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Delta-9-tetrahydrocannabinol Potentiates the Disruptive Effects of Phencyclidine on Repeated Acquisition in Monkeys[1]

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THOMPSON, D. M. AND P. J. WINSAUER. *Delta-9-tetrahydrocannabinol potentiates the disruptive effects of phencyclidine on repeated acquisition in monkeys.* PHARMACOL BIOCHEM BEHAV 23(6) 1051–1057, 1985.—Patas monkeys acquired a different four-response chain each session by responding sequentially on three keys or levers in the presence of four discriminative stimuli (geometric forms or numerals). 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 delta-9-tetrahydrocannabinol (THC) was administered PO 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 a higher dose of THC, which decreased rate in one of three subjects without affecting accuracy when given alone, the rate-decreasing and error-increasing effects of phencyclidine were generally even more pronounced. The results indicate that THC potentiates the disruptive effects of phencyclidine on complex operant behavior in monkeys.

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

PHENCYCLIDINE is frequently taken in combination with marijuana, but the possibility that this combination produces increased behavioral toxicity has not been thoroughly investigated [2]. In one of the few studies in this area, Pryor *et al.* [12] examined the effects of phencyclidine and delta-9-tetrahydrocannabinol (THC), alone and in combination, on responding under a fixed-ratio (FR 10) schedule of food presentation in rats. When given alone, phencyclidine (2.5 mg/kg, IP) decreased response rate, whereas THC (5 mg/kg, PO) had no effect. When given in combination, however, the two drugs produced a greater rate-decreasing effect than that produced by phencyclidine alone. Although the generality of these findings is limited because only a single dose of each drug was tested, the results suggest that THC potentiates the disruptive effect of phencyclidine on simple schedule-controlled behavior in rats.

The purpose of the present research was to investigate the effects of varying doses of phencyclidine and THC, alone and in combination, on complex operant behavior in primates. 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 or levers in the presence of four discriminative stimuli. Previous research with this behavioral baseline (e.g., [14,15]) has shown that phencyclidine (injected IM) decreases overall response rate and increases percent errors with increasing doses. To make the drug testing more efficient, a cumulative-dosing procedure [16] was used in the present study so that phencyclidine dose-effect curves for rate and accuracy could be obtained in a single day. The drug interaction was characterized by determining the direction and extent to which the phencyclidine dose-effect curves shifted after pretreatment with THC (administered PO). Another objective was to determine whether the effects of the combination were predictable from the individual actions of the two drugs.

METHOD

Subjects

One female and two male adult patas monkeys served. The female (Monkey B) had a long experimental history involving the repeated acquisition of response chains and had served in several previous drug studies (e.g., [14,15]). The two males (Monkeys M and V) had a brief history of repeated acquisition and were drug-naive at the start of the present study. All three subjects were maintained at about 90% of their free-feeding weights (range 5.9 to 9.1 kg) on a diet consisting of Noyes banana-flavored food pellets, Purina Monkey Chow, fruit, and vitamins. The pellets were earned

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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 for Monkey B has been described in detail elsewhere [14]. Briefly, this 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 panel was connected to solid-state scheduling and recording equipment located in an adjacent room.

Monkeys M and V were housed individually in a primate cage (Research Equipment Co., model LC-1103) measuring 83.6 cm by 98.2 cm by 87.4 cm. The bars were removed from one side of the cage and replaced with an aluminum panel. An array of three recessed levers (C. P. Clare Co., model C10647) was aligned horizontally to the right of the vertical midline of the panel. The levers were spaced 4 cm apart, center to center, and were 50 cm above the cage floor. Each lever required a minimum force of 0.98 N for activation. A relay mounted behind the panel clicked when any one of the three levers was pressed. An in-line projector (Industrial Electronic Engineers), mounted 4 cm above each lever, was used to project the discriminative stimuli (white numerals on a black background). An additional lever, which operated a pellet dispenser (R. Gerbrands Co.), was mounted 15 cm to the left and 6 cm up from the center of the left-hand lever. A green pilot lamp (No. 1820) was mounted 5 cm below the food lever. The pellet dispenser delivered 500-mg banana-flavored food pellets (P. J. Noyes Co.) into an aperture (8 cm by 8 cm) that was located 3 cm to the left from the center of the food lever. The response panels were connected to scheduling and recording equipment (an Apple IIe computer) located in an adjacent room.

