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Differential Effects of Phencyclidine and MDA on Complex Operant Behavior in Monkeys[1]

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THOMPSON, D. M. AND J. M. MOERSCHBAECHER. *Differential effects of phencyclidine and MDA on complex operant behavior in monkeys.* PHARMACOL BIOCHEM BEHAV 21(3)453–457, 1984.—In one component of a multiple schedule, patas monkeys acquired a different four-response chain each session by responding sequentially on three keys in the presence of four geometric forms (learning). In the other component, the four-response chain was the same each session (performance). The response chain in each component was maintained by food presentation under a fixed-ratio schedule. Errors produced a brief timeout but did not reset the chain. With increasing doses of phencyclidine the overall response rate in each schedule component decreased, the percent errors in each component increased, and there was less within-session error reduction (acquisition) in the learning component. MDA (3,4-methylenedioxyamphetamine), a hallucinogen that is self-administered in nonhuman primates, was similar to phencyclidine in producing dose-related rate-decreasing effects in both schedule components. Unlike phencyclidine, however, MDA had little or no effect on accuracy in either learning or performance.

Repeated acquisition Response chains Multiple schedule Phencyclidine MDA Key press Monkeys

PHENCYCLIDINE is often said to have stimulant, depressant, and hallucinogenic or psychotomimetic properties [3, 7, 8, 9, 14, 20, 21]. To investigate this "unusual spectrum of pharmacological activity" [8], we recently conducted a series of experiments that compared the effects of phencyclidine, *d*-amphetamine, and pentobarbital on complex operant behavior in monkeys [17, 18, 32, 33, 34]. In one such experiment, for example, patas monkeys were required to respond sequentially on three keys in the presence of four geometric forms [34]. Responding was maintained by food presentation under a multiple schedule of repeated acquisition and performance. In the repeated acquisition or learning component, the response sequence (chain) was different each session, whereas in the performance component, the chain was the same each session. When phencyclidine was administered (IM), the overall response rate decreased and the percent errors increased in both schedule components with increasing doses. In contrast, *d*-amphetamine generally decreased rate and increased errors in learning, but increased rate and had no effect on accuracy in performance. Previous research using the same [33] or a related [18] multiple-schedule baseline has shown that the effects of pentobarbital on overall rate and percent errors were generally similar to those of phencyclidine, except that performance accuracy was relatively unaffected by pentobarbital.

In the present research, a multiple schedule of repeated acquisition and performance of response chains in monkeys served as a behavioral baseline to compare phencyclidine with 3,4-methylenedioxyamphetamine (MDA), which is usually classified as a hallucinogenic agent [22, 23, 27]. MDA was selected because it has LSD-like effects on schedule-controlled responding [13] and because it is the only hallucinogen, besides phencyclidine, that has been clearly demonstrated to be a reinforcer for self-administration behavior in nonhuman primates [11,12].

METHOD

Subjects

Three adult female patas monkeys served. All subjects had experimental histories involving the repeated acquisition and performance of response chains. The subjects were maintained at about 90% of their free-feeding weights (range 5.9 to 6.8 kg) on a diet consisting of Noyes banana-flavored food pellets, Purina Monkey Chow, fruit, and vitamins. The pellets were either earned during the experimental session

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or, when necessary, provided after the session. Monkey Chow, fruit, and vitamins were given to each subject after the daily session. Water was continuously available.

Apparatus

Each subject was housed in a primate cage (Research Equipment Co., model LC-1001) measuring 66 cm by 74.9 cm by 93.9 cm. A removable response panel (BRS/LVE, model TIP-001), measuring 56 cm by 21.5 cm by 45 cm, was attached to the side of each subject's cage during the experimental session. Three response keys (BRS/LVE, press plate model PPC-012) were centered and aligned horizontally on the panel. The keys were spaced 11.5 cm apart, center to center, and 51.5 cm from the cage floor. Each key required a minimum force of 0.29 N for activation. An in-line projector (BRS/LVE, model IC 901-696), mounted behind each key, could project colors and geometric forms onto the key. A yellow pilot lamp (1.2 cm in diameter) was mounted 22.5 cm to the right and 17 cm up from the center of the right-hand key. A press on this lamp (0.34 N minimum force) closed a switch on which it was mounted. A food pellet aperture (5.5 cm in diameter) was located 15.5 cm to the right and 8 cm down from the center of the right-hand key. The response panels were connected to solid-state scheduling and recording equipment located in an adjacent room.

