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Rapid Acquisition of Oral Phencyclidine Self-Administration in Food-Deprived and Food-Satiated Rhesus Monkeys: Concurrent Phencyclidine and Water Choice

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Phencyclidine Oral self-administration Rhesus monkeys Food deprivation Concurrent schedule Fixed-ratio

RESEARCH in this laboratory has demonstrated that orally-delivered ethanol [23], etonitazene [8], pentobarbital [24] and phencyclidine [2,9] can be established as reinforcers using food-induced drinking procedures. According to these methods the monkeys are maintained at reduced body weights, and their daily food allotment is presented during a 3-hr session when the drug solution is the only available liquid. A substantial amount of post-prandial drinking results, and subsequently, drug-maintained responding persists in excess of control (water) levels even when concurrent food is no longer available during the session.

There are several differences in the oral self-administration model in comparison to the intravenous (IV) model. First, the acquisition period can be lengthy, requiring several months to a year of training before a drug can be demonstrated to function as a reinforcer. Second, it has been necessary to use concurrent food presentation to induce drug intake [8, 9, 23, 24]. Third, food-deprivation has been reported to be necessary to maintain oral drug self-administration behavior [9,10]. However, there are several advantages in pursuing a reliable animal oral self-administration model for investigating problems of drug abuse. The oral preparation lasts the life of the animal; it allows for studies involving within-subject comparisons, chronic drug self-administration and performance on complex schedules requiring extensive training. Furthermore, the latency in onset of drug effects after oral self-administration allows for a substantial amount of behavior to occur before responding is disrupted by drug effects.

In the present report, methods are described for rapidly demonstrating that orally-delivered phencyclidine functions as a reinforcer for rhesus monkeys. Food-induced drinking

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procedures were not used in this study; the monkeys were simply allowed access to a drug solution during daily 3-hr sessions, and food was given after the sessions. In Experiment 2, phencyclidine was established as a reinforcer without using a food-induced drinking procedure and without using food deprivation. In these experiments, a concurrent choice procedure was used in which phencyclidine and water were simultaneously available. Choice tests have many advantages: they eliminate additional control days or groups, they control for nonspecific changes in behavior that may result from subtle environmental alterations or baselines that shift over time, and they provide an additional dependent variable of choice or preference that is not initially affected by drug intake, and preference is independent of response rate. Choice procedures have been used with intravenous self-administration models to compare drugs with other reinforcers [1,12], to evaluate the effects of drug reinforcement magnitude on responding in rhesus monkeys [16–20], and in oral drug self-administration tests with rats [5,21] and rhesus monkeys [15].

METHOD

Animals

Eight adult male rhesus monkeys (*Macaca mulatta*) served. Four experimentally naive monkeys (M-C, M-E, M-J and M-R2) were used in Experiment 1. Two experimentally-naive (M-B1 and M-H) and two drug-experienced monkeys (M-A1 and M-G1) were used in Experiment 2. M-A1 and M-G1 had intravenous self-administration experience with a variety of compounds from several drug classes including phencyclidine. The monkeys were housed individually in their experimental chambers in a room maintained at 24°C, with a 12-hr light/dark cycle.

Apparatus

The experimental chambers were stainless-steel Hoeltge (No. HB-108) primate cages, equipped with a work panel on one wall. The work panel contained two liquid spouts spaced 30 cm from each other, and stimulus lights that signaled experimental events. The brass drinking spouts were 2.7 cm long and 1 cm in diameter. A drinkometer circuit was operated when the monkey placed his lip on the spout. The lip contact response operated a solenoid for approximately 120 msec and released 0.55 ml of liquid from the spout. The drinking spout contained no moving parts; therefore, feedback stimuli were provided by one of two pairs of small lights mounted directly behind a Plexiglas plate supporting the spout. When PCP was available from a spout, two small green lights were illuminated for the duration of each lip contact. Similarly, when water was available from a spout, two small white lights were illuminated for the duration of each lip contact. In addition to these feedback lights, larger green lights 12 cm above the drinking spouts were illuminated when water was available during sessions and intersession periods. This light blinked (10 times/sec) on the side where PCP was available during the session. Liquids were contained in covered stainless steel reservoirs, and there was no measurable evaporation. Experimental sessions were controlled automatically, and data were recorded and printed by microcomputers located in an adjacent room. Liquid responses and deliveries were also recorded on Gerbrands cumulative recorders. Complete details of the experimental chambers, drinking devices, and control and recording equipment have been described elsewhere [11, 13, 22].

