Pharmacology Biochemistry & Behavior, Vol. 20, pp. 779–787, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

The Effect of Second-Order Schedule History on Fixed-Ratio Performance Maintained by Orally-Delivered Phencyclidine in Rhesus Monkeys

MARILYN E. CARROLL

Psychiatry Department, Mayo Box 392, University of Minnesota, Minneapolis, MN 55455

Received 19 September 1983

CARROLL, M. E. *The effect of second-order schedule history on fixed-ratio performance maintained by orally-delivered phencyclidine in rhesus monkeys.* PHARMACOL BIOCHEM BEHAV **20**(5) 779–787, 1984.—Thirteen monkeys were trained to self-administer orally-delivered phencyclidine (0.25 mg/ml) and water under a concurrent fixed ratio (FR) 16 schedule. Phencyclidine was available from one lip-operated drinking device and water was available from another drinking device during daily 3-hr sessions. Seven monkeys were trained to respond under a second-order FR 240 (FR 20: brief stimulus) schedule. Upon completion of 4800 responses, the monkeys were allowed to self-administer 300 phencyclidine deliveries under an FR 1 schedule. After a mean of 33.3 sessions of second order schedule training, including 10 sessions at the terminal parameter, the monkeys were returned to the concurrent FR 16 schedule. Phencyclidine-maintained responding persisted at rates that were 42 percent higher than before second-order schedule training; however, concurrent water-maintained behavior increased only slightly. A second group of three monkeys were treated in an identical manner except that during second-order schedule training they received a saccharin solution (0.05%, wt/vol) instead of phencyclidine. After a mean of 30 sessions of second-order schedule training, including 10 sessions at the terminal parameter, the monkeys were returned to the concurrent FR 16 schedule, and there was no consistent change in phencyclidine or water deliveries. A third group of three monkeys received 300 phencyclidine deliveries at the same time after session onset and for the same total number of sessions as the monkeys that received second-order schedule training with phencyclidine; however, this group was not required to respond under the second-order schedule to gain access to the phencyclidine deliveries. This group also showed no substantial change in phencyclidine or water deliveries as a result of their training condition. Thus, second-order schedule training with phencyclidine as a reinforcer generated high rates of responding which later produced specific and persistent increases in drug-maintained behavior under a simple FR schedule. These findings suggest that drug-reinforced behavior can be markedly influenced by brief behavioral and drug histories as well as by variables that are operating at the time the drug is self-administered.

Drug history Environmental variables Oral drug self-administration Phencyclidine Rhesus monkeys Schedule history Second-order schedules

SECOND-ORDER schedules have been effectively used in the analysis of drug-reinforced behavior to maintain extended sequences of drug-maintained responding [14,26]. Under a second-order schedule, behavioral requirements specified by one schedule, such as a fixed ratio (FR) or fixed interval (FI), are considered as a unit of responding that is reinforced according to a second schedule [20,21]. Fixed-interval schedules with FR components are most commonly used in drug self-administration experiments [14]. These schedules generate high rates and long sequences of behavior, and they have been reported to increase low rates of responding for certain drugs such as nicotine [16]. Second-order schedules have also been used to provide a complex behavioral baseline upon which to compare reinforcers [11, 13, 22]. Such complex schedules may prevent intoxication and overdose as well as limit direct drug effects by scheduling long intervals between drug infusions or by providing all drug at the end of the session. A schedule which allows for drug access only at the end of the experimental sessions provides a means to separate responding maintained by a drug from other behavioral effects of the drug [12]. Second-order schedules also help elucidate the importance of environmental stimuli in the maintenance of drug-seeking behavior [13, 16, 17].

Most work concerned with second-order schedules of drug self-administration has involved the intravenous route of administration, whereby injections are temporally spaced throughout the session or all drug is provided at the end of the session upon schedule completion [14,26]. Responding under second-order schedules has also been maintained by intramuscular injections given by the experimenter at the end of the session [12, 15, 19]. However, the use of second-order schedules has not yet been extended to the oral route of drug self-administration.

The purpose of this study was to test the feasibility of training monkeys under a second-order schedule that has been shown to produce high rates of food-maintained responding [10]. Access to a fixed oral dose of phencyclidine was provided at the end of the experimental session. Performance maintained by a concurrent FR schedule was compared before and after second-order schedule training to determine whether the high response rates produced by the second-order schedule altered subsequent phencyclidine-maintained responding under a simple FR schedule.

METHOD

Animals

Thirteen adult male rhesus monkeys *(Macaca mulatta)* whose free-feeding weights ranged from 7.9 to 17.3 kg served as subjects. Two monkeys (M-B and M-R) had previous oral self-administration experience with etonitazene [5], phencyclidine analogs and quinine [3]. At the start of this experiment, each monkey was maintained at 85% of its free-feeding body weight by restricting access to food (Purina High Protein Monkey Chow, No. 5045). The monkeys were housed individually in their experimental chambers in a room maintained at 24°C, with a 12-hr light/dark cycle.

