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Cocaine Potentiates the Disruptive Effects of Phencyclidine on Repeated Acquisition in Monkeys[1]

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THOMPSON, D. M. AND P. J. WINSAUER. *Cocaine potentiates the disruptive effects of phencyclidine on repeated acquisition in monkeys.* PHARMACOL BIOCHEM BEHAV **23**(5) 823–829, 1985.—Patas monkeys acquired a different four-response chain each session by responding sequentially on three keys in the presence of four geometric forms. The response chain was maintained by food presentation under a fixed-ratio schedule. Errors produced a brief timeout but did not reset the chain. Each day there were four 15-min sessions, with a 10-min intersession interval. Cumulative dose-effect curves for phencyclidine were obtained by giving an IM injection before each of the four sessions; successive injections increased the cumulative dose by 1/4 log-unit steps. When phencyclidine was administered alone, overall response rate decreased and percent errors increased with increasing doses. When cocaine was injected IM before the first session at a dose that was ineffective when given alone, the phencyclidine dose-effect curves for both rate and accuracy tended to shift to the left. After pretreatment with the lowest effective dose of cocaine, which decreased rate without affecting accuracy when given alone, the rate-decreasing and error-increasing effects of phencyclidine were generally even more pronounced in two of three subjects. The results indicate that cocaine potentiates the disruptive effects of phencyclidine on complex operant behavior in monkeys.

Repeated acquisition Response chains Cumulative dosing Drug interaction Phencyclidine Cocaine Patas monkeys

BOTH cocaine and phencyclidine use are widespread, yet potential interactions, if such drugs were to be used together, are unknown. In addition, an investigation of cocaine in combination with phencyclidine might help to elucidate the mechanism(s) of action of these drugs.

There are at least two lines of evidence suggesting that cocaine may potentiate the behavioral effects of phencyclidine. First, Vanderwende *et al.* [26] recently reported that ketamine, a phencyclidine analog, produced effects (sleep and loss of the righting reflex) that were potentiated by cocaine in mice. This interaction seemed specific to ketamine-type drugs inasmuch as cocaine had no effect on sleep induced by pentobarbital. The second line of evidence consists of studies showing that certain behavioral effects of phencyclidine are potentiated by a cocaine-like drug, *d*-amphetamine. For example, Murray and Horita [17] reported that phencyclidine-induced stereotyped behavior in rats can be increased by a dose of *d*-amphetamine that was ineffective when given alone. In a related study, Balster and Chait [2] found that phencyclidine, at a dose having no effect when given alone, increased *d*-amphetamine-induced stereotypy in rats.

In research more closely related to the present study, Thompson and Moerschbaecher [24] assessed the effects of *d*-amphetamine-phencyclidine combinations on complex operant behavior in monkeys. More specifically, a repeated-acquisition task was used in which patas monkeys learned a different four-response chain each session by responding sequentially on three keys in the presence of four geometric forms. The response chain was maintained by food presentation under a fixed-ratio (FR) schedule; errors produced a brief timeout but did not reset the chain. In general, when phencyclidine and *d*-amphetamine were administered alone, overall response rate decreased and percent errors increased with increasing doses. When phencyclidine was administered in combination with *d*-amphetamine, the phencyclidine dose-effect curves tended to shift to the left as the dose of *d*-amphetamine was increased. Combinations of phencyclidine with a high dose of *d*-amphetamine generally produced supra-additive effects; i.e., the effects on rate and accuracy were greater than expected from simple addition of the effects of each drug given alone.

In the present research, the repeated acquisition of response chains in patas monkeys served as a behavioral baseline to assess the effects of cocaine-phencyclidine combinations. The objective was to provide a "systematic replication" [19] of the results obtained with *d*-amphetamine-phencyclidine combinations in the Thompson and Moerschbaecher [24] study in order to extend the generality of the findings across procedural variations. Although