Procedure

Baseline. With Monkey B, 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.

With Monkeys M and V, 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. In all other aspects (FR 5 schedule of food reinforcement, timeout duration of 5 sec, etc.), the procedure for Monkeys M and V was identical to the procedure described for Monkey B.

To establish a steady state of repeated acquisition in each subject, 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 [13]. 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 discriminative stimuli was always the same: horizontal line, triangle, vertical line, circle (reinforcement) for Monkey B; 1, 2, 3, 4 (reinforcement) for Monkeys M and V.

There were four 15-minute 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] $\times$ 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 Monkey B, 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. Phencyclidine (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 of phencyclidine are expressed in terms of the salt.

After the cumulative dose-effect curves for phencyclidine had been determined twice in each subject, 5.6 mg/kg of delta-9-tetrahydrocannabinol (THC) was tested alone. The THC, dissolved in absolute ethanol when obtained from the National Institute on Drug Abuse, was further diluted with ethanol to yield a concentration of 50 mg/ml. This stock solution was then stored in the dark under refrigeration. THC was administered by injecting the solution into a slice of banana and giving it to the subject to eat. The first session began 90 min after the subject had eaten the fruit. As a vehicle control (at the same presession time on another day), ethanol was injected into the fruit in the same volume as the THC dose. THC (or vehicle) tests were generally conducted