Apparatus

Each monkey was housed in a stainless-steel Hoeltge (No. HB-108) primate cage equipped with a work panel on one wall. The work panel contained two drinking spouts spaced 30 cm apart, and stimulus lights that signaled experimental events. The brass drinking spouts were 2.7 cm long and 1.2 cm in diameter. A drinkometer circuit was operated when the monkey placed its lip on the spout. During the 3-hr sessions, every 20th lip contact on the monkey's right drinking device operated a solenoid for approximately 20 msec releasing 0.02 ml of liquid from the spout. A lip contact on the monkey's left drinking spout operated a solenoid for approximately 120 msec releasing 0.55 ml of liquid from the spout. Two pairs of small "feedback" lights were mounted directly behind a Plexiglas plate supporting each spout, and they were used to signal responses. One pair of lights was white and the other pair was green. During the 3-hr sessions the two small green lights were illuminated for the duration of each lip contact. During the intersession periods, lip contact responses on either drinking device resulted in the release of 0.55 ml of water, and the two white lights were illuminated during lip contact. In addition to the feedback lights on the drinking devices, a large green jeweled light was mounted 12 cm above each drinking spout. The large green lights were illuminated when water was available during intersession, and a large green light blinked 10 times/sec on the side where a drug (or saccharin) solution was available during the session. Liquids were contained in covered stainless-steel reservoirs, and there was no measureable evaporation. Experimental sessions were automatically controlled, and data were recorded and printed by microcomputers located in an adjacent room. Liquid responses and deliveries were also recorded on cumulative response recorders. Complete details of the control and recording equipment, drinking devices, and experimental chambers have been described elsewhere ([9, 18, 27], respectively).

Phencyclidine HCl was provided by the National Institute on Drug Abuse (Research Triangle Institute: Research Triangle Park, NC) and sodium saccharin was purchased from Sigma Chemical Co. (St. Louis, MO). Concentrations refer to the salt. Solutions were prepared in tap water 20 hr before use, and they were presented at room temperature.

Procedure

All monkeys had been trained to respond under a concurrent FR 16 schedule for phencyclidine (0.25 mg/ml) and water according to procedures previously described [4,8]. Drug was available from one drinking device and water was available from the other. Each liquid delivery was contingent upon 16 lip-contact responses on that drinking device; the FR 16 schedules operated independently. Side positions of drug and water were reversed daily. These schedule parameters were held constant for several months before the present experiment began. Experimental sessions took place daily from 9:00 a.m. to 12:00 p.m. for some monkeys or from 10:00 a.m. to 1:00 p.m. for others. The number of liquid deliveries available under the FR 16 schedule was not limited except by the length of the session. Each 3-hr session was preceded and followed by a 1-hr timeout when solutions were changed and data were recorded. The monkeys were fed immediately after the session. During the timeout, stimulus lights were not illuminated, and behavior had no programmed consequences.

Effects of Second-Order Schedule Performance (Maintained by Phencyclidine) on Subsequent FR 16 Responding Maintained by Phencyclidine

Seven monkeys were trained under a second-order schedule designated as an FR 240 (FR 20:S) according to the notation of Kelleher [20,21]. Every 20 lip-contact responses (FR 20) on the right drinking spout resulted in a brief stimulus presentation. The brief stimulus consisted of 20-msec operation of the drinking device resulting in a 0.02 ml delivery of phencyclidine (0.25 mg/ml) and illumination of two small green lights on the drinking device for the duration of the lip contact. A small quantity of the drug solution was used as part of the brief stimulus complex because previous work with oral drug self-administration procedures indicated that taste is a more powerful stimulus than visual, auditory or olfactory cues [3,6]. The total amount of drug delivered during the 240 brief stimulus presentations was 1.2 mg. This amount does not reliably function as a reinforcer, and it was not expected to disrupt schedule-maintained performance [7,8]. Furthermore, later work (not reported here) revealed that water could be substituted for phencyclidine during the brief stimulus presentations, without any change in rate or pattern of responding. After 240 presentations of the brief stimulus (FR 240), the right drinking device and associated green lights became inoperative, and the monkeys were allowed access to 300 phencyclidine (0.25 mg/ml) deliveries (0.55 ml each) from the left drinking spout contingent upon lip-contact responses under an FR 1 schedule. At this time the large green light over the drinking spout blinked (10 Hz), and the two small green lights were illuminated for the duration of each lip contact. During second-order schedule training, the schedule parameters were gradually increased from FR 5 (FR 10:S) to the terminal value (See Table 1). After 10 sessions under the FR 240 (FR 20:S) parameters, the monkeys were returned to the concurrent FR 16 schedule with phencyclidine available from one drinking device and water available from the other; side positions were alternated daily. Liquid deliveries were not limited except by the 3-hr session duration, and responding

TABLE 1
SUMMARY OF TRAINING CONDITIONS

Second-Order Schedule	Number of Sessions
FR 5 (FR 10:S)	2
FR 10 (FR 10:S)	1–2
FR 20 (FR 10:S)	2
FR 40 (FR 10:S)	2
FR 80 (FR 10:S)	3–4
FR 160 (FR 10:S)	3–4
FR 200 (FR 10:S)	3–4
FR 240 (FR 10:S)	3–4
FR 240 (FR 20:S)	10

was then allowed to stabilize for at least 30 sessions. Time to complete second-order schedule requirements and response rates were determined by measuring cumulative response records.

