Pharmacology Biochemistry & Behavior, Vol. 20, pp. 137–143, 1984. © Ankho International Inc. Printed in the U.S.A.

Effects of Pentobarbital and *d*-Amphetamine on Oral Phencyclidine Self-Administration in Rhesus Monkeys

MARILYN E. CARROLL[1]

Department of Psychiatry, University of Minnesota, Minneapolis, MN 55455

Received 28 April 1983

CARROLL, M. E. *Effects of pentobarbital and d-amphetamine on oral phencyclidine self-administration in rhesus monkeys.* PHARMACOL BIOCHEM BEHAV **20**(1) 137–143, 1984.—Three rhesus monkeys self-administered phencyclidine (0.25 mg/ml) during daily 3-hr sessions. Water was also available under a concurrent fixed-ratio (FR) 16 schedule. In Experiment 1, saline or three doses of pentobarbital (2.5, 5 or 10 mg/kg) were injected 10 min before phencyclidine (and water) self-administration sessions. The 2.5 mg/kg pentobarbital dose increased phencyclidine-maintained responding, the 5 mg/kg dose produced mixed effects among the three monkeys, and the 10 mg/kg dose consistently decreased phencyclidine-maintained responding. Subsequently, a saccharin solution (0.03% wt/vol) replaced phencyclidine, and the pentobarbital pretreatment procedure was repeated. Pentobarbital produced dose-related decreases in saccharin-maintained responding. In Experiment 2, saline or three doses of *d*-amphetamine (0.05, 0.1 or 0.2 mg/kg) were injected 10 min before the phencyclidine self-administration sessions. The 0.05 mg/kg dose produced increases in phencyclidine-maintained responding, while the two higher doses produced dose dependent decreases in responding. When a saccharin solution (0.03%, wt/vol) replaced phencyclidine during the daily sessions, *d*-amphetamine produced only dose-related decreases in saccharin-maintained responding. These results indicate that pentobarbital and *d*-amphetamine have a biphasic effect on phencyclidine-maintained behavior; low doses increased responding and high doses decreased responding.

d-Amphetamine Drug interaction Oral drug self-administration Pentobarbital Phencyclidine Rhesus monkeys Saccharin

THERE has been considerable interest in the dissociative anesthetic, phencyclidine, due to its broad spectrum of central nervous system activity [19] and its widespread illicit use [6]. Phencyclidine is often abused in combination with other psychoactive drugs [40] as a result of its misrepresentation as another substance [34] or due to intentional polydrug abuse [20].

There have been a number of investigations of the effects of parenterally administered phencyclidine in combination with other psychoactive drugs. Generally, phencyclidine has been found to potentiate the action of barbiturates. Phencyclidine increased sleep time produced by hexobarbital and ethanol [46] and the lethality of pentobarbital [15] in mice. In rhesus monkeys [15,52] and patas monkeys [47] pentobarbital increased disruptive effects of phencyclidine on schedule-controlled behavior. However, phencyclidine did not increase pentobarbital's depressant effects in squirrel monkeys [14]. Phencyclidine has also been reported to increase disruptive effects of Δ^9-tetrahydro-cannibinol on conditioned avoidance behavior, rotarod performance, photocell activity and schedule-maintained performance in rats [43]. Phencyclidine increased amphetamine stereotypy in rats [3]; however, the two drugs produced infraadditive effects on schedule-controlled responding in rats [42].

The purpose of the present investigation was to study the effects of parenterally-administered pentobarbital and *d*-amphetamine on oral phencyclidine self-administration. With the exception of studies concerning specific blocking agents (e.g., [22–25, 27, 51]), there have been few reports of drug interactions in the self-administration context. While previous studies have shown that phencyclidine enhances or inhibits the disruptive effects of pentobarbital and *d*-amphetamine on schedule-controlled behavior, it was the goal of the present study to determine whether these drugs would increase or decrease phencyclidine self-administration. The effects of pentobarbital and *d*-amphetamine pretreatment on saccharin self-administration were also studied to compare effects due to drug interactions to the direct effects of pentobarbital and *d*-amphetamine on schedule-controlled behavior.

METHOD

Animals

Three adult male rhesus monkeys (M-A, M-M1 and M-R) were used in these experiments. Monkey M-A received previous exposure to phencyclidine and saccharin in a phencyclidine tolerance study [9], M-R had previous experience with

[1]Send reprint requests to: Dr. Marilyn E. Carroll, Department of Psychiatry, Mayo Box 392, University of Minnesota, Minneapolis, MN 55455.

etonitazene self-administration [10], and M-M1 and M-R previously self-administered quinine and phencyclidine analogs, N-ethyl-1-phencyclohexylamine and 1-[1-(2-thienyl) cyclohexyl] piperidine [7]. The monkeys were housed individually in their experimental chambers in a room maintained at 24°C, with a 12-hr light/dark cycle. Each monkey was maintained at 85% of his free-feeding body weight by restricting food access (Purina High Protein Monkey Chow, No. 5045). The 85% weights for monkeys M-A, M-M1 and M-R were 7.2, 8.1, and 9.1 kg, respectively.