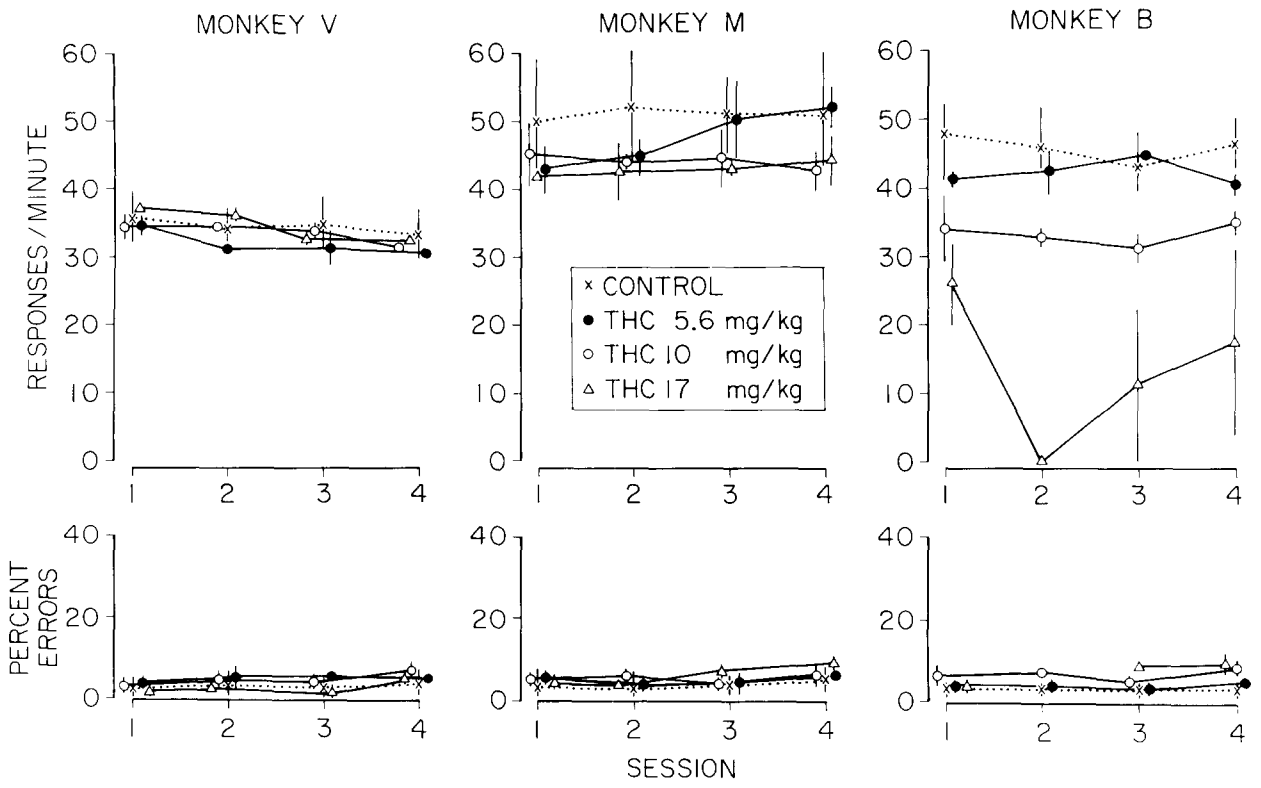

FIG. 1. Overall response rate and percent errors for each subject during the four sessions on control (saline or vehicle) days and on days when THC alone was administered before the first session. The points and vertical lines indicate the mean and range for 8–10 control days and for two determinations at each dose of THC. 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 (Monkey B, session 2, 17 mg/kg, both determinations).

once a week. The 5.6 mg/kg dose of THC, the route and presession time of administration, and the spacing of the drug days were selected on the basis of previous research with monkeys responding in discrimination tasks [5].

After 5.6 mg/kg of THC had been tested alone, this dose was tested in combination with phencyclidine. THC was administered PO 90 min before the first session (as described above) and phencyclidine was injected IM 10 min before the first session; only phencyclidine was administered (in cumulative doses) before each of the three subsequent sessions. The effects of this drug combination were determined twice for each subject (one determination per week), and then 5.6 mg/kg of THC alone was tested again. Next, using the same testing procedure, 10 mg/kg of THC was tested alone and in combination with cumulative doses of phencyclidine. The cumulative dose-effect curves for phencyclidine alone were then redetermined. Finally, 17 mg/kg of THC was tested alone. This was done to determine whether the effects obtained with phencyclidine in combination with 10 mg/kg of THC were similar to the effects of a higher dose of THC alone.

RESULTS

Figure 1 shows the overall response rate and percent errors for each subject during the four sessions on control (saline or vehicle) days and on days when THC alone was administered before the first session. (The data from the saline sessions and the vehicle (ethanol) sessions were combined because there was no apparent difference between these two sets of control data.) Under control conditions, the overall response rate for each subject was relatively constant across the four sessions, though Monkey V responded at a lower rate than the other two subjects. There were also individual differences in the effects of THC alone on response rate. In Monkey B, the overall response rate after 10 mg/kg of THC was below the control range during all four sessions. When the dose was increased to 17 mg/kg, a greater, though more variable, rate-decreasing effect was seen in this subject. In contrast, in the other two subjects, THC had little or no effect on overall response rate at any of the doses tested. This was also true for all three subjects in regard to the effects of THC alone on overall accuracy (percent errors).

Figure 2 shows the effects of cumulative doses of phencyclidine, alone and in combination with THC, 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 5.6 mg/kg of THC, which was an ineffective dose 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 B, where there was consistent overlap in the ranges of variability for the two sets of data points.

When phencyclidine was administered in combination with 10 mg/kg of THC, which had no effect in Monkeys V and M but decreased rate in Monkey B when given alone