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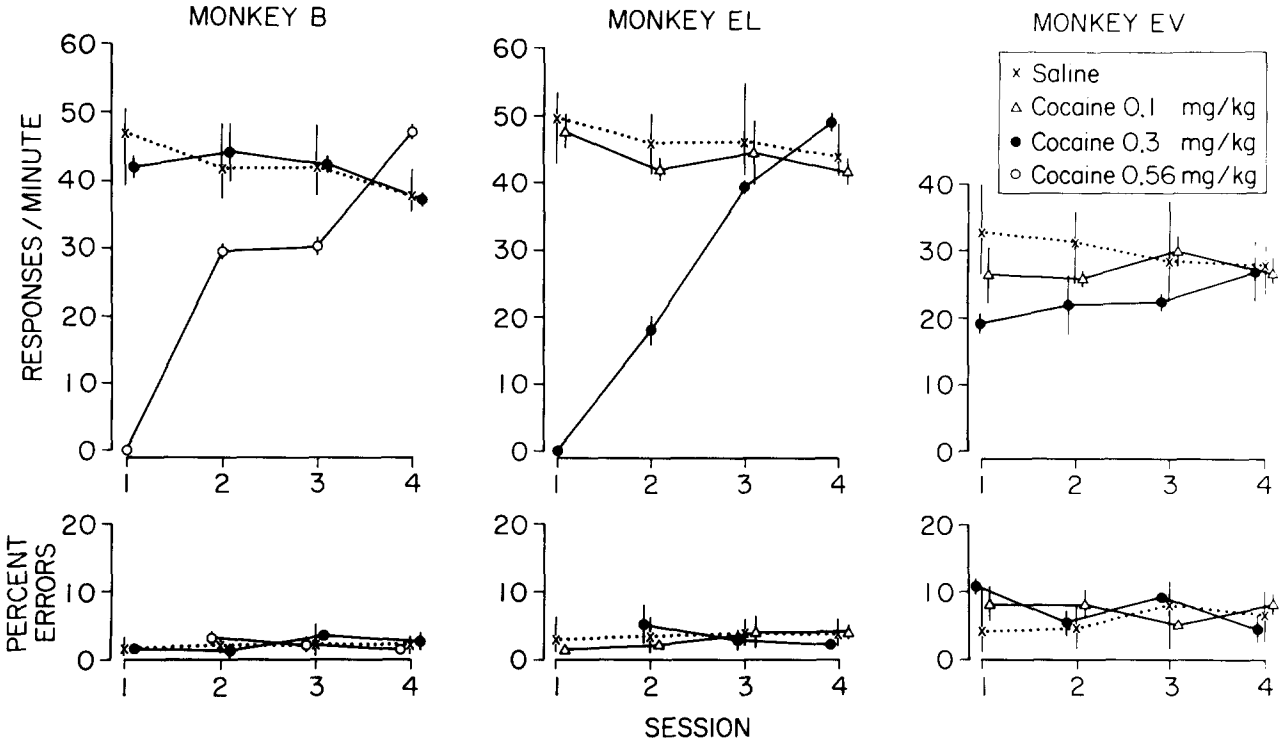

FIG. 1. Overall response rate and percent errors for each subject during the four sessions on control (saline) days and on days when cocaine alone was injected before the first session. The points and vertical lines indicate the mean and range for 6–8 control days and for two determinations at each dose of cocaine. The points without vertical lines indicate 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 zero.

it is generally true that the behavioral effects of cocaine and *d*-amphetamine are qualitatively similar [18], this is not always the case, especially in combination with other drugs. For example, in drug-discrimination studies with rats, when cocaine and *d*-amphetamine were administered in combination with alpha-methyl-para-tyrosine, cocaine discriminability was not affected [14] but *d*-amphetamine discriminability was attenuated [13]. Accordingly, it seemed worthwhile to determine whether cocaine and *d*-amphetamine produce similar behavioral effects in combination with phencyclidine. Another procedural variation involved the protocol for drug testing. To make the drug testing more efficient, a cumulative-dosing procedure [25] was used so that a dose-effect curve could be obtained in a single day. With this type of procedure, it is relatively easy to characterize drug interactions by determining the direction and extent to which the dose-effect curve for one drug shifts after pretreatment with another drug [12,28].

METHOD

Subjects

Three adult female patas monkeys served. All subjects had experimental histories involving the repeated acquisition 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 earned during the experimental sessions, and the Monkey Chow, fruit, and vitamins were provided after the last session each day. Water was continuously available.