Apparatus

The monkeys were housed in individual stainless-steel Hoeltge (No. HB-108) primate cages equipped with a work panel on one wall. The work panel contained two drinking spouts spaced 30 cm apart, with stimulus lights above and beside each drinking spout that signaled experimental events. Lip contacts on the brass drinking spouts were counted as responses, and after the appropriate number of responses were made, a solenoid released approximately 0.55 ml of liquid from the spout; liquid delivery terminated if the monkey removed his mouth from the spout before 0.55 ml of liquid was delivered. Operation of the solenoid also served as an auditory stimulus signaling a liquid delivery. The brass drinking spouts contained no moving parts; therefore, visual feedback stimuli for responses or lip contacts were provided by one of two pairs of small lights mounted directly behind a Plexiglas plate supporting each spout. When phencyclidine was available during the session, two small green lights were illuminated for the duration of each lip contact. Similarly, when water was available during the session, lip contacts resulted in illumination of two small white lights. In addition to these feedback lights, a larger green light 12 cm above the drinking spout was illuminated when water was available during sessions and intersessions. This light blinked (10 times/sec) when phencyclidine was available during the session. When a saccharin solution was present during the session, yellow lights replaced the green lights, and a green light continued to signal the presence of concurrent water. Liquids were contained in covered stainless-steel reservoirs to prevent evaporation. Complete details of the control and recording equipment, experimental chambers and drinking devices have been described elsewhere [12, 29, 36].

Phencyclidine was provided by NIDA (Research Triangle Institute, Research Triangle Park, NC) in the form of the hydrochloride salt. Sodium pentobarbital (Nembutal®) was obtained from Abbott Laboratories (North Chicago, IL). Nembutal® contains 50 mg sodium pentobarbital per ml of sterile saline containing 10% ethanol and 40% propylene glycol. Additional sterile saline was mixed with this solution to provide the desired dose. The *d*-amphetamine sulfate was obtained from Sigma Chemical Co. (St. Louis, MO). It was mixed in sterile saline, passed through a sterile 0.2 μm filter, and sterile saline was added to provide the desired dose. Pentobarbital and *d*-amphetamine concentrations were determined such that a constant injection volume of 2 ml for pentobarbital and 1 ml for *d*-amphetamine was injected. Sodium saccharin was obtained from the Sigma Chemical Co. (St. Louis, MO), and it was mixed in room temperature tap water.

Procedure

The monkeys had been trained to respond under a concurrent fixed-ratio (FR) 16 schedule for phencyclidine (0.25 mg/ml) and water during daily 3-hr sessions (9:30 a.m.–12:30 p.m.) according to methods previously described [11]. Both phencyclidine and water (or saccharin and water) were available throughout the session, and responding on one drinking device was independent of responding on the other. Side positions of the drug and water during sessions were alternated daily, and water was available from both drinking spouts during the intersession periods. Each session was preceded and followed by a 1-hr timeout for changing solutions and recording data. During the timeout, stimulus lights were not illuminated, and behavior had no programmed consequences. The monkeys' behavior had been stable under these conditions for several weeks before the start of these experiments. Before Experiment 2, concurrent phencyclidine (0.25 mg/ml)- and water-maintained responding were allowed to stabilize for at least ten sessions. Concurrent saccharin (0.03% wt/vol)- and water-maintained responding were allowed to stabilize for at least ten sessions before pentobarbital or *d*-amphetamine injections were given. Stability was defined as no steadily increasing or decreasing trend in the number of liquid deliveries and no change in the temporal pattern of responding.

Experiment 1. Effects of Pentobarbital on Phencyclidine- and Saccharin-Maintained Behavior

Saline and three doses (2.5, 5, and 10 mg/kg) of pentobarbital were tested five times each. The monkeys were injected IM 10 min before the session started, and each injection was separated by at least three sessions of stable responding. The five saline injections were given first and then pentobarbital injections were given in a nonorderly sequence. Saline injections were given before pentobarbital injections to obtain control data that was not influenced by possible conditioned increases or decreases in responding resulting from the injection procedure. During the course of the study, baseline phencyclidine-maintained responding gradually changed in two monkeys (M-A and M-M1), thus the session before each drug injection was considered as the nondrug control. Subsequently, a saccharin solution (0.3%, wt/vol) was substituted for phencyclidine and concurrent saccharin- and water-maintained responding (FR 16) was allowed to stabilize for at least 10 sessions. Side positions of saccharin and water were reversed every 21 days. This change in procedure was implemented to avoid contamination of other monkeys' water and drug solutions by the potent saccharin flavor. During intersession, water was available only from the spout that provided water during the sessions. Saline and pentobarbital (2.5, 5 and 10 mg/kg) injections were given as previously described.

Experiment 2. Effects of d-Amphetamine on Phencyclidine- and Saccharin-Maintained Behavior

Three doses (0.05, 0.1, and 0.2 mg/kg) of *d*-amphetamine (given in ascending order) and saline (given last) were tested five times each. Saline injections were given last to determine whether conditioned increases or decreases in responding would result from the injection procedure. Injections were given IM 10 min before the session, and each injection session was separated by at least three sessions of stable responding. Subsequently, a saccharin control condition was implemented as described in Experiment 1.