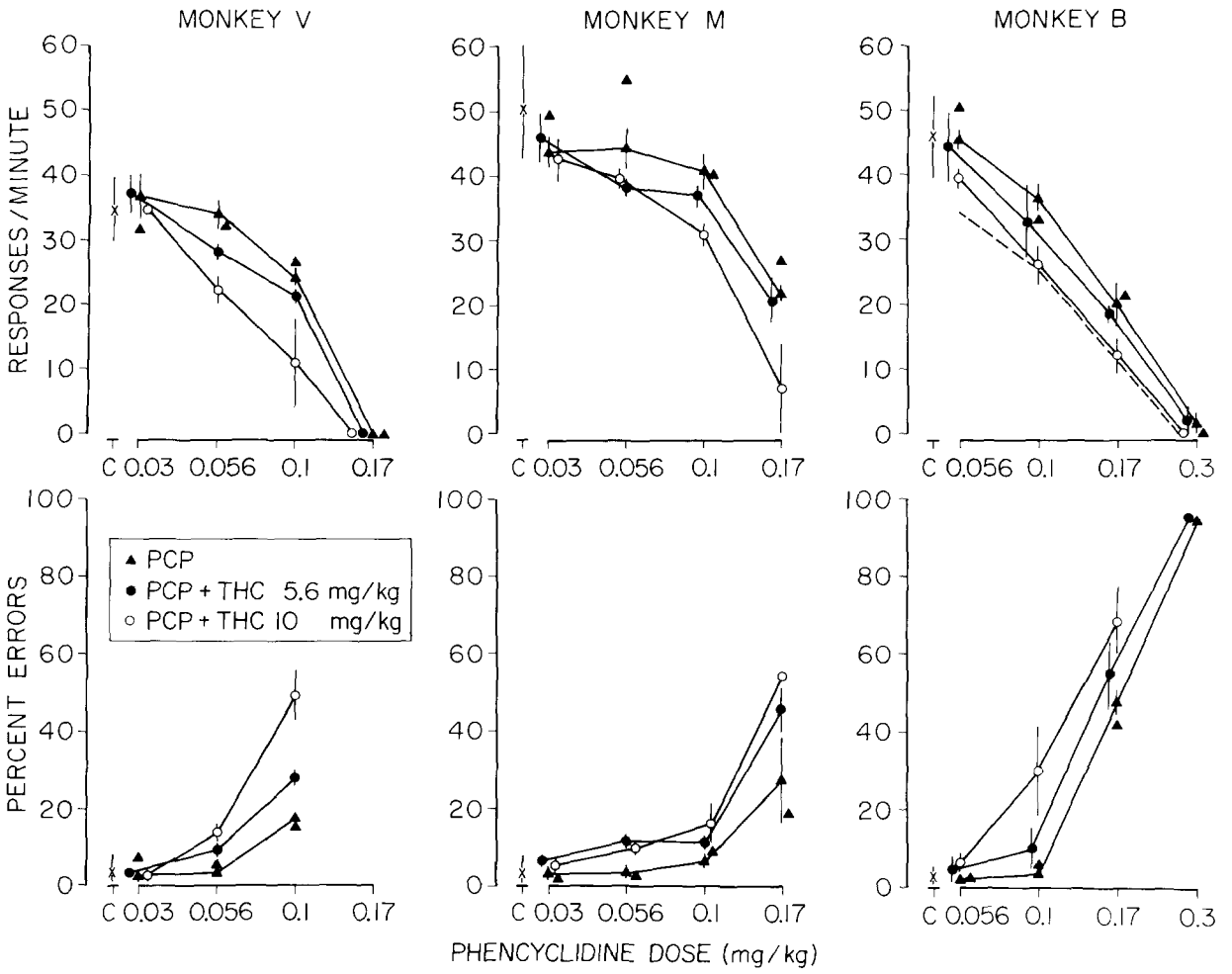

FIG. 2. Effects of cumulative doses of phencyclidine (PCP), alone and in combination with THC, on the overall response rate and percent errors for each subject. The points and vertical lines at C indicate the mean and range for 32–40 control (saline or vehicle) sessions. The points with vertical lines 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 THC. The dashed line (Monkey B) shows the predicted outcome of combining phencyclidine with THC if the rate-decreasing effects of phencyclidine alone (connected triangles) and the rate-decreasing effects of THC alone (10 mg/kg in Fig. 1) were additive.

(Fig. 1), the rate-decreasing and error-increasing effects tended to be greater than those obtained with the lower dose of THC in combination with phencyclidine. This dose-related shift in the curves was least evident in the accuracy data for Monkey M, though it is clear that at the highest dose of phencyclidine, the error-increasing effect was slightly greater with 10 mg/kg of THC than with 5.6 mg/kg. Additionally, a comparison of Fig. 2 with Fig. 1 indicates that the large rate-decreasing and error-increasing effects produced by phencyclidine in combination with 10 mg/kg of THC were quite different from the variable results obtained with a higher dose of THC alone (17 mg/kg). In general, the effects of phencyclidine alone were replicated after the THC-phencyclidine combinations were tested (see the unconnected triangles in Fig. 2).