Effects of Second-Order Schedule Performance (Maintained by Saccharin) on Subsequent FR 16 Responding Maintained by Phencyclidine

Three monkeys were exposed to conditions that were the same as those described in the previous section (in all unspecified details), except during second-order schedule training, a saccharin solution (0.05% wt/vol) was available from both drinking devices rather than phencyclidine. Phencyclidine (0.25 mg/ml) and water were concurrently available under the FR 16 schedule before and after second-order schedule training. This group received the same behavioral history as the initial group, except phencyclidine self-administration experience was replaced by saccharin self-administration experience during second-order schedule training.

Effects of Phencyclidine Exposure (Under an FR 1 Schedule) on Subsequent FR 16 Responding Maintained by Phencyclidine

Three monkeys initially received access to phencyclidine (0.25) and water under a concurrent FR 16 schedule. They served as a yoked control for the group of monkeys that received phencyclidine under a second-order schedule. Phencyclidine (300 deliveries) was available under an FR 1 schedule for the same number of sessions as the second-order schedule trained group. Phencyclidine was available after the mean number of minutes during the sessions when the other group completed the second-order schedule requirements and received access to phencyclidine. This group received the same amount of drug exposure as the initial group; however, they were not exposed to second-order schedule training.

RESULTS

The Effects of Second-Order Schedule Performance (Maintained by Phencyclidine) on Subsequent FR 16 Responding Maintained by Phencyclidine

The second-order schedule training under an FR 240 (FR 20:S) schedule was accomplished after a mean of 23.3 sessions for six monkeys. One of the seven monkeys (M-M) did not complete the second-order schedule requirements above the FR 160 (FR 10:S) parameter after extensive training, and its data were excluded from the analysis. During 10 sessions following training, schedule requirements were always completed, and 300 phencyclidine deliveries were obtained at the end of each session. Representative cumulative response records for the six monkeys that completed the schedule requirements are presented in Fig. 1. The monkeys typically responded immediately at the start of the session and continued with only a few short pauses until the second-order schedule requirements were completed and the 300 liquid deliveries were obtained. There was no evidence of any drug effect as a result of the 240 brief stimulus presentations. The mean number of minutes (±S.E.) to complete the second-order schedule requirements was 47.7 (±7.2), and the mean response rate was 1.67 (±0.27) responses/sec for the six monkeys. Five of the six monkeys reliably obtained the 300 phencyclidine deliveries within a mean of 3–4 min over the last five sessions; however, the mean for one monkey (M-H) was 14.2 min.

When the concurrent FR 16 schedule with phencyclidine and water available was reinstated, the rate of drug-maintained responding was considerably higher than before second-order schedule training. Table 2 shows the mean number of phencyclidine and water deliveries under the concurrent FR 16 schedule before and after second-order schedule training for the six monkeys that completed second-order schedule training. The mean number of phencyclidine deliveries increased by an overall mean of 42 percent among the six monkeys after the second-order schedule training. The overall rate of responding under the FR 16 schedule increased from 0.40 to 0.56 responses per second after second-order schedule training. Overall response rates under the FR 16 schedule were not compared to those under the second-order schedule, as the length of access to these schedules (3 hr vs. 47.7 min) and patterns of responding differed. These increases were immediately apparent when the concurrent FR 16 conditions were reinstated, and response rates remained irreversibly elevated for at least 30 sessions and for several months in monkeys whose experimental conditions were not changed after 30 sessions. The variability of daily rates of responding within monkeys was relatively low, although between monkeys there was wide variability in the percent increases. Second-order schedule training had little effect upon water-maintained responding; the number of water deliveries slightly increased in five of the six monkeys. When monkey M-M, that did not complete second-order schedule training, was returned to the concurrent FR 16 schedule there was no change in its performance. The patterns of responding under the FR 16 schedule before and after second order schedule training are presented in Fig. 2. Aside from the increased rates of responding after second order schedule training, there were no substantial changes in the patterns of responding. As previously reported [4], phencyclidine-maintained responding generally followed a negatively-accelerated function with most responding occurring during the first hour of the session.