Throughout this study, the baseline number of phencyclidine and saccharin deliveries changed and did not return to

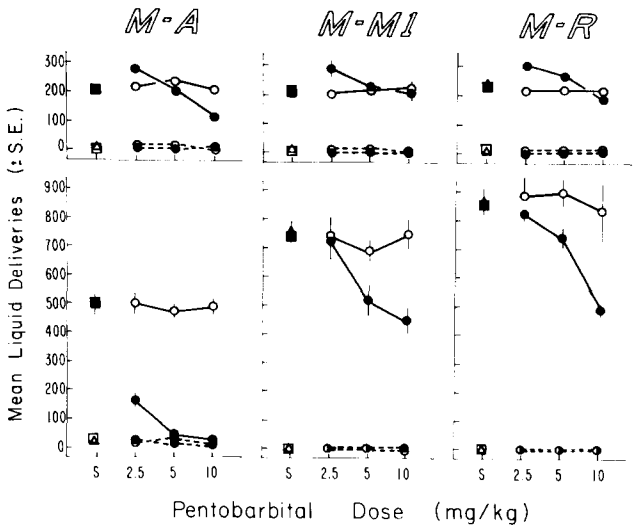

FIG. 1. Mean phencyclidine (0.25 mg/ml) and water (upper frames) or saccharin and water (lower frames) deliveries are presented for three monkeys (M-A, M-M1 and M-R) at three pentobarbital doses (2.5, 5 and 10 mg/kg) and saline (S). Phencyclidine (0.25 mg/ml) and saccharin (0.03%, wt/vol) were each available with water under a concurrent FR 16 schedule. Filled triangles—phencyclidine (upper frames) or saccharin deliveries (lower frames) when saline was injected 10-min before the session. Open triangles concurrent water deliveries. Filled squares—phencyclidine or saccharin deliveries and open squares—water deliveries during the sessions immediately preceding those sessions when saline was injected. Filled circles—phencyclidine or saccharin (solid lines) and water (dotted lines) deliveries when pentobarbital was injected 10-min before the session. Open circles phencyclidine or saccharin (solid lines) and water (dotted lines) deliveries during the sessions immediately preceding those when pentobarbital was injected. Each point represents a mean (±S.E.) of five sessions. Absence of vertical lines indicates that the S.E. fell within the area of the point.

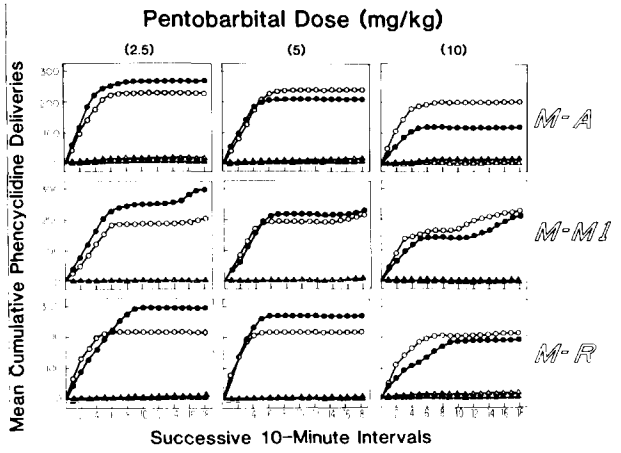

FIG. 2. Cumulative phencyclidine (circles) and water (triangles) deliveries are presented for three monkeys (M-A, M-M1 and M-R) over successive 10-min intervals during 3-hr sessions. Filled symbols—pentobarbital (2.5, 5, or 10 mg/kg) was injected IM 10 min before the phencyclidine and water self-administration sessions. Open symbols—sessions immediately preceding those when pentobarbital was injected. Each point represents a mean of five sessions. Phencyclidine (0.25 mg/ml) and water were available under a concurrent FR 16 schedule.

the initial saline pretreatment levels. Thus, the session before each drug injection was used as the nondrug control.

RESULTS

Experiment 1. Effects of Pentobarbital on Phencyclidine- and Saccharin-Maintained Behavior

Figure 1 shows that at the low dose (2.5 mg/kg), pentobarbital pretreatment produced increases in phencyclidine-maintained behavior in all three monkeys. At the intermediate dose (5 mg/kg) the results were mixed: M-R's phencyclidine deliveries increased, and M-A and M-M1's showed no changes. At the highest dose (10 mg/kg) pentobarbital produced decreases in phencyclidine-maintained responding, compared with the other two doses, in all three monkeys. However, only monkey M-A showed a decrease below control levels. There were no systematic changes in water-maintained responding as a result of saline or pentobarbital pretreatment in any of the monkeys at any of the doses tested.

The number of liquid deliveries from sessions when saline was injected was close to the number of liquid deliveries during sessions preceding those when drug injections were given. That there were almost no differences between sessions when saline was injected and the sessions immediately preceding them, suggests that small differences (e.g., 5 mg/kg in M-R) between drug-pretreatment sessions and those preceding them represent a significant drug effect.

Figure 2 shows cumulative phencyclidine and water deliveries as a function of pentobarbital dose. The increases in total session phencyclidine deliveries at the 2.5 pentobarbital dose were due to increased rates of responding during the first half of the session and to occasional drinking bouts during the last two hours of the session. Decreased phencyclidine-maintained responding at the 10 mg/kg pentobarbital dose was due to lowered response rates during the first half of the session. However, two monkeys (M-M1 and M-R) showed increased responding during the last two hours of the session.

Pentobarbital produced only dose-related decreases in saccharin-maintained behavior (See Fig. 1). The number of saccharin deliveries was higher than that reported for phencyclidine in all three monkeys. The monkey with the highest baseline rate of saccharin-maintained responding (M-R) showed the smallest decrease in saccharin deliveries due to pentobarbital, while the monkey with the lowest baseline rate (M-A) showed the greatest disruption. Water-maintained responding was low when saccharin was concurrently available, and it did not change systematically as a function of pentobarbital dose. There were no changes in saccharin- or water-maintained responding as a result of altering side positions every 21 days.

Figure 3 shows cumulative saccharin and water deliveries as a function of pentobarbital dose for pretreatment sessions and the sessions immediately preceding them. The decreases in saccharin deliveries after pentobarbital pretreatment were due to lowered response rates during the first half of the session. One monkey (M-R) showed high rates of responding during the second half of the session at all three pentobarbital doses, while monkey M-M1 showed this pattern of responding only at the lowest dose (2.5 mg/kg).