Drugs

Phencyclidine HCl (National Institute on Drug Abuse: Research Triangle Institute) solutions were prepared in tap water at least 20 hr before use, and all liquids were presented at room temperature. Concentrations are expressed in terms of the salt.

Procedure

Experimental sessions took place from 10:00 a.m. to 1:00 p.m. each day, seven days per week. Each 3-hr session was preceded and followed by a 1-hr timeout during which solutions were changes and data were recorded. During the timeout, stimulus lights were not illuminated, and behavior had no programmed consequences. Liquids were available only as a result of lip contacts on the drinking spouts. During the 19-hr intersession period (2:00 p.m. to 9 a.m.), water was available ad lib under a fixed-ratio (FR) 1 schedule. Each lip contact on the drinking spout resulted in one liquid delivery. During the 3-hr sessions, liquids (water or phencyclidine) were initially available under an FR 1 schedule. Feeding conditions and changes in FR values are specified below.

Experiment 1: Acquisition procedure with food deprivation. Initially water was available from both drinking spouts under an FR 1 schedule during the 3-hr sessions, and the monkeys had free access to food. Purina High Protein Monkey Chow was available in food hoppers attached to the cages 24 hr per day. After five sessions of stable behavior were obtained, phencyclidine (0.25 mg/ml) was substituted for water at both drinking spouts during the sessions.

During the next phase, the monkeys were reduced to 85% of their free-feeding weights by allowing them access to only 75 g of Purina High Protein Monkey Chow each day and then daily amounts necessary to maintain them at the 85% weights, Food was given after the session (1:00 p.m.), and intersession water became available 1 hr later (2:00 p.m.). Reduction to the 85% weights under this feeding regimen requires approximately 45–60 days; thus, the monkeys were in negative caloric balance throughout most of the acquisition phase. After FR 1 behavior stabilized under reduced feeding conditions, the FR requirement was increased to 2 and then to 4 and 8. Each condition (see Table 1) was held constant until at least five sessions of stable behavior were obtained. Stability was defined as no steadily increasing or decreasing trend over five consecutive sessions. At FR 8, concurrent water was introduced. Instead of receiving phencyclidine from both drinking spouts, phencyclidine was available from one spout, and water was available from the other; both were under an FR 8 schedule. Side positions of phencyclidine and water were reversed daily, and during the intersession period, water was available from both spouts. After behavior stabilized for five sessions, the FR was increased to 16.

Experiment 2: Acquisition procedure without food deprivation. The monkeys in this group always had free access to food during the acquisition procedure. Initially, water was available from both drinking spouts under an FR 1 schedule during the 3-hr sessions. After five sessions of stable behavior were obtained, phencyclidine (0.25 mg/ml) was substituted for water at both drinking spouts during the sessions. The FR values were subsequently increased from 1 to 2, 4 and 8 allowing behavior to stabilize for at least five sessions at each value. At FR 8, concurrent water was introduced.

TABLE 1

MEAN* SESSION LIQUID DELIVERIES

Feeding Condition	Food Satiated		Food Deprived							
Fixed Ratio	1	1	1	2	4	8	8†	8†	16†	16†
							Concurrent FR Schedule			
Concentration	0	0.25	0.25	0.25	0.25	0.25	0.25 and 0		0.25 and 0	
Monkey										
M-C	619.4	1039.8	1676.6	1283.6	893.2	428.4	420.0	233.2	291.2	54.5
M-E	795.8	794.4	2122.6	1658.6	801.2	389.6	477.0	131.6	190.6	6.6
M-J	615.6	539.8	903.8	965.6	876.4	600.0	435.6	154.6	376.0	47.6
M-R2	1042.8	1073.8	1438.4	1176.5	801.0	357.4	206.8	72.0	270.4	38.2
Mean (N=4)	768.4	861.8	1535.4	1270.9	842.9	443.8	384.9	147.8	282.1	36.7
Mean S.E.s‡	64.1	70.1	59.1	49.8	68.8	20.7	31.9	58.5	15.9	8.2
Mean Total Sessions	7.3	9.7	9.8	6.5	5.7	5.5	7.3		10.3	

*Individual means are calculated from the last five sessions at each condition. Conditions were run continuously in the order indicated from left to right.