The Effects of Second-Order Schedule Performance (Maintained by Saccharin) on Subsequent FR 16 Responding Maintained by Phencyclidine

Second-order schedule training under the FR 240 (FR

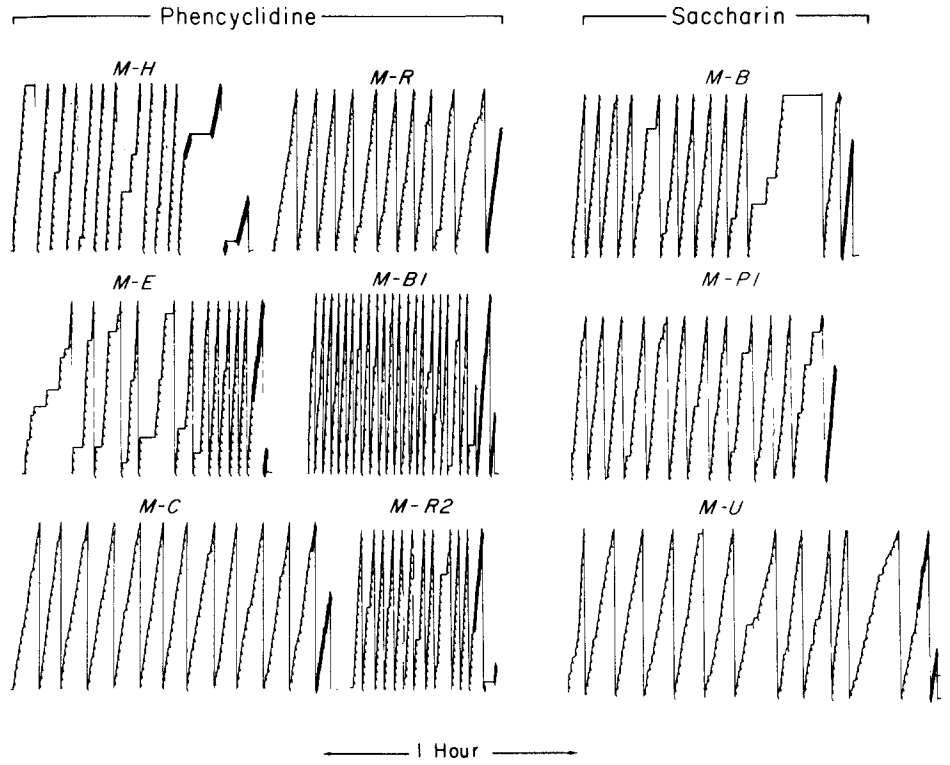

FIG. 1. Sample cumulative response records are presented for each of the nine monkeys that completed the second-order schedule FR 240 (FR-20:S) training. The six monkeys on the left received phencyclidine deliveries upon completion of the second-order schedule requirements, and the three on the right received saccharin. The records were selected as those with the total number of liquid deliveries closest to the mean of the last five sessions during second-order schedule training. The pen stepped across the page with each response, and downward deflections of the pen represent brief stimulus presentations that occurred after every 20 responses. Closely spaced pen deflections at the far right of each record represent the 300 phencyclidine deliveries obtained under an FR 1 schedule. The pens reset at about 400–450 responses, except for M-B1's pen which reset at 250 responses. Sessions lasted for a mean of 47.7 min for the monkeys receiving phencyclidine and 70.5 min for the monkeys receiving saccharin.

20:S) schedule was completed after a mean of 20 sessions for the three monkeys. Representative cumulative response records (See Fig. 1) were similar to those obtained with phencyclidine. The mean number of minutes (±S.E.) to complete the second-order schedule requirements was 70.5 (±10.4), and the mean response rate was 1.13 (±0.38) responses/sec for the three monkeys. All three monkeys reliably obtained the 300 saccharin deliveries within 3–4 min.

Table 3 shows the number of phencyclidine and water deliveries under the concurrent FR 16 schedule before and after second-order schedule training with saccharin. There was no consistent difference in the number of phencyclidine deliveries before or after second-order schedule training. The overall rate of responding under the FR 16 schedule was 0.40 responses/sec before second-order schedule training and 0.39 after training. Water-maintained responding slightly increased after second-order schedule training. Figure 3 shows that there was no consistent change in the patterns of responding as a result of second-order schedule training.

Effects of Phencyclidine Exposure (Under an FR 1 Schedule) on Subsequent FR 16 Responding Maintained by Phencyclidine

Table 4 shows the number of concurrent phencyclidine and water deliveries for three monkeys that received 300 phencyclidine deliveries under an FR 1 schedule without responding under a second-order schedule. There were no consistent differences in the number of phencyclidine deliveries before or after FR 1 phencyclidine access. The overall rate of responding under the FR 16 schedule was 0.53 responses/sec before and after exposure to phencyclidine under the FR 1 schedule. Water-reinforced responding slightly increased in two of the three monkeys. Figure 4 shows that the patterns of responding did not change as a result of FR 1 phencyclidine access.