Apparatus

The apparatus has been described in detail elsewhere [24]. Briefly, each subject was housed in a primate cage with a removable response panel, which was attached to the side of the cage during the experimental session. Three response keys (press plates) were centered and aligned horizontally on the panel. An in-line projector, mounted behind each key, could project colors and geometric forms onto the key. A yellow pilot lamp (mounted on a switch) was located above a food pellet aperture to the right of the keys. The response panels were connected to solid-state scheduling and recording equipment located in an adjacent room.

Procedure

Baseline. 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 re-

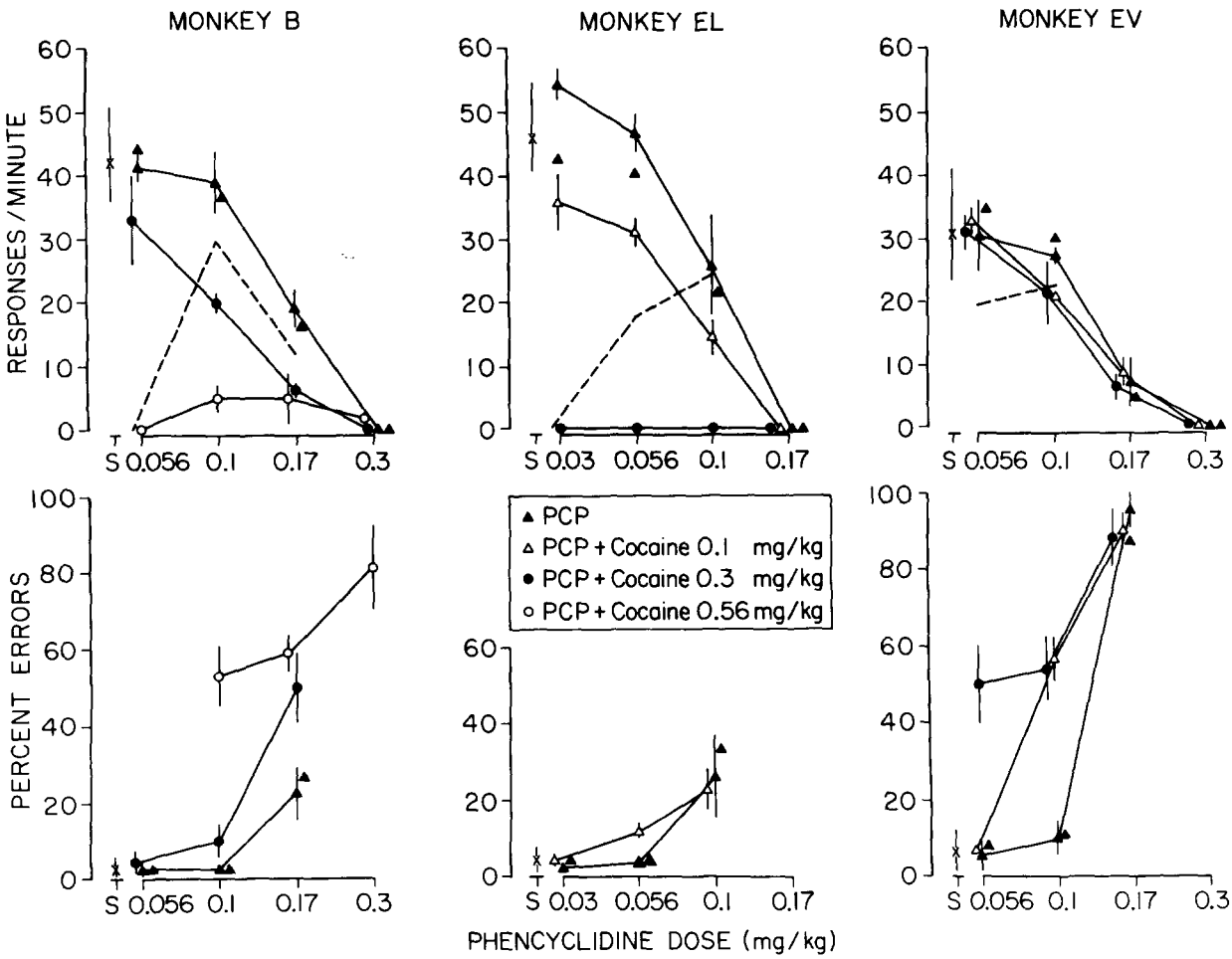

FIG. 2. Effects of cumulative doses of phencyclidine (PCP), alone and in combination with cocaine, on the overall response rate and percent errors for each subject. The points and vertical lines at S indicate the mean and range for 24–32 saline control sessions. The points with vertical lines in the dose-effect curves indicate the mean and range for two determinations; the points without vertical lines indicate 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. The unconnected triangles show a redetermination of the dose-effect data for phencyclidine alone after phencyclidine was tested in combination with cocaine. The dashed lines show the predicted outcome of combining phencyclidine with cocaine if the rate-decreasing effects of phencyclidine alone (connected triangles) and the rate-decreasing effects of cocaine alone (0.56 or 0.3 mg/kg in Fig. 1) were additive.

sponses 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 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 [20]. 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).

There were four 15-min sessions each day (Monday through Friday), with a 10-min intersession interval. The data for each session were analyzed in terms of (a) the overall response rate (total responses/min, excluding timeouts), and (b) the overall accuracy or percent errors ((errors/total responses) × 100). In addition to these measures based on session totals, within-session changes in responding were monitored by a cumulative recorder. 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) as the session progressed.

Drug testing. Before the drug testing began, the repeated-acquisition baseline was stabilized. The baseline was considered stable when the session totals (response rate and percent errors) no longer showed systematic change from day to day. After baseline stabilization (four sessions per day for 15–20 days), cumulative dose-effect data were obtained for phencyclidine hydrochloride. The drug was dissolved in saline and injected IM (*gluteus m.*) 10 min before each session. Successive injections increased the cumulative dose by 1/4 log-unit steps. For example, with Monkeys B and EV, 0.056 mg/kg of phencyclidine was injected before the first session, 0.044 mg/kg (producing a cumulative dose of 0.1 mg/kg) was injected before the second session, 0.07 mg/kg (producing a cumulative dose of 0.17 mg/kg) was injected before the third session, and 0.13 mg/kg (producing a