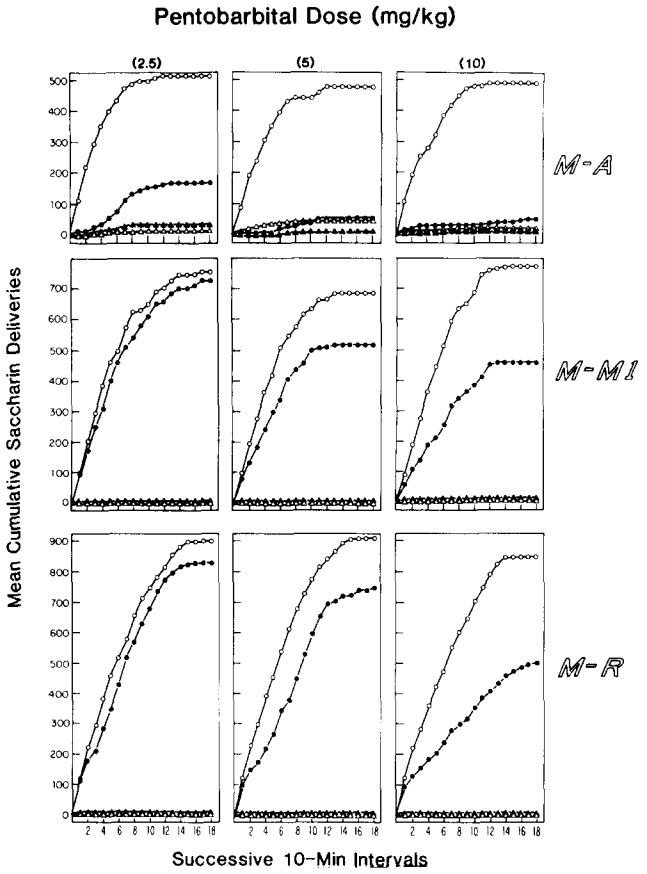

FIG. 3. Cumulative saccharin (circles) and water (triangles) deliveries are presented for three monkeys (M-A, M-M1 and M-R) over successive 10-min intervals during 3-hr sessions. Filled symbols—pentobarbital (2.5, 5, and 10 mg/kg) was injected IM 10 min before the saccharin and water self-administration session. Open symbols—sessions immediately preceding those when pentobarbital was injected. Each point represents a mean of five sessions. Saccharin (0.03%, wt/vol) and water were available under a concurrent FR 16 schedule.

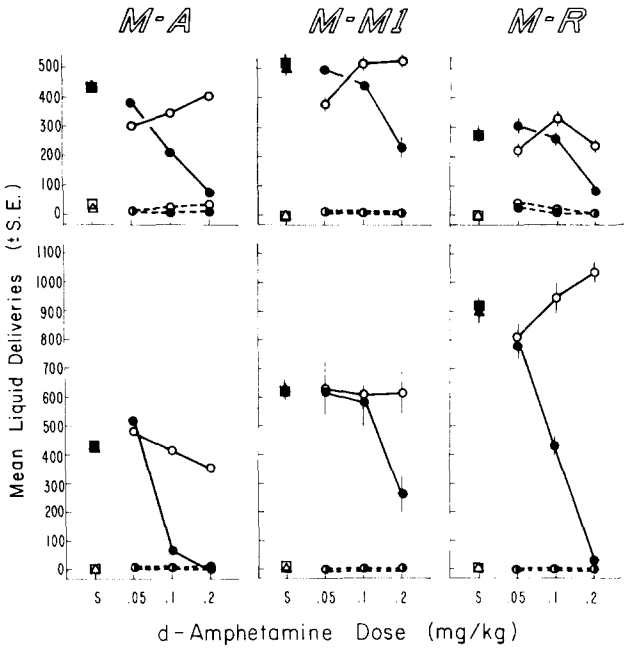

FIG. 4. Mean phencyclidine (0.25 mg/ml) and water (upper frames) or saccharin and water (lower frames) deliveries are presented for three monkeys (M-A, M-M1 and M-R) at three *d*-amphetamine doses (0.05, 0.1 and 0.2 mg/kg) and saline (S). Phencyclidine (0.25 mg/ml) and saccharin (0.03%, wt/vol) were each available with water under a concurrent FR 16 schedule. Filled triangles—concurrent water deliveries. Filled squares—phencyclidine or saccharin deliveries and open squares—water deliveries during the sessions immediately preceding those sessions when saline was injected. Filled circles—phencyclidine or saccharin (solid lines) and water (dotted lines) deliveries when *d*-amphetamine was injected 10-min before the sessions. Open circles—phencyclidine or saccharin (solid lines) and water (dotted lines) deliveries during the sessions immediately preceding those when *d*-amphetamine was injected. Each point represents a mean (±S.E.) of five sessions. Absence of vertical lines indicates that the S.E. fell within the area of the point.

Experiment 2. Effects of d-Amphetamine on Phencyclidine- and Saccharin-Maintained Behavior

Figure 4 shows that the lowest *d*-amphetamine dose (0.05 mg/kg) produced substantial increases in phencyclidine-maintained responding (compared with responding during the previous session) in all three monkeys. The other doses resulted in dose-dependent decreases in phencyclidine-maintained responding in all three monkeys. There were no systematic changes in water-maintained responding, except that M-A showed depressed water responding at the 0.1 and 0.2 mg/kg doses.