DISCUSSION

These experiments extended the schedule conditions under which oral drug-self administration behavior is maintained. Previous oral drug self-administration studies have typically employed simple FR schedules (e.g., [5, 8, 23]. In the present experiment, rhesus monkeys were readily trained under a second-order FR 240 (FR 20:S) schedule suggesting that response-based, second-order schedules and possibly other complex schedules are feasible for investigating behavior reinforced by orally-delivered drugs. The second-order schedule resulted in high rates of responding for a mean of 47.7 min per session with a total of 4800 re-

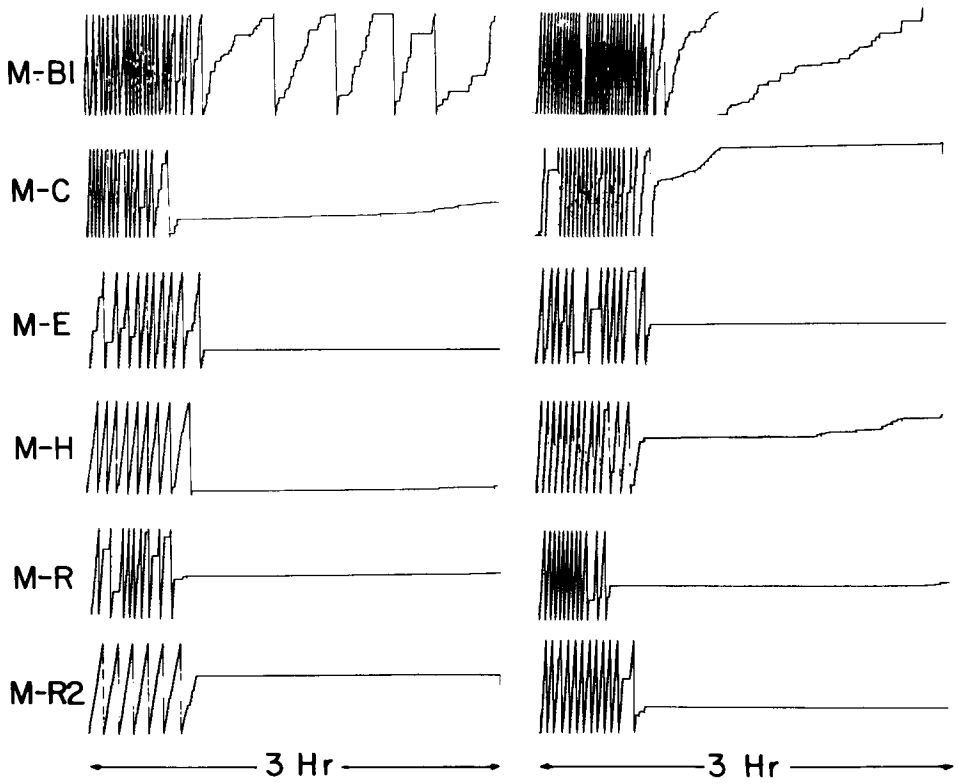

FIG. 2. Sample cumulative response records are presented for six monkeys that completed second-order schedule training with phencyclidine available upon completion of schedule requirements. The records on the left show phencyclidine-maintained responding under the concurrent FR 16 schedules (for phencyclidine and water) before second-order schedule training with phencyclidine, and the records on the right show FR 16 performance after second-order training. The records were selected as those with the total number of liquid deliveries closest to the mean of the last five sessions before (left) or after (right) second-order schedule training. The pen stepped across the page with each response, and downward deflections of the pen represent liquid deliveries (0.55 ml) that occurred after every 16 responses. The pens reset at about 400–450 responses, except for M-B1's pen which reset at 250 responses.

sponses leading to drug access. Previous studies of oral drug self-administration using simple schedules have reported maximum FRs of 4 for etonitazene [5], 16 for phencyclidine [3,4] and 64 for pentobarbital [24]. As previously noted [14], the patterns of responding maintained under the components of the second-order schedule were similar to those maintained under simple FR schedules. High, steady rates of responding were maintained by each brief stimulus presentation, and overall high rates throughout the session were maintained by drug access after completion of all schedule components. The advantage of applying second-order schedules to studies of behavior reinforced by orally-delivered drugs is that there are little or no direct drug effects on behavior leading to drug access, and the rate of behavior is also not directly affected by the aversive taste of the drug.

Response rates under the concurrent FR 16 schedule were irreversibly increased after relatively brief exposure to the second-order schedule. Gradual increases (over several months) in monkeys' rates of drug-maintained responding previously have been noted. For instance, one monkey (M-G1) showed a mean of 249.8 and 302.6 phencyclidine deliveries during food satiation and deprivation, respectively, after initial training, [4] and over a year later, the means had increased to 455.6 and 370.4 during food satiation and deprivation, respectively [7]. These increases and the ones reported in the present study could be explained by the development of more efficient responding on the lip-operated drinking devices. However, it should be noted that in the present experiment, marked increases occurred after only 30 days. Furthermore, the saccharin-treated animals would also be expected to be more efficient, and their response rates did not increase. The increased phencyclidine-maintained FR responding cannot be explained by tolerance, as the increases were not shown in a group of three monkeys that received the same number of phencyclidine deliveries (300 per day) for the same number of sessions without the second-order schedule training. Also, there were two monkeys (M-B1 and M-C) that received more than 300 phencyclidine deliveries under the FR 16 schedule before second-order schedule training with phencyclidine began.