cumulative dose of 0.3 mg/kg) was injected before the fourth session. As a control, saline was injected IM 10 min before each of the four sessions on another day.

After the cumulative dose-effect curves for phencyclidine had been determined twice in each subject, cocaine alone was tested. Cocaine hydrochloride (dissolved in saline) or saline was injected IM 10 min before the first session. Several doses of cocaine were tested until the lowest effective dose for each subject was determined; this dose was defined as the lowest dose that had a reliable effect on overall response rate during the first session. The lowest effective dose of cocaine (0.3 mg/kg for Monkeys EL and EV or 0.56 mg/kg for Monkey B) was then administered in combination with phencyclidine. Both drugs were injected IM (one on the right side, the other on the left) 10 min before the first session; only phencyclidine was injected (in cumulative doses) before each of the three subsequent sessions. The effects of this drug combination were determined twice for each subject, and then the lowest effective dose of cocaine alone was tested again. Next, using the same testing procedure, an ineffective dose of cocaine when given alone, either 0.1 mg/kg (Monkeys EL and EV) or 0.3 mg/kg (Monkey B), was administered in combination with cumulative doses of phencyclidine. Finally, the cumulative dose-effect curves for phencyclidine alone were redetermined.

Throughout testing, drug (or saline) sessions were generally conducted on Tuesdays and Fridays, with baseline sessions (no injections) occurring on Mondays, Wednesdays, and Thursdays. 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 overall response rate and percent errors for each subject during the four sessions on control (saline) days and on days when cocaine alone was injected before the first session. On days when saline was injected (either before the first session or before all four sessions), there was a slight downward trend in the mean overall response rate for each subject across the four sessions, though the ranges of variability overlapped considerably. When cocaine was administered alone before the first session, the lowest effective dose (0.56 mg/kg for Monkey B or 0.3 mg/kg for Monkeys EL and EV) produced rate-decreasing effects, which diminished as the sessions progressed. During the first session after this dose, the overall response rate was either zero (Monkeys B and EL) or well below the control range (Monkey EV). During the fourth session, which started 85 min after this dose was injected, the overall response rate was either somewhat above (Monkey B) or within (Monkeys EL and EV) the control range. In contrast to its effects on rate, this dose of cocaine had little or no effect on accuracy (percent errors) during any of the four sessions. At a lower dose of cocaine alone, either 0.3 mg/kg (Monkey B) or 0.1 mg/kg (Monkeys EL and EV), there was generally no effect on rate or accuracy.