In two of the three monkeys (M-A and M-M1), the number of phencyclidine deliveries before the *d*-amphetamine injection session gradually increased, over several months, as the drug dose was increased. When saline was injected at the end of the drug series, the number of phencyclidine deliveries remained at the elevated level. However, there was very little difference in phencyclidine deliveries between sessions when saline was injected and the sessions immediately preceding them. Thus, it did not appear that the injection procedure alone was responsible for increased phencyclidine maintained responding. Due to shifts in baselines over time, data from sessions immediately preceding drug injections were clearly a more appropriate control than the saline data.

An analysis of the time course of responding revealed that increases in phencyclidine deliveries at the 0.05 mg/kg dose resulted from increased response rates during the first hour of the session; there was almost no responding during the last two hours of the session (see Fig. 5). Decreases at the other two doses (0.1 and 0.2 mg/kg) were generally due to lowered response rates during the first hour of the session.

There were no differences in saccharin-maintained responding at the lowest *d*-amphetamine dose (compared with the sessions before injections); however, there were dose-dependent decreases at the higher doses (See Fig. 4). Concurrent water-deliveries remained low and unaffected by *d*-amphetamine dose. There were no changes in saccharin-

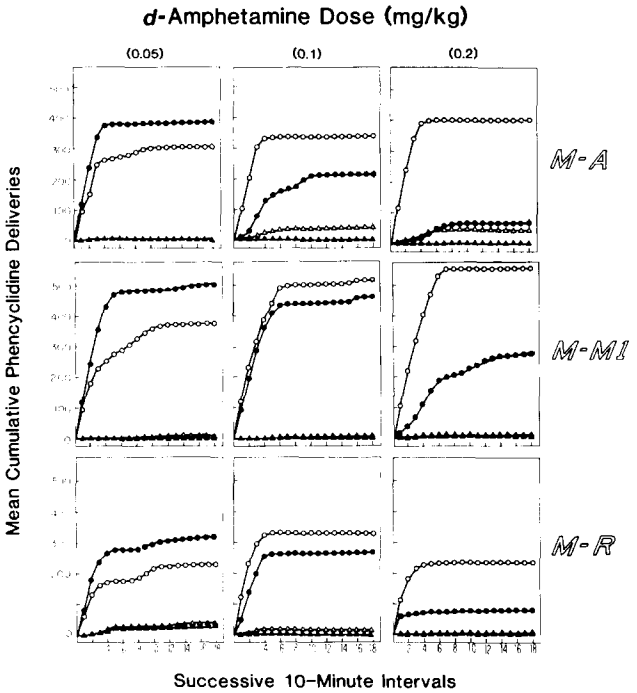

FIG. 5. Cumulative phencyclidine (circles) and water (triangles) deliveries are presented for three monkeys (M-A, M-M1 and M-R) over successive 10-min intervals during 3-hr sessions. Filled symbols—*d*-amphetamine (0.05, 0.1 and 0.2 mg/kg) was injected IM 10 min before the phencyclidine and water self-administration sessions. Open symbols—sessions immediately preceding those when *d*-amphetamine was injected. Each point represents a mean of five sessions. Phencyclidine (0.25 mg/ml) and water were available under a concurrent FR 16 schedule.

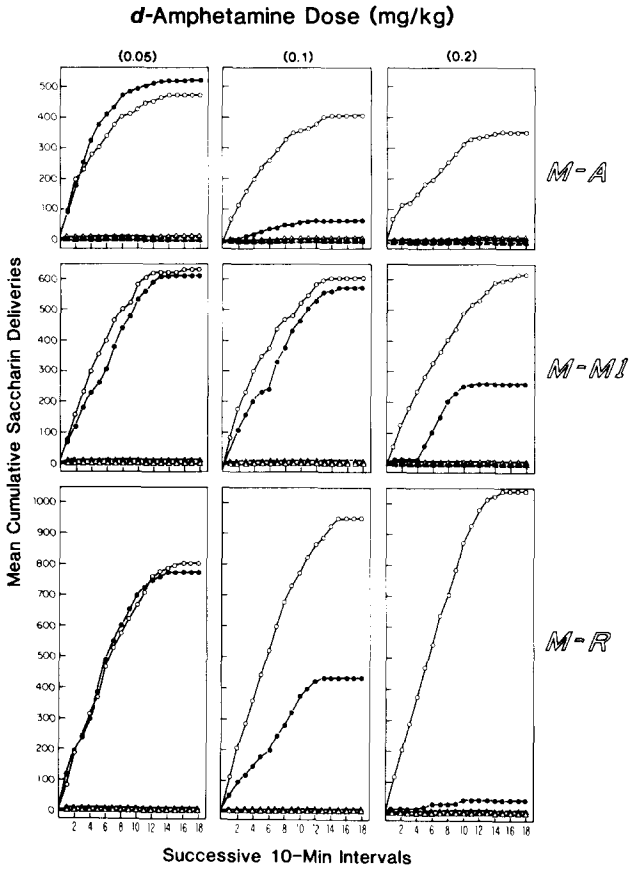

FIG. 6. Cumulative saccharin (circles) and water (triangles) deliveries are presented for three monkeys (M-A, M-M1 and M-R) over successive 10-min intervals during 3-hr sessions. Filled symbols—*d*-amphetamine (0.05, 0.1 and 0.2 mg/kg) was injected IM 10 min before the saccharin and water self-administration sessions. Open symbols—sessions immediately preceding those when *d*-amphetamine was injected. Each point represents a mean of five sessions. Saccharin (0.03% wt/vol) and water were available under a concurrent FR 16 schedule.

or water-maintained responding as a result of altering side positions every 21 days.