Persistence of high response rates due to a specific behavioral history has been reported by Weiner [27] who showed that humans trained to respond under an FR 40 schedule for points (exchangeable for money) did not decrease their response rates when they were exposed to a fixed-interval (FI) 10 sec schedule that also cost them points for responding. However, in the present experiment, training under the second-order schedule alone was not sufficient to produce

TABLE 2

MEAN* LIQUID DELIVERIES (±S.E.) UNDER A CONCURRENT FR 16 SCHEDULE

Monkey	Before second-order schedule training: Phencyclidine (0.25 mg/ml)	Before second-order schedule training: Water	After second-order schedule training: Phencyclidine (0.25 mg/ml)	After second-order schedule training: Water	Percent increase in phencyclidine deliveries
M-B1	375.0 (10.6)	81.6 (12.1)	501.8 (12.2)	85.4 (18.7)	33.8
M-C	364.8 (16.2)	75.0 (28.3)	486.8 (15.6)	83.0 (17.9)	33.4
M-E	266.2 (16.8)	61.2 (25.4)	326.4 (12.0)	59.4 (4.5)	22.6
M-H	237.2 (7.4)	9.0 (3.7)	342.6 (10.7)	15.8 (4.3)	27.8
M-R	216.0 (18.2)	0.7 (0.2)	305.0 (6.5)	1.7 (1.1)	41.2
M-R2	171.6 (5.0)	1.0 (0.4)	301.6 (8.7)	3.6 (1.5)	75.8
Group Mean Mean S.E.	271.8 (12.3)	38.1 (11.7)	377.4 (10.9)	41.4 (8.0)	42.0 (7.4)†

*Means are for the last five sessions of stable behavior at each condition.
†S.E. of mean for six monkeys.

TABLE 3

MEAN* LIQUID DELIVERIES (±S.E.) UNDER A CONCURRENT FR 16 SCHEDULE

Monkey	Before second-order schedule training: Phencyclidine (0.25 mg/ml)	Before second-order schedule training: Water	After second-order schedule training: Phencyclidine (0.25 mg/ml)	After second-order schedule training: Water	Percent increase or decrease (−) in phencyclidine deliveries
M-B	375.8 (19.7)	0 0	419.8 (9.3)	0 (0)	11.7
M-P1	203.2 (5.0)	22.4 (11.3)	186.8 (11.6)	30.0 (12.8)	−8.1
M-U	223.0 (12.2)	5.6 (1.4)	185.0 (7.6)	18.6 (4.5)	−17.0
Group Mean Mean S.E.	267.3 (12.3)	9.3 (4.2)	263.9 (9.5)	16.2 (5.8)	−1.3†

*Means are for the last five sessions of stable behavior at each condition.
†Percent change in group.

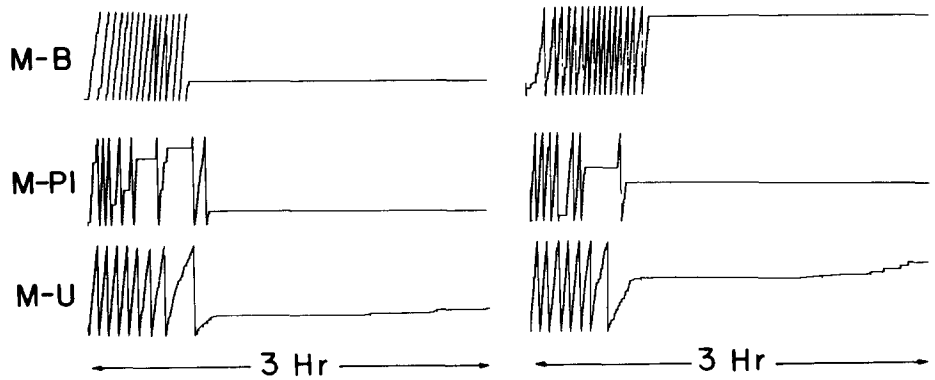

FIG. 3. Sample cumulative response records are presented for three monkeys that completed second-order schedule training with phencyclidine available upon completion of schedule requirements. The records on the left show phencyclidine-maintained responding under the concurrent FR 16 schedules (for phencyclidine and water) before second-order schedule training with saccharin, and the records on the right show FR 16 performance after second-order schedule training. The records were selected as those with the total number of liquid deliveries closest to the mean of the last five sessions before (left) or after (right) second-order schedule training. The pen stepped across the page with each response, and downward deflections of the pen represented liquid deliveries (0.55 ml) that occurred after every 16 responses. The pens reset at about 400–450 responses.

