. The increased intersubject variability during food satiation did not appear to be due to lengthy exposure to concurrent phencyclidine concentrations over periods of food satiation and deprivation, because Group 2, which did not have prior exposure to concurrent phencyclidine concentrations, also showed these variable results when tested with one phencyclidine concentration during food satiation. In fact, Groups 1 and 2 showed a similar range of mixed experimental outcomes when there were differences in baseline response rates between the two groups. The mean overall number of liquid deliveries was much higher for Group 1 than for Group 2. This is partly explained by individual differences, as there were 3 of 8 monkeys in Group 1 with mean liquid deliveries between 700 and 800, and mean liquid-delivery values were more homogeneous for Group 2. However, increased tolerance development may have ex-

plained the greater number of liquid deliveries in Group 1. The two groups consumed phencyclidine for the same length of time before and during testing, but Group 1, receiving two concurrent phencyclidine concentrations, obtained more total drug deliveries than Group 2, and the average concentration consumed by Group 1 was higher (0.39 mg/mL) than that consumed by Group 2 (0.25 mg/mL).

The high rate of phencyclidine-maintained responding during food satiation in some monkeys appeared to be related to other factors. First, the proportion of experimental sessions (phencyclidine self-administration) spent during food satiation prior to the onset of the current experiments was correlated with high rates of phencyclidine-maintained responding in the present study as well as with overall increased responding during food satiation as compared with food deprivation. These differences may be attributable to differential rates of tolerance development under the two feeding conditions. A second variable, training history, also seemed to be related to the present results. It was reported in an earlier study that monkeys that were initially introduced to phencyclidine while food satiated showed substantial phencyclidine-maintained responding when later tested while food satiated, whereas another group that initially self-administered the drug while food deprived responded at very low rates for most phencyclidine concentrations when tested during food satiation (Carroll & Stotz, 1984). All 6 of the monkeys from this previous experiment (M-B2, M-B, M-G2, M-P1, M-M, and M-G1) were used in the present experiment. Four of the monkeys (M-B2, M-B, M-P1, and M-G1) showed the same differences between responding during food satiation and deprivation as they had in the initial experiment. The other 2 monkeys (M-G2 and M-M), which had initially shown higher rates of responding during food deprivation than during food satiation, increased responding during food satiation or showed no change across feeding conditions, respectively, in the present experiment. The changes in these monkeys' behavior may have been due to additional experience with phencyclidine and other drugs after the initial training experiment. Two other monkeys in Experiment 2 (M-A1 and M-B1) had initially been introduced to phencyclidine while food satiated, and their rates of drug-reinforced responding during food satiation in the present experiment were the same or greater than when they were food deprived. In contrast, 3 other monkeys (M-A, M-K, and M-B) that were initially trained to drink phencyclidine while food deprived showed higher rates of responding during food deprivation in the present experiment. Thus, initial exposure to a drug during food satiation and/or extensive access to the drug while food satiated (vs. food deprived) appear to result in higher rates of drug-maintained responding during food satiation.

When all the monkeys were exposed to repeated cycles of food deprivation and satiation in Experiment 2, there were no consistent trends toward increased drug-reinforced responding during food satiation across monkeys. Three monkeys (M-B1, M-E, and M-G1) showed slight increases over the repeated cycles; however, their rates of phencyclidine-maintained responding were already very high. Those that responded at low rates during food satiation (M-A, M-B2, M-K, M-P1, and M-R) showed slight decreases or no change when food satiated the second time. A comparison of these results with data from previous studies (e.g., Carroll & Stotz, 1984) suggests that increased responding during food satiation occurs gradually over many months or years. The gradual increase in drug-maintained responding during food satiation resulted in drug intakes (mg/kg) that were nearly identical during food satiation and deprivation. It is interesting that this gradual stabilization of drug intake (mg/kg) over different feeding conditions occurred over an extended period of time, whereas changes in the magnitude and patterns of responding as a result of changes in drug concentration or feeding conditions occurred rapidly (within the first session when a parameter was changed).

The failure to find consistent differences in concentration preference and overall responding as a function of the feeding condition (food satiation vs. food deprivation) was unexpected. Previous research in this laboratory has yielded large differences in drug intake due to altered feeding conditions in nearly every animal tested (Carroll & Meisch, 1984). The earlier findings of low rates of drug-maintained responding during food satiation were obtained with a number of drugs from different major pharmacological classes, different species, different routes of self-administration, and different schedules of reinforcement (Carroll & Meisch, 1984). However, most of the animals studied

were drug naive, and they were initially introduced to the drug when they were food deprived. A small proportion of their total experimental time in contact with the drug was spent in the food-satiation condition.

The present results also indicate that the temporal pattern of responding is more sensitive to changes in the feeding conditions than is overall rate of responding, as reported previously (Carroll, 1982). Although there was considerable variability across monkeys with respect to the number of phencyclidine deliveries obtained during food satiation, the characteristic patterns of responding were different during food satiation and deprivation for all monkeys. The fact that patterns of responding across a 3-hr session differed markedly when feeding conditions were changed suggests that the generality of results from drug self-administration experiments may be limited to the feeding condition that is in effect during testing, and that percentage of free-feeding body weight is a variable that should be controlled in such experiments.

In summary, these experiments demonstrated that when two different phencyclidine concentrations are available (contingent upon responses on lip-operated drinking spouts) most monkeys select the higher concentration. The selection of the higher concentration occurs at the onset of the sessions, indicating that taste or other immediate postingestional effects are important factors. There was considerable variability across subjects with respect to the effects of food satiation and deprivation on phencyclidine-reinforced responding. About one third of the monkeys increased response rates during food deprivation, one third decreased, and the remainder showed no changes from the food-satiation condition. Analysis of the results suggests that monkeys that have had extensive experience with phencyclidine self-administration while food satiated and/or those that were initially trained to self-administer phencyclidine while food satiated were more likely to respond at higher rates when food satiated than when food deprived. These monkeys also consumed more phencyclidine while food satiated than did monkeys whose drug-reinforced responding was enhanced by food deprivation. Most previous research has shown that animals that were relatively naive with respect to drug exposure and food deprivation showed low or negligible drug-maintained responding during food satiation and high rates of responding during food deprivation. The current findings suggest that food deprivation has its major rate-enhancing effects during acquisition and the early stages of maintenance of drug-reinforced behavior. Food deprivation initially elevates drug-maintained behavior, but with repeated exposure to the drug and food satiation, responding during food satiation increases such that drug intake (mg/kg) is relatively constant across feeding conditions.

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