Figure 6 shows cumulative saccharin and water deliveries for the *d*-amphetamine pretreatment sessions at each dose and the sessions immediately preceding them. At the lowest dose (0.05 mg/kg), cumulative saccharin delivery functions were nearly identical. Decreases in total saccharin deliveries at the two higher doses were reflected in decreased responding during the first half of the session.

DISCUSSION

Previous investigations of the effects of pentobarbital on schedule-controlled behavior have shown rate increasing effects at low to moderate doses and dose-dependent rate decreases at higher doses (e.g., [26, 30–32, 48, 52]). Others have shown only rate decreasing effects (e.g., [33, 37, 38]). The present study extended previous findings to behavior maintained by orally-delivered phencyclidine and saccharin. Pentobarbital pretreatment increased phencyclidine-maintained behavior at the lowest dose; it had no systematic effect at the intermediate dose, and it produced no change or only a small decrease in the number of phencyclidine deliveries at the highest dose. In contrast, pentobarbital pretreatment resulted in substantial decreases in saccharin-maintained responding. These differences were probably not due to differences in control rates of responding [17, 18, 45]. As the control rates among the three monkeys differed substantially, and decreases in saccharin-maintained responding did not differ systematically as a function of control rate. Furthermore, the number of water deliveries did not increase as a result of pentobarbital pretreatment.

That pentobarbital pretreatment did not increase saccharin- or water-maintained behavior indicates that the increase in phencyclidine-reinforced behavior can not be attributed to nonspecific increases in behavior reinforced by a liquid substance. These data confirm other reports that there is a specific interaction between pentobarbital and phencyclidine [3, 14, 47, 52]. The interaction may be due to a number of factors or a combination of effects. For instance, pentobarbital may decrease or antagonize the reinforcing efficacy of phencyclidine, it may increase the reinforcing efficacy of the drug, or it may alter the metabolism and distribution of phencyclidine. It is unlikely that tolerance contributed to the effects of the drug combination, since (1) pentobarbital injections were given only after behavior had returned to baseline levels, (2) several days intervened between injections and (3) pentobarbital doses were given in a nonorderly sequence, but similar results were obtained among monkeys.

Generally, *d*-amphetamine, at low to moderate doses, affects schedule-controlled performance by decreasing high baseline rates of behavior and increasing low rates, and at high doses it decreases responding [5, 16, 28, 50]. In the present study, *d*-amphetamine produced results similar to those found with pentobarbital; at low doses *d*-amphetamine increased phencyclidine-maintained behavior. However, at higher doses it decreased the number of phencyclidine deliveries. Similarly, the low dose did not produce any systematic changes in saccharin-maintained behavior; however, higher doses resulted in dose-dependent decreases in the number of saccharin deliveries. The increases in phencyclidine-reinforced responding due to *d*-amphetamine pretreatment are assumed to result from interactive effects of the drugs rather than to nonspecific increases in behavior, as saccharin- and water-reinforced behavior did not increase after *d*-amphetamine. Rates of behavior maintained by saccharin were considerably higher than those maintained by phencyclidine in two of the three monkeys; however, similar relationships between saccharin- and drug-reinforced behavior were found in all three monkeys. Thus, it is unlikely that the differences were due to rate-dependent effects. Time course data for both pentobarbital and *d*-amphetamine pretreatment indicate that both the rate increasing and decreasing effects occurred early in the 3-hr sessions.

The effects of orally-delivered phencyclidine on phencyclidine-maintained behavior must also be considered in an analysis of the results of the present experiments. The effects of phencyclidine alone on schedule-controlled behavior have been described as being more like *d*-amphetamine than the barbiturates [1, 2, 14, 15, 39, 50]. Orally delivered phencyclidine has been shown to increase saccharin-maintained performance [9] and food-reinforced responding [11], while self-administration of higher concentrations decreased saccharin- and food-reinforced responding. This biphasic effect has previously been shown with parenterally-administered phencyclidine in the pigeon [49], mouse [41], and rat [35,39]. However, others have reported only dose-dependent decreases in responding under a food-reinforced chain fixed interval (FI) FR schedule in rhesus monkeys [2], and squirrel monkeys [14], and in FR responding in the rat [44]. Thus, the apparent interactions between phencyclidine and pentobarbital or *d*-amphetamine may have been greatly altered if a different phencyclidine concentration had been used.

The oral route of phencyclidine and saccharin self-administration provided a long-lasting preparation to study drug interactions. However, substantial shifts in the number of liquid deliveries occurred over time. For instance, from the time pentobarbital was initially tested until *d*-amphetamine injections were given, the baseline number of phencyclidine deliveries had increased nearly two-fold. This gradual increase in phencyclidine deliveries has previously been reported (cf., [8,13]), although it is not known whether it is due to tolerance, increased reinforcing efficacy of the drug, increased efficiency with the lip-operated drinking spouts or to a combination of factors. Given the long term instability of baselines, the most appropriate control condition appeared to be the sessions before drug injections rather than the saline pretreatment sessions.

In conclusion, the present experiment showed that oral phencyclidine self-administration was consistently elevated by low doses of pentobarbital or *d*-amphetamine. The same pentobarbital or *d*-amphetamine doses produced no effect or response-rate decreases in saccharin-maintained behavior. It is difficult to interpret the nature of this interaction, since each of the drugs produce both biphasic (increased responding at low doses and decreased responding at high doses) and rate-dependent effects. The generality of this result may be limited by the rate and pattern of responding, schedule of reinforcement, type of dependent measure (e.g., accuracy vs. response rate [4, 37, 47]), and type of drug. However, the present results emphasize the importance of considering drug interactions as a variable controlling drug self-administration.