TABLE 4

MEAN* LIQUID DELIVERIES (±S.E.) UNDER A CONCURRENT FR 16 SCHEDULE

Monkey	Before exposure to 300 phencyclidine deliveries per sessions (FR 1) Phencyclidine (0.25 mg/ml)	Water	After exposure to 300 phencyclidine deliveries per session (FR 1) Phencyclidine (0.25 mg/ml)	Water	Percent increase or decrease (−) in phencyclidine deliveries
M-A	397.0	29.8	332.4	11.4	−16.3
	(16.1)	(7.0)	(5.5)	(3.2)	
M-M1	437.0	0.4	487.4	3.4	11.5
	(18.5)	(0.2)	(35.8)	(0.7)	
M-S	239.8	5.6	256.4	9.0	6.9
	(11.7)	(3.2)	(9.0)	(5.5)	
Group Mean	357.9	11.9	358.7	7.9	0.2
Mean S.E.	(15.4)	(3.6)	(16.8)	(3.1)	

*Means are for the last five sessions of stable behavior at each condition.

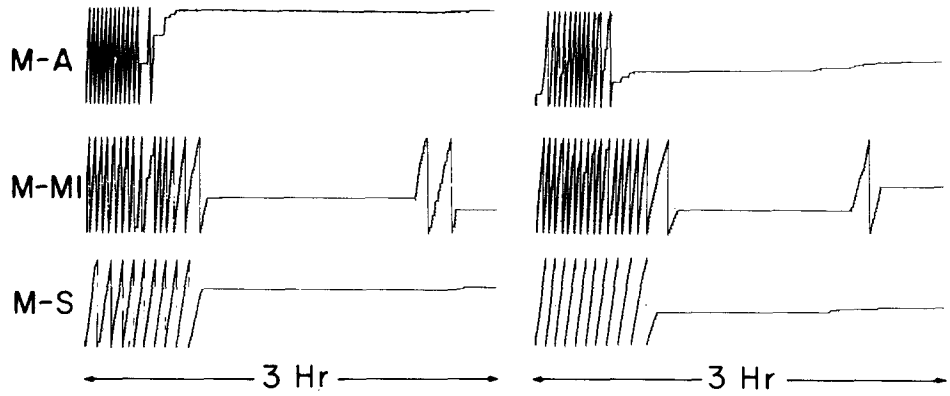

FIG. 4. Sample cumulative response records are presented for three monkeys that received 300 phencyclidine deliveries under an FR 1 schedule for 33 sessions. The records on the left show phencyclidine-maintained responding under the concurrent FR 16 schedules (for phencyclidine and water) before FR1 phencyclidine access, and records on the right show FR 16 performance after FR 1 phencyclidine access. The records were selected as those with the total number of liquid deliveries closest to the mean of the last five sessions before (left) or after (right) FR 1 phencyclidine access. The pen stepped across the page with each response, and downward deflections of the pen represent liquid deliveries (0.55 ml) that occurred after every 16 responses. The pens reset at about 400–450 responses.

the higher FR rates. Three monkeys that received the same amount of second-order schedule experience with saccharin as the reinforcer did not show increases in phencyclidine-reinforced FR behavior. It should be noted that the rate of responding during second-order training was slightly lower for the saccharin group than for the phencyclidine group, and this difference may have contributed to the absence of increased phencyclidine deliveries after second-order schedule training. However, if this difference was an important determinant of the results, one would expect that a slightly lower rate during training would result in smaller increases after training rather than no increases. Thus, the present findings appeared to be a specific result of a combined behavioral and drug history. Previous studies have shown that prior behavioral experience [2] and combined behavioral and drug experience [1,25] can substantially alter subsequent behavioral effects of parenterally-administered drugs. The present findings emphasize the importance of combined effects of drug and behavioral histories to behavior maintained by orally-delivered phencyclidine.

ACKNOWLEDGEMENTS

I am grateful to Kathy Manion, Dana Stotz and Jane Wright for their technical assistance and to Dr. Richard A. Meisch for his helpful comments on the manuscript. This research was supported by NIDA grants DA 02486 and DA 03240 to M. E. Carroll and DA 00944 to R. A. Meisch.

