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Effects of Phencyclidine, Ketamine and MDMA on Complex Operant Behavior in Monkeys[1]

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THOMPSON, D. M., P. J. WINSAUER AND J. MASTROPAOLO. *Effects of phencyclidine, ketamine and MDMA on complex operant behavior in monkeys.* PHARMACOL BIOCHEM BEHAV **26**(2) 401–405, 1987.—In one component of a multiple schedule, patas monkeys acquired a different four-response chain each session by responding sequentially on three levers in the presence of four numerals (acquisition). 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. After IM administration, phencyclidine, ketamine, and MDMA (3,4-methylenedioxymethamphetamine or "ecstasy") each produced dose-related decreases in overall response rate in both schedule components, though ketamine and MDMA were less potent (on a mg/kg basis) than phencyclidine. At high doses of each drug, the marked decrease in overall response rate was due primarily to a long initial pause. Ketamine was similar to phencyclidine in producing dose-related increases in percent errors in both schedule components, but the maximal error-increasing effect was considerably smaller with ketamine. This quantitative difference appeared to be related to the shorter duration of ketamine's effects on accuracy. Unlike phencyclidine and ketamine, MDMA had no effect on accuracy in either acquisition or performance. The results indicate that MDMA disrupts complex operant behavior to a lesser extent than phencyclidine-type drugs.

Repeated acquisition Response chains Multiple schedule Phencyclidine Ketamine MDMA Patas monkeys

PREVIOUS research in this laboratory has attempted to characterize the effects of phencyclidine on complex operant behavior in monkeys by comparing phencyclidine with *d*-amphetamine, pentobarbital and MDA (3,4-methylenedioxyamphetamine) [7, 8, 16–19]. The rationale for comparing phencyclidine with these three drugs is based on previous reports that phencyclidine has stimulant, depressant, and hallucinogenic properties (see review in [19]). In one series of experiments [16–19], patas monkeys were required to respond sequentially on three keys in the presence of four geometric forms. Responding was maintained by food presentation under a multiple schedule of repeated acquisition and performance. In the acquisition component, the response sequence (chain) was different each session, whereas in the performance component, the chain was the same each session. In general, each of the four drugs (administered IM) produced dose-related decreases in the overall response rate in both components of the multiple schedule. The only exception was that the lower doses of *d*-amphetamine tended to increase the overall response rate in the performance component. The four drugs differed to a greater extent in their effects on accuracy. At high doses, phencyclidine increased percent errors in both acquisition and performance, whereas pentobarbital and *d*-amphetamine increased percent errors in acquisition but had little or no effect on performance accuracy. In contrast, MDA had little or no effect on accuracy in either acquisition or performance.

The finding that MDA had virtually no error-increasing effect was unexpected 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 (see review in [19]) and both drugs have been shown to maintain self-administration behavior in nonhuman primates [5,6]. In view of this unexpected finding with MDA, the present research compared the effects of a related drug, MDMA (3,4-methylenedioxymethamphetamine or "ecstasy"), and phencyclidine in patas monkeys responding under a multiple schedule of repeated acquisition and performance. Little is known about the effects of MDMA on schedule-controlled behavior in animals, though one might reasonably assume that such effects would be similar to those of MDA, given the close structural similarity between the two drugs.

To provide an additional comparison, the present re-

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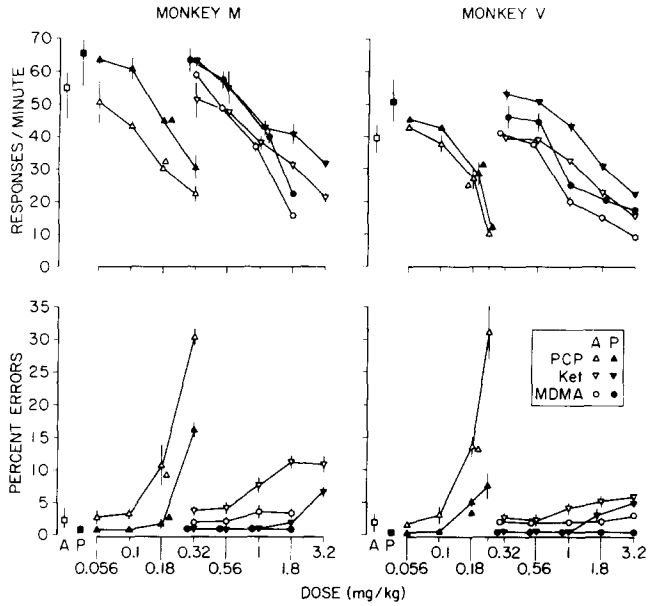