ACKNOWLEDGEMENTS

The author wishes to thank Dana Stotz, Heidi Noetzel, James Pedersen and Kevin Ryan for their assistance in conducting the experiments. This work was supported by NIDA grant DA 02486 and a grant from the Committee on Problems of Drug Dependence, Inc. to M. E. Carroll and NIDA grant DA 00944 to R. A. Meisch.

REFERENCES

1. Balster, R. L. and J. B. Baird. Effects of phencyclidine and pentobarbital on spaced responding in mice. *Pharmacol Biochem Behav* **11:** 617–623, 1979.
2. Balster, R. L. and L. C. Chait. The behavioral pharmacology of phencyclidine. *Clin Toxicol* **9:** 513–528, 1976.
3. Balster, R. L. and L. D. Chait. The effects of phencyclidine on amphetamine stereotypy in rats. *J Pharmacol Eur* **48:** 445–450, 1978.
4. Branch, M. N. Behavior as a stimulus: Joint effects of *d*-amphetamine and pentobarbital. *J Pharmacol Exp Ther* **189:** 33–41, 1974.
5. Branch, M. N. and L. R. Gollub. A detailed analysis of the effects of *d*-amphetamine on behavior under fixed-interval schedules. *J Exp Anal Behav* **29:** 385–392, 1978.
6. Burns, R. S. and S. E. Lerner. Phencyclidine: An emerging drug problem. *Clin Toxicol* **9:** 473–475, 1976.
7. Carroll, M. E. Oral self-administration of phencyclidine analogs by rhesus monkeys: Conditioned taste and visual reinforcers. *Psychopharmacology (Berlin)* **78:** 116–120, 1982.
8. Carroll, M. E. Rapid acquisition of oral phencyclidine self-administration in food-deprived and food-satiated rhesus monkeys: Concurrent phencyclidine and water choice. *Pharmacol Biochem Behav* **17:** 341–346, 1982.
9. Carroll, M. E. Tolerance to the behavioral effects of orally self-administered phencyclidine. *Drug Alcohol Depend* **9:** 213–224, 1982.
10. Carroll, M. E. and R. A. Meisch. Etonitazene as a reinforcer: Oral intake of etonitazene by rhesus monkeys. *Psychopharmacology (Berlin)* **59:** 225–229, 1978.
11. 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.
12. 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.
13. Carroll, M. E. and D. C. Stotz. Increased phencyclidine self-administration due to food deprivation: Interaction with concentration and training conditions. A manuscript submitted for publication 7/83.
14. Chait, L. D. and R. L. Balster. Effects of combinations of phencyclidine and pentobarbital on schedule-controlled behavior in the squirrel monkey. *Pharmacol Biochem Behav* **9:** 201–205, 1978.
15. Chait, L. D. and R. L. Balster. Interaction between phencyclidine and pentobarbital in several species of laboratory animals. *Commun Psychopharmacol* **2:** 351–356, 1978.