†Phencyclidine (0.25 mg/ml) and water (0) were concurrently available.

‡Numbers represent the mean (N=4) standard errors of each monkey's liquid deliveries during the last five sessions.

Phencyclidine and water were both available during the sessions under a FR 8 schedule. Side positions were reversed daily, and during intersession periods water was available from both spouts. When behavior stabilized for five sessions, the FR was increased to 16. The monkeys were subsequently food-deprived by allowing them access to 75 g of Purina High Protein Monkey Chow each day and then a daily amount necessary to maintain them at 85% of their free-feeding body weights. Food was given after the session (1:00 p.m.), and intersession water became available 1 hr later (2:00 p.m.).

RESULTS

Experiment 1: Acquisition Procedure with Food Deprivation

Table 1 shows mean session liquid deliveries for each sequential experimental manipulation. When phencyclidine (0.25 mg/ml) was substituted for water while the monkeys were food satiated, there was a substantial increase in M-C's liquid deliveries, a decrease in M-J's, and the other two monkeys' (M–E, M–R2) liquid deliveries remained relatively constant. When the monkeys were food deprived, the number of phencyclidine deliveries nearly doubled and stabilized after a mean of 9.8 sessions, although the monkeys had not yet reached their 85% weights. As the fixed-ratio requirement was increased from 1 to 8 there was a consistent decline in the number of liquid deliveries from an overall mean of 1535.4 to 443.8. When the concurrent water condition was implemented, the number of phencyclidine deliveries remained relatively constant. However, the mean number of phencyclidine deliveries was nearly three times higher than mean water deliveries indicating that the drug was functioning as a reinforcer. At this point the monkeys had been exposed to phencyclidine for a mean of 37.2 sessions. In three of the monkeys (M-J, M-E, and M-C) water deliveries were relatively high under the concurrent FR 8 schedule. This was partially due to a strong preference for the left drinking device (or the device nearest the front of the cage) regardless of whether drug or water was present (drug and water positions were alternated daily). When the FR was increased to 16, the side preferences disappeared. The increase from FR 8 to 16 reduced the number of water deliveries by 75%, and the number of phencyclidine deliveries by 27%. At FR 16, phencyclidine deliveries exceeded water deliveries by at least seven times.

Experiment 2: Acquisition Procedure without Food Deprivation

Table 2 shows the number of session liquid deliveries for each sequential experimental manipulation. The overall water intake among these four monkeys was considerably lower than for the monkeys in Experiment 1; however, these differences are representative of the individual differences that have been noted previously in this laboratory. When phencyclidine (0.25 mg/ml) was substituted for water, M-A1's liquid deliveries increased, M-B1's remained the same and the other two monkeys (M-G1, M-H) showed a decrease in liquid deliveries. As the FR was increased from 1 to 8, there was only a slight decrease in the mean number of liquid deliveries from 290.5 to 245. When the concurrent water condition was introduced at FR 8, there was a slight decline in the number of phencyclidine deliveries. However, the mean number of phencyclidine deliveries was almost three times higher than the number of water deliveries indicating that phencyclidine was functioning as a reinforcer after 25.9 sessions of drug access. Water deliveries under the FR 8 schedule were also high in this group due to position preferences. Two monkeys preferred the right side and one preferred the left regardless of whether drug or water was present. These side preferences disappeared when the FR was increased to 16. The increase from FR 8 to 16 reduced the number of water deliveries by 57% and phencyclidine deliveries by 22%. At FR 16, phencyclidine deliveries exceeded water deliveries by at least nine times. Phencyclidine de-