FIG. 1. Effects of varying doses of phencyclidine (PCP), ketamine (Ket) and MDMA on the overall response rate and percent errors in the acquisition (A) and performance (P) components of the multiple schedule for each subject. The unconnected points with vertical lines at the far left in each panel indicate the mean and range for 12 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 3.2 mg/kg in Monkey V) or an instance in which the range is encompassed by the point. The unconnected triangles at 0.18 mg/kg of phencyclidine show a redetermination after the other two drugs were tested.

search also examined the effects of ketamine, a phencyclidine analog. Although it is generally true that the behavioral effects of ketamine and phencyclidine are qualitatively similar [1], this is not always the case. For example, Byrd [3] has reported that in squirrel monkeys responding under a fixed-interval (FI) schedule of shock presentation, phencyclidine had amphetamine-like effects but ketamine did not. With phencyclidine, the dose-effect curve was inverted-U shaped, with increases in overall response rate at intermediate doses. In contrast, ketamine produced only dose-related decreases in the overall rate of FI responding. Accordingly, it seemed worthwhile to determine the extent to which ketamine has phencyclidine-like effects on complex operant behavior.

METHOD

Subjects

Two adult male patas monkeys served. Both subjects had experimental histories involving the repeated acquisition of response chains. The subjects were maintained at about 90% of their free-feeding weights (7.7 and 9.1 kg) on a diet consisting of Noyes banana-flavored food pellets, Purina Monkey Chow, fruit, and vitamins. The pellets were earned during the experimental sessions, and the Monkey Chow, fruit, and vitamins were provided after the session each day. Water was continuously available.

Apparatus

The apparatus has been described in detail elsewhere [20]. Briefly, each subject was housed in a primate cage with a response panel attached to one side of the cage. An array of three recessed levers was aligned horizontally to the right of the vertical midline of the panel. An in-line projector, mounted above each lever, was used to project the discriminative stimuli (white numerals on a black or green background). To the left of the three levers was an additional lever, which operated a pellet dispenser; a green pilot lamp was mounted below this food lever. The response panels were connected (via a Med Associates interface) to scheduling and recording equipment (an Apple IIe computer, programmed in BASIC, and a cumulative recorder) located in an adjacent room.

Procedure

Baseline. A multiple schedule with acquisition and performance components served as the baseline. During the *acquisition* component, one of four numerals (1, 2, 3, 4) was projected onto a black background above all three response levers. The subject's task was to learn a four-response chain by pressing the correct lever in the presence of each numeral, e.g., 1—Left correct; 2—Right correct; 3—Center correct; 4—Right correct. When the chain was completed, the lights above the response levers turned off and the green lamp below the food lever was illuminated. A press on the food lever 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 pellet (500 mg) when the food lever was pressed. When the subject pressed an incorrect lever (e.g., the left or right lever when the center lever was correct), the error was followed by a 5-sec timeout. During the timeout, the lights above the levers were off and responses were ineffective. An error did not reset the chain; i.e., the stimuli above the response levers after the timeout were the same as before the timeout.

To establish a steady state of repeated acquisition, the four-response chain in the acquisition 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 [15]. 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 numerals was always the same: 1, 2, 3, 4 (reinforcement).

During the *performance* component of the multiple schedule, the four numerals 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 acquisition component.

Sessions were conducted daily, Monday through Friday. Each session began in the acquisition component, which then alternated with the performance component after 10 reinforcements or 15 min, 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