Figure 2 shows the effects of cumulative doses of phencyclidine, alone and in combination with cocaine, on the overall response rate and percent errors for each subject. When phencyclidine was administered alone, the response rate decreased and the percent errors increased with increasing doses. When phencyclidine was administered in combination with either 0.3 mg/kg (Monkey B) or 0.1 mg/kg (Monkeys EL and EV) of cocaine, which were ineffective doses when given alone (Fig. 1), the dose-effect curves for both rate and accuracy tended to shift to the left relative to those for phencyclidine alone. This shift was least evident in the rate data for Monkey EV and in the accuracy data for Monkey EL. Note, however, that in Monkey EV, 0.1 mg/kg of phencyclidine alone had no effect on overall response rate, whereas this dose in combination with 0.1 mg/kg of cocaine produced a small but reliable rate-decreasing effect. Similarly, in Monkey EL, 0.056 mg/kg of phencyclidine alone had no effect on percent errors, whereas this dose in combination with 0.1 mg/kg of cocaine produced a small but reliable error-increasing effect.

When phencyclidine was administered in combination with either 0.56 mg/kg (Monkey B) or 0.3 mg/kg (Monkeys EL and EV) of cocaine, which were the lowest effective doses when given alone (Fig. 1), the rate-decreasing and error-increasing effects tended to be greater than those obtained with the lower doses of cocaine in combination with phencyclidine in two of three subjects (Fig. 2). An interesting exception occurred in the data of Monkey B, where 0.56 mg/kg of cocaine, which had a delayed rate-increasing effect when given alone (Fig. 1), produced a slight but consistent attenuation of the large rate-decreasing effect seen at the highest dose of phencyclidine. Note, however, that most of the responses that occurred after this drug combination were errors. A related finding in Monkey EV is the large error-increasing effect seen when 0.3 mg/kg of cocaine was given in combination with the lowest dose of phencyclidine; this drug combination had no effect on the overall response rate even though 0.3 mg/kg of cocaine alone had a rate-decreasing effect (Fig. 1). In general, the effects of phencyclidine alone were replicated after the cocaine-phencyclidine combinations were tested (see the unconnected triangles).

The dashed lines in Fig. 2 show the predicted outcome of combining phencyclidine with cocaine if the rate-decreasing effects of phencyclidine alone (connected triangles) and the rate-decreasing effects of cocaine alone (0.56 or 0.3 mg/kg in Fig. 1) were additive. (Dashed lines are not shown for percent errors since cocaine alone generally had no effect on accuracy; the predicted outcome here is simply the dose-effect curve for phencyclidine alone.) When administered alone, each drug was considered to have an effect on response rate to the extent that the data points fell outside of the control range [24]. Accordingly, the rate-decreasing effect of phencyclidine alone was calculated by subtracting the overall response rate at a given dose of phencyclidine from the minimum control rate, yielding a difference score. If the response rate at a given dose of phencyclidine fell within the control range, the dose was considered to have no effect, and the difference score was assigned a value of 0. The same type of calculation was made for cocaine alone (if rate was decreased in Fig. 1), and the sum of the two difference scores defined the additive effect on response rate [24]. In general, when phencyclidine and cocaine (0.56 mg/kg in Monkey B or 0.3 mg/kg in Monkeys EL and EV) were administered in combination, the effects on rate were either supra-additive (i.e., greater than expected from simple addition of the effects of each drug given alone) or additive. The supra-additive effects occurred at the two intermediate doses of phencyclidine in Monkeys B and EL, whereas additive effects were found at the lowest dose of phencyclidine in these subjects and at 0.1 mg/kg of phencyclidine in Monkey EV. The only exception occurred at the lowest dose of phencyclidine in Monkey EV, where the outcome of the combination (no effect on overall response rate) was less than additive.