REFERENCES

1. Bacotti, A. V. and J. W. McKearney. Prior and ongoing experience as determinants of the effects of *d*-amphetamine and chlorpromazine on punished behavior. *J Pharmacol Exp Ther* **211:** 80–85, 1979.
2. Barrett, J. E. Behavioral history as a determinant of the effects of d-amphetamine on punished behavior. *Science* **198:** 67–69, 1977.
3. Carroll, M. E. Oral self-administration of phencyclidine analogs by rhesus monkeys: Conditioned taste and visual reinforcers. *Psychopharmacology (Berlin)* **78:** 116–120, 1982.
4. Carroll, M. E. Rapid acquisition of oral phencyclidine self-administration food-deprived and food-satiated rhesus monkeys: Concurrent phencyclidine and water choice. *Pharmacol Biochem Behav* **17:** 341–346, 1982.
5. Carroll, M. E. and R. A. Meisch. Etonitazene as a reinforcer: Oral intake of etonitazene by rhesus monkeys. *Psychopharmacology (Berlin)* **59:** 225–229, 1978.
6. Carroll, M. E. and R. A. Meisch. Concurrent etonitazene and water intake in rats: Role of taste, olfaction and auditory stimuli. *Psychopharmacology (Berlin)* **74:** 197–200, 1981.
7. Carroll, M. E. and R. A. Meisch. Increased drug-reinforced behavior due to food deprivation. In: *Advances in Behavioral Pharmacology*, vol 4, edited by T. Thompson and P. B. Dews. New York: Academic Press, in press.
8. Carroll, M. E. and R. A. Meisch. Oral phencyclidine (PCP) self-administration in rhesus monkeys: Effects of feeding conditions. *J Pharmacol Exp Ther* **214:** 339–346, 1980.
9. Carroll, M. E., P. A. Santi and R. L. Rudell. A microcomputer system for the control of behavioral experiments. *Pharmacol Biochem Behav* **14:** 415–417, 1981.
10. Findley, J. D. and J. V. Brady. Facilitation of large ratio performance by use of conditioned reinforcement. *J Exp Anal Behav* **8:** 125–129, 1965.
11. Goldberg, S. R. Comparable behavior maintained under fixed-ratio and second-order schedules of food presentation, cocaine injection or *d*-amphetamine injection in the squirrel monkey. *J Pharmacol Exp Ther* **186:** 18–30, 1973.
12. Goldberg, S. R. Stimuli associated with drug injections as events that control behavior. *Pharmacol Rev* **27:** 325–340, 1975.

13. Goldberg, S. R., R. T. Kelleher and D. M. Goldberg. Fixed-ratio responding under second-order schedules of food presentation or cocaine injection. *J Pharmacol Exp Ther* **218:** 271–281, 1981.
14. Goldberg, S. R., R. T. Kelleher and W. H. Morse. Second-order schedules of drug injection. *Fed Proc* **34:** 1771–1776, 1975.
15. Goldberg, S. R., W. H. Morse and D. M. Goldberg. Behavior maintained under a second-order schedule by intramuscular injection of morphine or cocaine in rhesus monkeys. *J Pharmacol Exp Ther* **199:** 278–286, 1976.
16. Goldberg, S. R., R. D. Spealman and D. M. Goldberg. Persistent behavior at high rates maintained by intravenous self-administration of nicotine. *Science* **214:** 573–575, 1981.
17. Goldberg, S. R. and A. Tang. Behavior maintained under second-order schedules of intravenous morphine injection in squirrel and rhesus monkeys. *Psychopharmacology (Berlin)* **51:** 235–242, 1977.
18. Henningfield, J. E. and R. A. Meisch. Drinking device for rhesus monkeys. *Pharmacol Biochem Behav* **4:** 609–610, 1976.
19. Katz, J. L. A comparison of responding maintained under second-order schedules of intramuscular cocaine injection or food presentation in squirrel monkeys. *J Exp Anal Behav* **32:** 419–431, 1979.
20. Kelleher, R. T. Chaining and conditioned reinforcement. In: *Operant Behavior: Areas of Research and Application*, edited by W. K. Honig. New York: Appleton-Century-Crofts, 1966, pp. 160–212.
21. Kelleher, R. T. Conditioned reinforcement in second-order schedules. *J Exp Anal Behav* **9:** 475–485, 1966.
22. Kelleher, R. T. and S. R. Goldberg. Fixed-interval responding under second-order schedules of food presentation or cocaine injection. *J Exp Anal Behav* **28:** 14–24, 1977.
23. Meisch, R. A. and J. E. Henningfield. Drinking of ethanol by rhesus monkeys: Experimental strategies for establishing ethanol as a reinforcer. *Exp Med Biol* **85B:** 443–463, 1977.
24. Meisch, R. A., D. J. Kliner and J. E. Henningfield. Pentobarbital drinking by rhesus monkeys: Establishment and maintenance of pentobarbital-reinforced behavior. *J Pharmacol Exp Ther* **217:** 114–120, 1981.
25. Smith, J. B., M. N. Branch and J. W. McKearney. Changes in the effects of *d*-amphetamine on escape responding by its prior effects on punished responding. *J Pharmacol Exp Ther* **207:** 159–164, 1978.
26. Spealman, R. D. and S. R. Goldberg. Drug self-administration by laboratory animals: Control by schedules of reinforcement. *Annu Rev Pharmacol Toxicol* **18:** 313–339, 1978.
27. Weiner, H. Human behavioral persistence. *Psychol Rec* **20:** 445–456, 1970.