Procedure

Baseline. A multiple schedule with learning and performance components served as the baseline. During the *learning* component, one of four geometric forms (horizontal line, triangle, vertical line, circle) was projected onto a red background on all three response keys. The subject's task was to learn a four-response chain by pressing the correct key in the presence of each form, e.g., horizontal line—Left correct; triangle—Right correct; vertical line—Center correct; circle—Right correct. When the chain was completed, the keylights turned off and the yellow lamp over the food pellet aperture was illuminated. A press on the yellow lamp then reset the chain. The four-response chain was maintained by food presentation under an FR 5 schedule; i.e., every fifth completion of the chain produced a food pellet (500 mg) when the yellow lamp was pressed. When the subject pressed an incorrect key (e.g., the left or right key when the center key was correct), the error was followed by a 5-sec timeout. During the timeout, the keys were dark and responses were ineffective. An error did not reset the chain; i.e., the stimuli on the keys after the timeout were the same as before the timeout.

To establish a steady state of repeated acquisition, the four-response chain in the learning component was changed from session to session. The chains were carefully selected to be equivalent in several ways and there were restrictions on their ordering across sessions [31]. An example of a typical set of six chains is as follows: Left-Right-Center-Right (LRCR), CLRL, LRLC, RCRL, CLCR, RCLC; the order of the associated forms was always the same: horizontal line, triangle, vertical line, circle (reinforcement).

During the *performance* component of the multiple schedule, the four geometric forms were projected on a green background and the four-response chain remained the same (LCLR) from session to session. In all other aspects (FR 5 schedule of food reinforcement, timeout duration of 5 sec, etc.), the performance component was identical to the learning component.

Sessions were conducted daily, Monday through Friday. Each session began in the learning component, which then alternated with the performance component after 10 reinforcements or 15.5 min (±30 sec), whichever occurred first. Each session was terminated after 100 reinforcements or 2 hr, whichever occurred first. The data for each session were analyzed in terms of (a) the overall response rate (total responses/min, excluding timeouts) in each component and (b) the overall accuracy or percent errors [(errors/total responses) × 100] in each component. In addition to these measures based on session totals, within-session changes in responding were monitored by a cumulative recorder. For example, acquisition of the response chain in the learning component was indicated by within-session error reduction, i.e., a decrease in the frequency of errors (per reinforcement) as the session progressed.

Drug testing. After baseline stabilization (20–30 sessions), dose-effect data were obtained for phencyclidine hydrochloride and *dl*-3,4-methylenedioxyamphetamine (MDA) hydrochloride. Dose-effect curves were determined twice for each drug, in the following order: phencyclidine, MDA, MDA, phencyclidine. The doses of each drug were tested in a mixed order. The drugs were dissolved in saline and injected IM (*gluteus m.*) 5 min presession. Drug sessions were generally conducted on Tuesdays and Fridays, with control sessions (saline, IM 5 min presession) occurring on Thursdays, and baseline sessions (no injections) on Mondays and Wednesdays. The volume of each injection was 0.05 ml/kg body weight. All doses are expressed in terms of the salt of each drug.

RESULTS

Figure 1 shows the effects of varying doses of phencyclidine and MDA on the overall response rate and overall accuracy in each component of the multiple schedule for each subject. A drug was considered to have an effect to the extent that the dose data fell outside of the control range. Despite individual differences in the control ranges, phencyclidine decreased the overall response rate and increased the percent errors in both schedule components with increasing doses. The rate-decreasing and error-increasing effects at a given dose of phencyclidine were generally greater in the learning component than in the performance component. MDA was similar to phencyclidine in producing dose-related decreases in overall response rate in both schedule components, though MDA was less potent (on a mg/kg basis) in this regard. Unlike phencyclidine, however, MDA had little or no effect on percent errors in either schedule component. This was true even in cases where the rate-decreasing effects of the two drugs were approximately equivalent (e.g., Monkey B, learning: phencyclidine, 0.3 mg/kg and MDA, 1 mg/kg).