16. Clark, F. C. and B. J. Steele. Effects of *d*-amphetamine on performance under a multiple schedule in the rat. *Psychopharmacologia* **9:** 157–159, 1966.
17. Dews, P. B. A behavioral effect of amobarbital. *Arch Exp Pathol Pharmak* **248:** 296–307, 1964.
18. Dews, P. B. The effects of pentobarbital, methamphetamine, and scopolamine on performances in pigeons involving discriminations. *J Pharmacol Exp Ther* **115:** 380–389, 1955.
19. Domino, E. F. Neurobiology of phencyclidine (Sernyl), a drug with an unusual spectrum of pharmacological activity. *Int Rev Neurobiol* **6:** 303–347, 1964.
20. Garey, R. E., L. A. Weisberg and R. G. Heath. Phencyclidine: An overview. *J Psychedel Drugs* **9:** 280–285, 1977.
21. Garza, R., de la and C. E. Johanson. Effects of haloperidol and psysostigmine on self-administration of local anesthetics. *Pharmacol Biochem Behav* **17:** 1295–1299, 1982.
22. Goldberg, S. R., F. Hoffmeister and U. U. Schlichting. Morphine antagonist: Modification of behavioral effects by morphine dependence. In: *Drug Addiction: I Experimental Pharmacology*, edited by J. M. Singh, L. Miller and H. Lal. Mount Kisco, NY: Futura Publishing Co., 1972, pp. 31–48.
23. Goldberg, S. R., F. Hoffmeister, U. U. Schlichting and W. Wuttke. Aversive properties of nalorphine and naloxone in morphine-dependent rhesus monkeys. *J Pharmacol Exp Ther* **179:** 268–276, 1971.
24. 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.
25. Goldberg, S. R., J. H. Woods and C. R. Schuster. Nalorphine-induced changes in morphine self-administration in rhesus monkeys. *J Pharmacol Exp Ther* **176:** 464–471, 1971.
26. Hanson, H. M., J. J. Witoslawski and E. H. Campbell. Drug effects in squirrel monkeys trained on a multiple schedule with a punishment contingency. *J Exp Anal Behav* **10:** 565–569, 1967.
27. Harrigan, S. E. and D. A. Downs. Continuous intravenous naltrexone effects on morphine self-administration in rhesus monkeys. *J Pharmacol Exp Ther* **204:** 481–486, 1978.
28. Heffner, T. G., R. B. Drawbough and M. J. Zigmond. Amphetamine and operant behavior in rats: Relationship between drug effect and control response rate. *J Comp Physiol Psychol* **86:** 1037–1039, 1974.
29. Henningfield, J. E. and R. A. Meisch. Drinking device for rhesus monkeys. *Pharmacol Biochem Behav* **4:** 609–610, 1976.
30. Herrnstein, R. J. and W. H. Morse. Selective action of pentobarbital on component behaviors of a reinforcement schedule. *Science* **124:** 367–368, 1956.
31. Jensen, M. A. and T. I. Thompson. Interaction of methadone and pentobarbital on chained fixed-interval performance in pigeons. *Pharmacol Biochem Behav* **16:** 271–278, 1982.
32. Laties, V. G. and B. Weiss. Influence of drugs on behavior controlled by internal and external stimuli. *J Pharmacol Exp Ther* **152:** 388–396, 1966.
33. Leander, J. D. and D. E. McMillan. Rate-dependent effects of drugs. I. Comparisons of *d*-amphetamine, pentobarbital and chlorpromazine on multiple and mixed schedules. *J Pharmacol Exp Ther* **188:** 726–739, 1974.
34. Lundberg, G. D., R. C. Gupta and S. H. Montgomery. Phencyclidine: Patterns seen in street drug analysis. *Clin Toxicol* **9:** 503–511, 1976.
35. Martin, P., A. Griffin and M. Rivers. Behavioral tolerance and loss of tolerance to phencyclidine in rats. A paper presented at the 88th Annual Meeting of the American Psychological Association, September, 1980, Montreal, Canada.
36. Meisch, R. A. and J. E. Henningfield. Drinking of ethanol by rhesus monkeys: Experimental strategies for establishing ethanol as a reinforcer. In: *Alcohol Intoxication and Withdrawal: Experimental Studies, III* b, edited by M. M. Gross. New York: Plenum, 1977, pp. 443–463.
37. Moerschbaecher, J. M. and D. M. Thompson. Effects of phencyclidine, pentobarbital and *d*-amphetamine on the acquisition and performance of conditional discriminations in monkeys. *Pharmacol Biochem Behav* **13:** 887–894, 1980.
38. Morse, W. H. The use of operant conditioning techniques for evaluating the effects of barbiturates on behavior. In: *The First Hahnemann Symposium on Psychosomatic Medicine*. Philadelphia: Lea and Febiger, 1962, pp. 275–281.
39. Murray, T. F. The effects of phencyclidine on operant behavior in the rat: Biphasic effect and tolerance development. *Life Sci* **22:** 195–201, 1978.
40. Petersen, R. C. and R. C. Stillman. Phencyclidine: An overview. In: *Phencyclidine (PCP) Abuse: An Appraisal*, edited by R. C. Petersen and R. C. Stillman. Rockville, MD: Department of Health, Education and Welfare, 1978, pp. 1–17.
41. Pinchasi, I., S. Maayani and M. Sokolovsky. On the interaction of drugs with the cholinergic nervous system. III. Tolerance to phencyclidine derivatives—*in vivo* and *in vitro* studies. *Biochem Pharmacol* **26:** 1671–1679, 1977.
42. Poling, A., J. Cleary, K. Jackson and S. Wallace. *d*-Amphetamine and phencyclidine alone and in combination: Effects on fixed-ratio and interresponse-time-greater-than-t-responding of rats. *Pharmacol Biochem Behav* **15:** 357–361, 1981.
43. Pryor, G. T., S. Husain, F. Larsen, C. E. McKenzie, J. D. Carr and M. C. Braude. Interactions between Δ^9-tetrahydrocannabinol and phencyclidine hydrochloride in rats. *Pharmacol Biochem Behav* **6:** 123–136, 1977.
44. Ruffing, D. M. and E. F. Domino. First dose behavioral tolerance to phencyclidine on food-rewarded bar pressing in the rat. *Psychopharmacology (Berlin)* **69:** 1–4, 1980.
45. Smith, C. B. Effects of *d*-amphetamine upon operant behavior of pigeons: Enhancement by reserpine. *J Pharmacol Exp Ther* **146:** 167–174, 1964.
46. Stone, C. J. and R. B. Forney. The effects of phencyclidine on ethanol and sodium hexobarbital in mice. *Toxicol Appl Pharmacol* **40:** 177–183, 1977.
47. Thompson, D. M. and J. M. Moerschbaecher. Phencyclidine in combination with pentobarbital: Supra-additive effects on complex operant behavior in patas monkeys. *Pharmacol Biochem Behav* **16:** 159–165, 1982.
48. Waller, M. B. and W. H. Morse. Effects of pentobarbital on fixed-ratio reinforcement. *J Exp Anal Behav* **6:** 125–130, 1963.
49. Wenger, G. R. The effect of phencyclidine and ketamine on schedule-controlled behavior in the pigeon. *J Pharmacol Exp Ther* **196:** 172–179, 1976.
50. Wenger, G. R. and P. B. Dews. The effects of phencyclidine, ketamine, *d*-amphetamine and pentobarbital on schedule-controlled behavior in the mouse. *J Pharmacol Exp Ther* **196:** 616–623, 1976.
51. Woods, J. H., D. A. Downs and J. Carney. Behavioral functions of narcotic antagonists: Response-drug contingencies. *Fed Proc* **34:** 1777–1784, 1975.
52. Woolverton, W. L. and R. L. Balster. Effects of combinations of phencyclidine and pentobarbital on fixed-interval performance in rhesus monkeys. *J Pharmacol Exp Ther* **217:** 611–618, 1981.