TABLE 2
MEAN* SESSION LIQUID DELIVERIES

Feeding Condition	Food Satiated									Food Deprived	
Fixed Ratio	1	1	2	4	8	8†	8†	16†	16†	16†	16†
						Concurrent FR schedule					
Concentration	0	0.25	0.25	0.25	0.25	0.25 and 0		0.25 and 0		0.25 and 0	
Monkey											
M-A1	427.0	521.0	550.2	554.3	535.0	405.2	262.3	240.2	131.2	355.6	9.8
M-B1	153.2	158.0	123.0	102.6	56.4	87.4	56.4	100.2	17.4	267.0	25.3
M-G1	527.6	212.8	214.8	186.4	141.0	206.6	89.0	249.8	20.8	302.6	18.6
M-H	563.0	271.0	339.2	289.0	247.6	217.8	136.2	122.2	64.0	205.8	65.2
Mean (N=4)	417.7	290.5	306.8	283.1	245.0	229.3	135.9	178.1	58.4	282.8	29.7
Mean S.E.s‡	51.8	28.3	33.4	16.7	16.2	18.1	9.2	12.3	6.2	15.4	6.4
Mean Total Sessions	8.5	9.0	7.0	4.7	5.2	6.5		8.3		14.0	

*Individual means are calculated from the last five sessions at each condition. Conditions were run continuously in the order indicated from left to right. At FR 4, M-A1 was run only 3 sessions.
†Phencyclidine (0.25 mg/ml) and water (0) were concurrently available.
‡Numbers represent the mean (N=4) standard errors of each monkey's liquid deliveries during the last five sessions.

liveries in this food-satiation group were considerably lower than those of the food deprivation group in Experiment 1. When the monkeys in Experiment 2 were subsequently food deprived, the number of phencyclidine deliveries nearly doubled and stabilized after a mean of 14 sessions, although the monkeys had not yet reached their 85% weights. Under conditions of food deprivation, the mean number of phencyclidine deliveries (282.8) was similar to that of the four monkeys in Experiment 1 (282.1). The variability between monkeys was high; however, daily session variability within monkeys was low.

The pattern of responding during food satiation and deprivation was distinctly different both between groups (Experiment 1 vs 2) and within the monkeys in Experiment 2. Figure 1 shows mean cumulative phencyclidine deliveries during the 3-hr sessions for the food-satiation and -deprivation conditions in Experiments 1 and 2. An analysis of the time course of responding for all monkeys in Experiment 2 during food satiation indicated that 50% of the total phencyclidine deliveries had not occurred until 90 minutes into the 3-hr session and 75% had not occurred until 130 minutes. During food deprivation, responding typically occurred during one large drinking bout at the beginning of the session. In both groups, during food deprivation 50% of the phencyclidine deliveries had been obtained by 30 minutes and 75% had been obtained by 60 minutes. The change in the pattern of responding occurred almost immediately (1–4 sessions) in Experiment 2 when the food-satiated monkeys were food deprived. There were no systematic changes in the patterns of water-maintained responding as a function of food satiation or deprivation.

Figure 2 shows representative cumulative records from M-H. The sessions were chosen as those with the total number of liquid deliveries closest to the overall group means during food satiation and deprivation. During food satiation, responding typically occurred in several drinking bouts, separated by long pauses, throughout the session. Often the monkeys did not initiate responding until several minutes of the session had elapsed. During food deprivation, responding almost always occurred in one continuous drinking bout beginning immediately at session onset and lasting throughout the first hr of the session. Occasionally, there was one smaller second burst of drinking during the second or third hr of the session. Examination of cumulative records indicated that local response rates within each FR appeared to be similar under food-satiation and -deprivation conditions.

DISCUSSION

In both experiments it was rapidly demonstrated that phencyclidine was functioning as a reinforcer. The mean number of daily phencyclidine sessions required to demonstrate that the drug was functioning as a reinforcer was only 37.2 and 25.9 in Experiments 1 and 2, respectively, compared with a mean of 132.4 for an acquisition procedure reported in an earlier paper [9]. It is likely that the present acquisition procedure (Experiment 2) could have been further shortened had the water baseline (FR 1) and five-session stability criterion been eliminated. In the previous report on phencyclidine [9] and in studies of oral etonitazene [5] and pentobarbital [24] self-administration, an ascending concentration series was presented during the food-induced drinking phase. In the present study this step was eliminated by initially presenting a relatively high [9] drug concentration. In addition, the use of the concurrent choice procedure substantially contributed to this shortened acquisition procedure. In the present study, as well as in previous work with ethanol [14] and phencyclidine [9], it was shown that increases in FR value were necessary to unequivocally demonstrate that a drug was functioning as a reinforcer.