Figure 2 shows the pattern of responding during a representative control session (one that approximated the mean for both overall response rate and overall accuracy in each schedule component) and during two drug sessions for Monkey EL. In the control record (top), errors decreased in frequency in the learning component as the session progressed; i.e., acquisition occurred. After the first 5 min of this session, there were long runs of correct responses that were separated by brief pauses in both components and virtually no errors were made. When a high dose of phencyclidine (0.17 mg/kg) was administered, responding was initially disrupted in both schedule components, as indicated by long

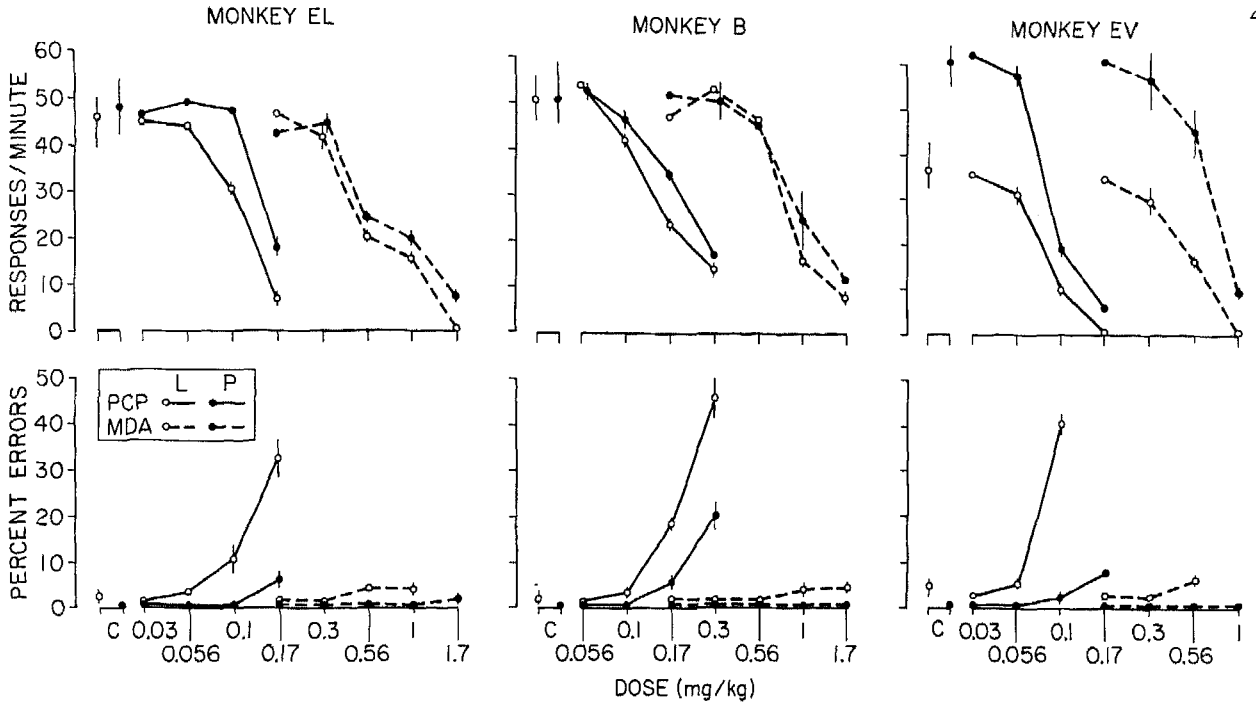

FIG. 1. Effects of varying doses of phencyclidine (PCP) and MDA on the overall response rate and percent errors in the learning (L) and performance (P) components of the multiple schedule for each subject. The points with vertical lines at C indicate the mean and range for 16 control (saline) sessions; the points without vertical lines (percent errors in performance) indicate that the range is encompassed by the point. The points with vertical lines in the dose-effect curves indicate the mean and range for two determinations; the points without vertical lines indicate either a single determination (at the lower doses) or an instance in which the range is encompassed by the point. Points for percent errors have been omitted in cases where the overall response rate was virtually zero.