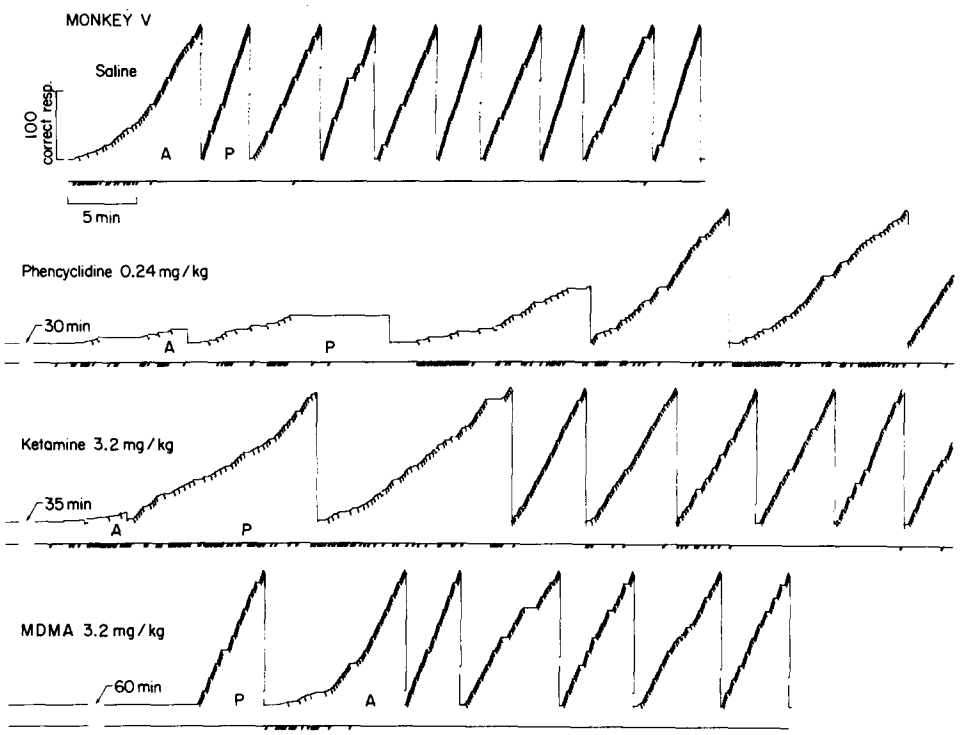

FIG. 2. Cumulative records for Monkey V showing the pattern of responding under a multiple schedule with acquisition (A) and performance (P) components during a representative control session (saline) and during sessions preceded by injections of phencyclidine (0.24 mg/kg), ketamine (3.2 mg/kg), and MDMA (3.2 mg/kg). The saline record represents a complete session (100 reinforcements). In the drug records, periods of no responding (30, 35 and 60 min, indicated by arrows) and the last 12.5 min of the session (phencyclidine and ketamine) 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 (after 10 reinforcements or 15 min) reset the stepping pen.

responding were monitored by the cumulative recorder and computer. For example, acquisition of a response chain was indicated by within-session error reduction, i.e., a decrease in the frequency of errors (per reinforcement) in the acquisition component as the session progressed.

Drug testing. After baseline stabilization (20 sessions), dose-effect data were obtained for phencyclidine hydrochloride, *dl*-3,4-methylenedioxymethamphetamine (MDMA) hydrochloride, and ketamine hydrochloride (Ketalar), in that order. The drugs were dissolved in saline and injected IM *(gluteus m.)* 10 min presession. The doses of each drug were tested in a mixed order and there were generally two determinations for each dose. All doses are expressed in terms of the salt of each drug.

Throughout testing, drug sessions were generally conducted on Tuesdays and Fridays, with control sessions (saline, IM 10 min presession) occurring on Thursdays, and baseline sessions (no injections) on Mondays and Wednesdays. The volume of each injection (drug or saline) was 0.05 ml/kg body weight. Approximately 7 days of baseline sessions intervened between the end of a series of injections with one drug and the start of a series with another. Finally, the effects of an intermediate dose of phencyclidine (0.18 mg/kg) were redetermined after the other two drugs were tested. This probe was conducted to determine whether the baseline sensitivity had changed as a result of the subjects' drug history.

RESULTS

Figure 1 shows the effects of varying doses of phencyclidine, ketamine and MDMA 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 differences in the control ranges for acquisition and performance, phencyclidine decreased overall response rate and increased percent errors in both schedule components with increasing doses. Though less potent (on a mg/kg basis) than phencyclidine, both ketamine and MDMA were similar to phencyclidine in producing dose-related decreases in overall response rate in both schedule components. Note, however, that at a given dose in a given component, the rate-decreasing effects tended to be greater with MDMA than with ketamine. Although ketamine was similar to phencyclidine in producing dose-related increases in percent errors in both schedule components, the maximal error-increasing effect was considerably smaller with ketamine. This was true even in cases where the rate-decreasing effects of the two drugs were approximately equivalent (e.g., Monkey M, acquisition: phencyclidine, 0.32 mg/kg and ketamine,

TABLE 1

PERCENT ERRORS IN THE FIRST ACQUISITION AND PERFORMANCE COMPONENTS WITH RESPONDING AT THE HIGHEST DOSE OF EACH DRUG*

	Monkey M			Monkey V		
	Dose (mg/kg)	Acq.	Perf.	Dose (mg/kg)	Acq.	Perf.
Control Range†		2.4–9.2	0–1.5		2.0–11.1	0–0.5
PCP	0.32	60.1	57.9	0.24	53.3	29.8
Ketamine	3.2	52.4	44.2	3.2	57.6	17.0
MDMA	1.8	7.1	0.5	3.2	8.3	0

*First determinations.
†Based on 12 saline sessions.

3.2 mg/kg). Unlike phencyclidine and ketamine, MDMA had no effect on percent errors in either schedule component even at doses that produced marked decreases in overall response rate. In general, the effects of 0.18 mg/kg of phencyclidine were replicated after the other two drugs were tested (see the unconnected triangles), thereby indicating that the baseline sensitivity had not changed as a result of the subjects' drug history.