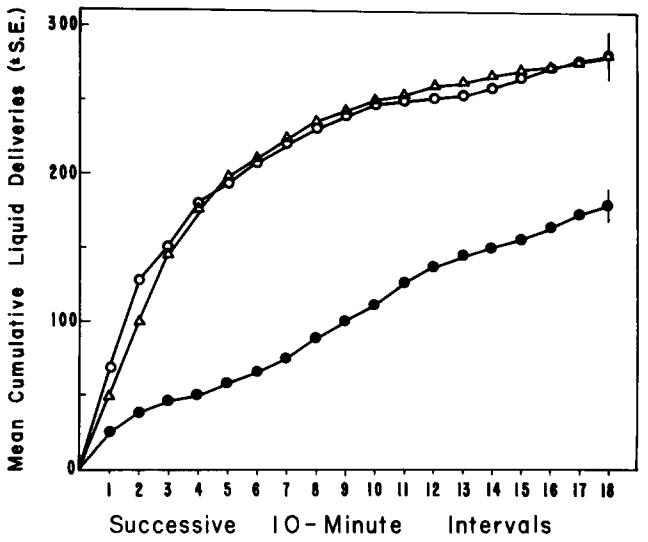

FIG. 1. Mean cumulative phencyclidine (0.25 mg/ml) deliveries are presented over successive 10-min intervals during 3-hr sessions. The schedule for liquid deliveries was a concurrent FR 16 for phencyclidine and water. Each point refers to a mean of 20 sessions (4 monkeys × the last 5 sessions of stable behavior). Vertical standard error bars refer to the mean (N=4) standard errors of each monkey's phencyclidine deliveries during the last 5 sessions. Triangles refer to Experiment 1 during the final condition; the monkeys were food deprived. Filled circles refer to Experiment 2 when the monkeys were food satiated and open circles to the final condition when the monkeys were food deprived. There were no changes in the pattern of water deliveries as a function of food deprivation or satiation.

FIG. 2. Cumulative records are presented for monkey M-H representing a 3-hr food satiation session (upper record) and a 3-hr food deprivation session (lower record). The records from these sessions were selected as those with the total number of liquid deliveries closest to the mean values for all monkeys. The pen stepped across the page with each response, and downward deflections of the pen represent phencyclidine deliveries. The pen reset at 400 responses.

Neither schedule-induced polydipsia (e.g., [8,9]) nor food-induced drinking procedures (e.g. [24]) were necessary to establish phencyclidine drinking in the present experiments. It was also found in Experiment 2 that food deprivation was not necessary during the acquisition phase to produce phencyclidine drinking and demonstrate its reinforcing effects. However, in both groups food deprivation greatly enhanced phencyclidine-reinforced behavior. Similar increases in oral drug self-administration as a result of food deprivation have been previously reported [3, 4, 6, 7, 9, 10]. A difference between the present results (Experiment 2) and previous data was that phencyclidine functioned as a reinforcer during food satiation for monkeys that had been trained during satiation (Experiment 2). In a previous experiment, phencyclidine did not function as a reinforcer during food satiation in monkeys that were trained under food deprivation conditions and for whom the drug served as a reinforcer during food deprivation [9]. Thus, the use of food deprivation during initial drug access may yield greater drug intake, but it may limit the conditions under which a drug may later function as a reinforcer.

There were several differences in the results of Experiments 1 and 2 due to different feeding conditions. The food-satiation group's responding did not decrease substantially with an increase in the FR requirement from 1 to 16, while the food-deprivation group decreased their response rate by more than six times over the same increases in FR. However, it should be noted that the groups were not matched for initial liquid intake levels. Almost all responding in the food-deprivation group occurred withing the first hour of the 3-hr session, and responding always began immediately at the start of the session. These patterns are similar to those reported previously [5, 9, 15, 24]. Responding was more sporadic in the food-satiation group; it often began several min after the session started and continued in bursts throughout the entire 3-hr session. When the food-satiation group was food-deprived, response patterns became characteristic of the food-deprivation group within a few sessions. These results suggest that phencyclidine is a less effective reinforcer under food satiation conditions; however, further work is necessary to separate the effects of food deprivation and satiation on response rate, drug intake and reinforcing efficacy.

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