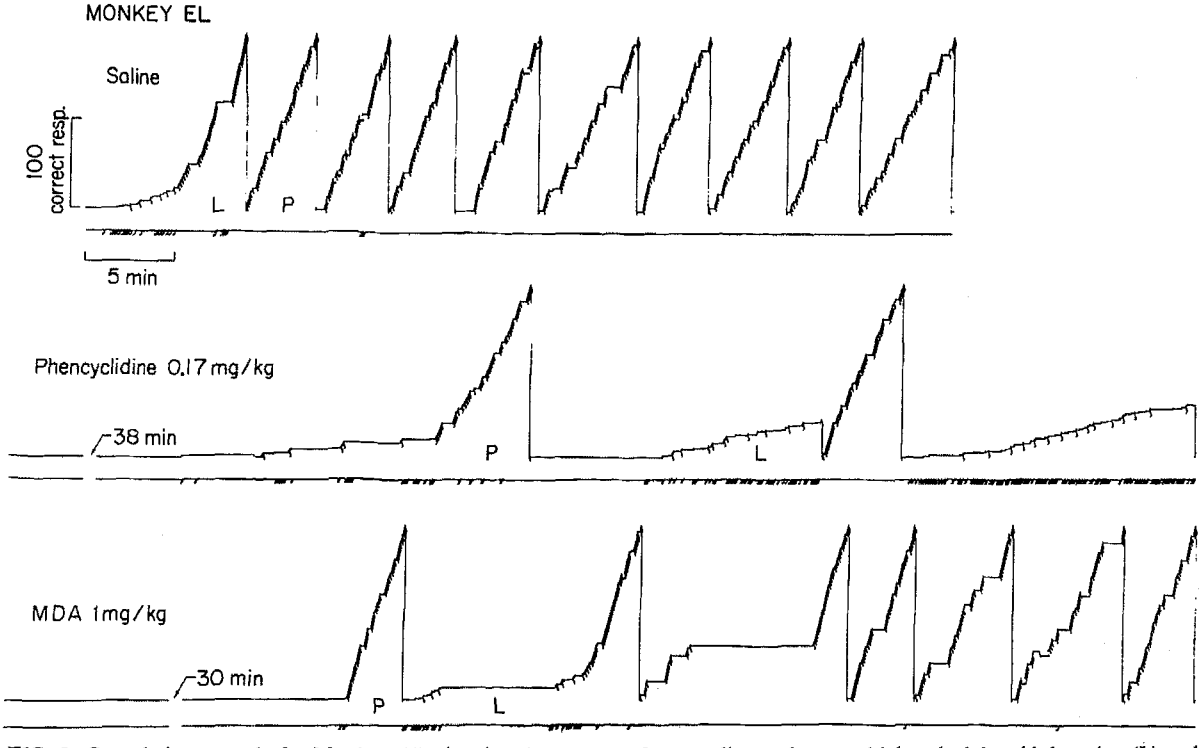

FIG. 2. Cumulative records for Monkey EL showing the pattern of responding under a multiple schedule with learning (L) and performance (P) components during a representative control session (saline) and during sessions preceded by injections of phencyclidine (0.17 mg/kg) and MDA (1 mg/kg). The top record (saline) represents a complete session (100 reinforcements). In the lower two records, periods of no responding (38 and 30 min, indicated by arrows) and the last cycle of the multiple schedule have been omitted. The response pen stepped upward with each correct response and was deflected downward each time the four-response chain was completed. Errors are indicated by the event pen (below each record), which was held down during each timeout. A change in components of the multiple schedule reset the stepping pen.

TABLE 1

SUMMARY OF DRUG EFFECTS ON REPEATED ACQUISITION (LEARNING) AND PERFORMANCE IN MONKEYS*

	% Errors (at high doses)		Overall Response Rate (at lower doses)	
	Learning	Performance	Learning	Performance
Phencyclidine	increase	increase	decrease	decrease
Pentobarbital	increase	little or no effect	decrease	decrease
d-Amphetamine	increase	little or no effect	decrease	increase
MDA	little or no effect	little or no effect	decrease	decrease

*Results are from the present study and previous research [17, 18, 32, 33, 34]; all drugs were administered IM.

periods of pausing and large error-increasing effects. As the session progressed, the disruptive effects on rate and accuracy persisted in the learning component, with no sign of acquisition, but not in the performance component, where the pattern of responding returned to control. When a high dose of MDA (1 mg/kg) was administered, the initial effect was similar to that produced by phencyclidine (0.17 mg/kg), namely, a long period of no responding in both schedule components. However, unlike phencyclidine, MDA did not disrupt accuracy in either learning or performance when responding resumed, although some pausing was still evident. In general, these within-session effects of phencyclidine and MDA in Monkey EL were replicated in the other two subjects.