Figure 2 shows the within-session effects of the highest dose of each drug in Monkey V. In the control record (top), errors decreased in frequency in the acquisition component as the session progressed; i.e., acquisition occurred. After the first 5 min of this session, virtually no errors were made and there were long runs of correct responses that were separated by brief pauses in both components, though the rate of correct responding was somewhat higher in the performance component. Phencyclidine (0.24 mg/kg) produced large disruptive effects on rate and accuracy in both schedule components, as indicated by a long initial pause and then a low rate of correct responding with frequent errors. Although the rate of correct responding in each component increased as the session progressed, the rates near the end of the 2-hr session had still not returned to control. Like phencyclidine, ketamine (3.2 mg/kg) produced a long initial pause in both schedule components and then a low rate of correct responding with frequent errors during the acquisition component. During the next performance and acquisition components, however, the rate of correct responding was considerably higher than with phencyclidine, though errors still occurred frequently. During the remainder of the session, the rate-decreasing and error-increasing effects of ketamine were much smaller than those of phencyclidine, indicating that ketamine had a shorter duration of action. When MDMA (3.2 mg/kg) was administered, the initial effect was similar to that produced by phencyclidine and ketamine, namely, a long period of no responding in both schedule components. However, unlike phencyclidine and ketamine, MDMA did not disrupt accuracy in either acquisition or performance when responding resumed, although some pausing was still evident. In general, the within-session effects of the three drugs in Monkey V were replicated in the other subject.

Table 1 shows the percent errors in the first acquisition and performance components after the initial pause for the drug sessions depicted in Fig. 2; corresponding data for Monkey M are also shown. In both subjects, ketamine was similar to phencyclidine in producing large error-increasing effects in both schedule components, whereas the values for MDMA fell within the control range. The similarity in the error-increasing effects of ketamine and phencyclidine is more apparent in Table 1 than in Fig. 1 (lower panels) because Fig. 1 is based on session totals, and the effects of ketamine on accuracy did not persist throughout the session (see Fig. 2).

DISCUSSION

The present results showed that ketamine and phencyclidine had qualitatively similar effects on complex operant behavior in patas monkeys. Both drugs decreased overall response rate and increased percent errors in both schedule components with increasing doses. Although the dose-effect curves (Fig. 1) indicate that the maximal error-increasing effect was considerably smaller with ketamine than with phencyclidine, this quantitative difference seems to be related to the shorter duration of ketamine's effects on accuracy. The cumulative records (Fig. 2) show that, after an initial pause, a high dose of ketamine had large error-increasing effects in both acquisition and performance, but such effects did not persist as long as those produced by phencyclidine. The present results extend the generality of previous findings obtained with less complex operant behavior. For example, Tang and Franklin reported that both ketamine and phencyclidine impaired the acquisition [13] and performance [14] of a brightness discrimination in rats. As another example of the similarity, in rhesus monkeys trained to discriminate ketamine from saline, both ketamine and phencyclidine decreased response rate at doses that produced 90% or greater ketamine-appropriate responding [12]. The present results therefore support the conclusion based on previous findings, including those from self-administration studies in rhesus monkeys (e.g., [2,9]), that "ketamine acts very much like PCP" [1].

In contrast to ketamine and phencyclidine, MDMA had no effect on accuracy in either schedule component even at doses that produced marked decreases in overall response rate (Figs. 1 and 2). At such doses, there was a long initial pause, but when responding resumed, performance accuracy was unaffected and the pattern of acquisition (error reduction) was essentially the same as that observed during control sessions. Similar results were previously obtained with MDA in patas monkeys responding under the same type of

multiple schedule [19]. That MDMA and MDA produced qualitatively similar behavioral effects might be expected, of course, on the basis of the close structural similarity between the two drugs. On the same basis, one might also expect that MDMA, like MDA [5], would be self-administered in nonhuman primates and would have MDA-like biochemical effects. With regard to the latter point, it has recently been reported that MDA selectively destroys serotonin nerve terminals in rat brain [10]. As the investigators pointed out, however, it would be premature to extrapolate this finding to humans because the doses of MDA required for neurotoxicity in the rat were about 3–5 times higher than those required to produce hallucinogenic effects in man (approximately 1.5–3 mg/kg). It might also be added in this regard that we never observed any long-lasting behavioral effects of MDA at the relatively low doses we studied in patas monkeys (0.17–1.7 mg/kg) [19].

The present results with MDMA are also in contrast to the disruptive effects on accuracy produced by LSD in monkeys responding in various discrimination tasks (e.g., [4,11]). While this difference suggests that MDMA 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, decrease or have no effect on accuracy, depending on procedural variables, such as the type of discriminative stimuli used (see review in [19]).

In summary, the present study showed that ketamine has phencyclidine-like effects and MDMA has MDA-like effects on complex operant behavior in monkeys. Unlike phencyclidine and ketamine, MDMA did not disrupt accuracy in acquisition or performance, thereby suggesting that MDMA has a lower potential for producing acute behavioral toxicity than phencyclidine-type drugs.

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