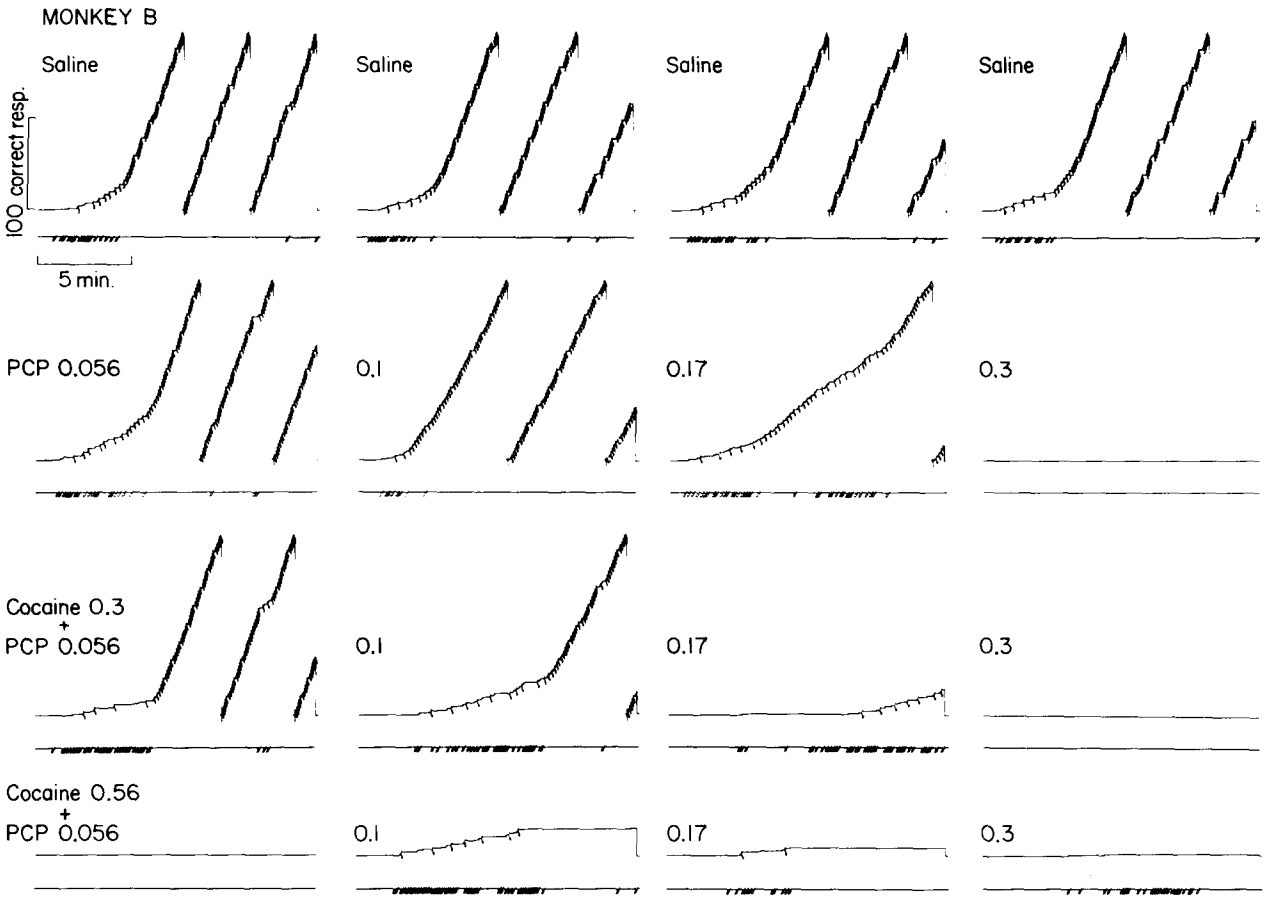

FIG. 3. Within-session effects of cumulative doses of phencyclidine (PCP), alone and in combination with cocaine, in Monkey B. Each row of four cumulative records is from a different day. On each day, there were four 15-min sessions (shown left to right), each with a different four-response chain (the 10-min intersession interval is not shown to scale). The top row shows sessions that were preceded by saline injections, the second row shows sessions that were preceded by increasing cumulative doses (mg/kg) of phencyclidine alone, and the third and fourth rows show sessions that were preceded by the cumulative doses of phencyclidine in combination with 0.3 or 0.56 mg/kg of cocaine (injected before the first session). 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.