DISCUSSION

The rate-decreasing and error-increasing effects obtained in the present study when phencyclidine was administered are consistent with previous research showing that phencyclidine produces dose-related disruptive effects on behavior in various discrimination tasks. For example, Brown and Bass [6] found that phencyclidine disrupted the performance of rhesus monkeys in an oddity-discrimination task; it decreased the rate of correct responding in a dose-dependent manner and, at higher doses, increased errors. In baboons trained to respond in a standard psychophysical procedure to determine auditory and visual thresholds, high doses of phencyclidine completely disrupted performance [15]. More recently, McMillan [16] reported that phencyclidine disrupted the performance of pigeons in a delayed matching-to-sample task; matching accuracy was decreased at doses that decreased response rate. Phencyclidine has also been reported to disrupt the acquisition [29] and performance [30] of a brightness discrimination in rats. Finally, in research more closely related to the present study, it was found that phencyclidine disrupted the behavior of patas monkeys under a multiple schedule of repeated acquisition and performance of either conditional discriminations [18] or four-response sequences [17, 33, 34]. As in the present study, with increasing doses of phencyclidine the overall response rate in each schedule component decreased, the percent errors in each component increased, and there was less within-session error reduction (acquisition) in the learning component. The performance component tended to be less sensitive than the learning component to the drug effects.

MDA was found to be similar to phencyclidine in producing dose-related decreases in overall response rate in both schedule components, but, unlike phencyclidine, MDA had little or no effect on overall accuracy in either schedule component. The rate-decreasing effects of MDA extend the generality of a previous finding obtained with less complex schedule-controlled behavior; namely, Harris *et al.* [13] reported that MDA produced a dose-related decrease in overall rate in rats responding on a single lever under an FR schedule. That MDA had virtually no error-increasing effect was unexpected, however, on the basis of reported similarities between MDA and phencyclidine. For example, both drugs have been reported to produce hallucinogenic or psychotomimetic effects in man [7, 8, 9, 14, 20, 21, 23, 27] and both drugs have been shown to maintain self-administration behavior in nonhuman primates [11,12]. On the other hand, Shannon [25] has reported that MDA and phencyclidine differ in their discriminative stimulus properties in rats. On the basis of such drug-discrimination data, one might expect that MDA and phencyclidine would have different effects on accuracy in the present study, although the nature of the difference would be difficult to predict.

The present results with MDA are also in contrast to the disruptive effects on accuracy produced by LSD in monkeys responding in various discrimination tasks [6, 10, 24, 26]. While this difference suggests that MDA is less disruptive than LSD, a direct comparison between these two drugs in the same discrimination task is needed. Research with pigeons has indicated that LSD may either increase [5], decrease [28] or have no effect [2, 4, 19, 35] on accuracy, depending on procedural variables, such as the type of discriminative stimuli used [1].

In summary, the present study is the last in a series of experiments [17, 18, 32, 33, 34] that has attempted to characterize the effects of phencyclidine on complex operant behavior in monkeys by comparing phencyclidine with *d*-amphetamine, pentobarbital, and MDA. The rationale for comparing phencyclidine with these three drugs is based on previous reports that phencyclidine has stimulant, depressant, and hallucinogenic properties [3, 7, 8, 9, 14, 20, 21]. Table 1 summarizes the major findings from this series of experiments; the general trends are indicated, though

there were occasional exceptions. As can be seen, of the three comparison drugs, phencyclidine is most similar to pentobarbital, when the effects on both overall accuracy and overall rate in both schedule components are considered. It should also be noted that almost all of the differences among the four drugs are seen in the effects on accuracy rather than rate. In regard to accuracy, phencyclidine is the most disruptive, whereas MDA is the least.

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