Figure 3 shows the within-session effects of cumulative doses of phencyclidine, alone and in combination with cocaine, in Monkey B. The top row of cumulative records shows the pattern of responding during four saline sessions from one day. As can be seen in each of these records, errors decreased in frequency as the session progressed; i.e., acquisition occurred. After the first 5 min of each saline session, there were frequent runs of correct responses emitted at a high rate and relatively few errors were made. The runs of correct responses were often preceded by brief pauses. The second row of records shows four sessions that were preceded by increasing cumulative doses of phencyclidine. The lowest dose (0.056 mg/kg) was ineffective; the pattern of responding during this session was similar to that seen in the saline sessions. After the second injection of phencyclidine (a cumulative dose of 0.1 mg/kg), the rate of correct responding was slightly decreased in comparison to control, but acquisition (within-session error reduction) was not disrupted. The third injection of phencyclidine (a cumulative dose of 0.17 mg/kg) produced a large decrease in the rate of correct responding and a substantial increase in errors, though acquisition still occurred. After the fourth injection of phencyclidine (a cumulative dose of 0.3 mg/kg), there was no responding during the session.

The third row of records in Fig. 3 shows four sessions that were preceded by increasing cumulative doses of phencyclidine in combination with 0.3 mg/kg of cocaine (injected before the first session). After pretreatment with this dose of cocaine, which was ineffective when given alone (Fig. 1), a cumulative dose of 0.1 mg/kg of phencyclidine (second session) now produced a large decrease in the rate of correct responding and a noticeable increase in errors. When the cumulative dose of phencyclidine was then increased to 0.17 mg/kg, there was much greater disruption of the pattern of responding than after this dose of phencyclidine alone, as indicated by the increased pausing, the low rate of correct responding, and the large increase in the relative frequency of errors with no sign of acquisition. The bottom row of records shows four sessions that were preceded by increasing cumulative doses of phencyclidine in combination with 0.56 mg/kg of cocaine (injected before the first session). The effect seen during the first session (no responding) was the same as that produced by this dose of cocaine alone (Fig. 1). However, during the second and third sessions, when 0.56

mg/kg of cocaine alone had only small rate-decreasing effects (Fig. 1), this dose of cocaine in combination with phencyclidine produced long periods of pausing, and when responding did occur, errors were more frequent than correct responses. During the fourth session, when 0.56 mg/kg of cocaine alone had a rate-increasing effect (Fig. 1), more responding occurred than after 0.3 mg/kg of phencyclidine alone, but almost all of the responses were errors. In general, the within-session effects of phencyclidine, alone and in combination with cocaine, in Monkey B were replicated with the other two subjects, although the particular doses and the magnitude of the effects varied.

DISCUSSION

When phencyclidine was administered alone, the responding of patas monkeys in a repeated-acquisition task was disrupted as the cumulative dose increased; i.e., the overall response rate decreased, the percent errors increased, and there was less within-session error reduction (acquisition). These effects are comparable to previously reported effects of phencyclidine on the responding of pigeons under similar conditions of repeated acquisition and cumulative dosing [25]. The disruptive effects obtained with cumulative doses of phencyclidine are also similar to those previously found with non-cumulative doses in patas monkeys responding in a repeated-acquisition task with only one session per day (e.g., [24]). The time required to test the drug, however, was substantially reduced in the present study. Instead of testing only two doses per week, a dose-effect curve could be obtained in a single day with the cumulative-dosing procedure.

The rate-decreasing effects found with phencyclidine alone (Fig. 2) extend the generality of previous findings obtained with less complex schedule-controlled behavior in monkeys. For example, in rhesus monkeys responding on a single key under an FR 10 schedule of food presentation, the overall response rate decreased as the dose of phencyclidine (non-cumulative, administered IM) was increased from 0.05 to 0.2 mg/kg [1]. A similar dose-related decrease in the rate of FR responding was recently reported for rhesus monkeys in a drug-discrimination task involving cumulative doses of phencyclidine [28]. The error-increasing effects found with phencyclidine alone (Fig. 2) complement the results obtained with other discrimination techniques. For example, Brown and Bass [4] 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. More recently, McMillan [15] reported that phencyclidine disrupted the performance of pigeons in a matching-to-sample task; matching accuracy was decreased at doses that decreased response rate.

When cocaine was administered alone before the first session, the lowest effective dose produced rate-decreasing effects, which diminished as the sessions progressed (Fig. 1). This finding is consistent with previous reports that cocaine generally decreases the rate of responding under simple FR schedules of food presentation in rhesus monkeys [10, 27, 29] and under second-order FR schedules maintaining repeated acquisition in patas monkeys [16,22]. A delayed rate-increasing effect of cocaine, such as that seen in Monkey B, has also been reported for rhesus monkeys responding under a second-order schedule [8]. Although the lowest effective dose of cocaine alone in regard to response rate had little or no effect on percent errors (Fig. 1), it is likely that cocaine would have disrupted accuracy had higher doses been tested. Previous studies with patas monkeys [16,22] and pigeons (e.g., [23]) in repeated-acquisition tasks and with pigeons in a matching-to-sample task [3] have all shown that high doses of cocaine produce error-increasing effects.

When cocaine was administered before the first session at a dose that was ineffective when given alone, the phencyclidine dose-effect curves for both rate and accuracy tended to shift to the left (Fig. 2). After pretreatment with the lowest effective dose of cocaine, which decreased rate without affecting accuracy when given alone, the rate-decreasing and error-increasing effects of phencyclidine were generally even more pronounced in two of three subjects. The shift to the left in the dose-effect curves can not be attributed to the development of "supersensitivity" to phencyclidine (i.e., an increased sensitivity due to repeated drug administration) since the effects of phencyclidine alone were replicated after the cocaine-phencyclidine combinations were tested. Probably the most reasonable interpretation of the shift in the phencyclidine dose-effect curves is that cocaine "potentiated" the effects of phencyclidine (cf. [9]). This interpretation is supported by the finding that certain dose combinations of cocaine and phencyclidine produced greater rate-decreasing effects than expected from simple addition of the effects of each drug given alone. In general, the effects found with cocaine-phencyclidine combinations in the present research provide a "systematic replication" [19] of the results obtained with *d*-amphetamine-phencyclidine combinations in the Thompson and Moerschbaecher [24] study, thereby extending the generality of the findings across procedural variations (specific drug and dosing technique).

In discussing the ability of cocaine to potentiate ketamine-induced sleep in mice, Vanderwende *et al.* [26] suggested that catecholamine systems appear to be involved. Since ketamine is a phencyclidine analog, it is tempting to speculate that these systems may also be involved in the cocaine-phencyclidine potentiation observed in the present study. In support of this notion, Colpaert *et al.* [6] reported that phencyclidine substituted for cocaine in rats trained to discriminate cocaine from saline. It was suggested that this substitution was mediated by the ability of both drugs to increase the functional availability of dopamine through presynaptic mechanisms. As several studies have shown (see review in [7]), both cocaine and phencyclidine release dopamine and inhibit its reuptake. On the other hand, Cunningham and Appel [7] reported that haloperidol, a dopamine antagonist, failed to attenuate the (partial) substitution of phencyclidine for cocaine, and suggested that some other, non-dopaminergic mechanism is involved. Furthermore, in rats trained to discriminate phencyclidine from vehicle, cocaine failed to mimic phencyclidine [5]. Until these apparent discrepancies in the literature are explained, and until the relevance of the dopaminergic actions of phencyclidine and cocaine to their behavioral effects in primates is determined (cf. [11]), it would seem premature to speculate further about the possible biochemical mechanism(s) underlying the cocaine-phencyclidine potentiation observed in the present study.

Although cocaine generally potentiated the disruptive effects of phencyclidine, there were two notable exceptions in the data (Fig. 2). In one case (Monkey B), 0.56 mg/kg of cocaine, which had a delayed rate-increasing effect when given alone, produced a slight but consistent attenuation of the large rate-decreasing effect seen at the highest dose of

phencyclidine. In the other case (Monkey EV), the lowest dose of phencyclidine, which was ineffective when given alone, antagonized the small rate-decreasing effect of 0.3 mg/kg of cocaine. It is important to note, however, that in both cases, the effects on accuracy differed from the effects on rate. In Monkey B, most of the responses that occurred after the drug combination were errors, and in Monkey EV, the drug combination produced a large error-increasing effect, even though the overall response rate was within the control range. The accuracy measure, therefore, provides new information about a drug interaction that would be difficult to predict from the effects on response rate (cf. [21]).

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