The dashed line in Fig. 2 (Monkey B) shows the predicted outcome of combining phencyclidine with THC if the rate-decreasing effects of phencyclidine alone (connected triangles) and the rate-decreasing effects of THC alone (10 mg/kg in Fig. 1) were additive. (A dashed line is not shown for percent errors since THC alone had little or no effect on accuracy.) 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. 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 THC alone (if rate was decreased in Fig. 1), and the sum of the two difference scores defined the additive effect on response rate [14]. In general, when phencyclidine was administered in combination with 10 mg/kg of THC in Monkey B, the effects on rate were additive. The only exception occurred at the

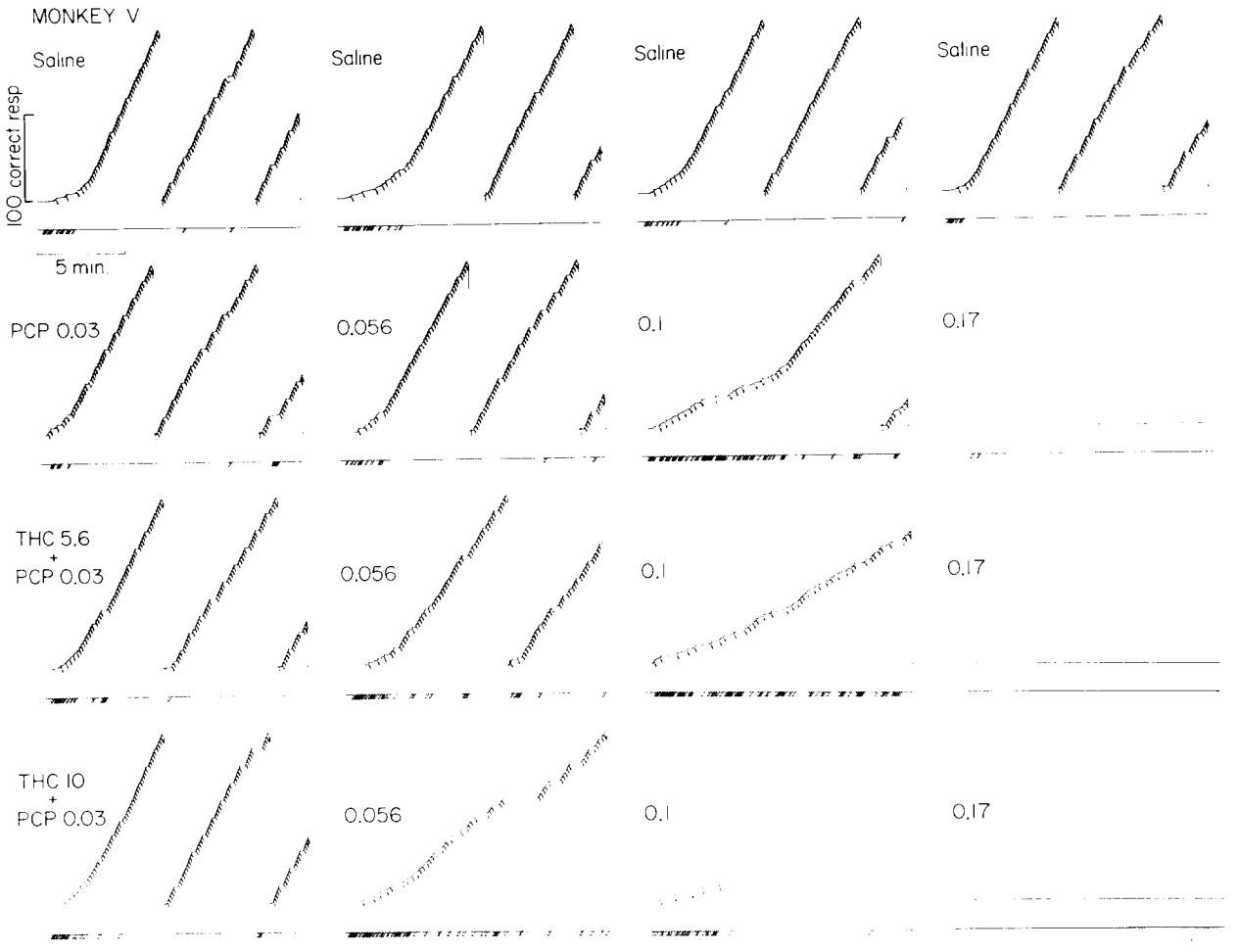

FIG. 3. Within-session effects of cumulative doses of phencyclidine (PCP), alone and in combination with THC, in Monkey V. Each row of four cumulative records is from a different day. On each day, there were four 15-min sessions (shown left to right), each with a different four-response chain (the 10-min 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 5.6 or 10 mg/kg of THC (administered 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.

lowest dose of phencyclidine, where the outcome of the combination (no effect on overall response rate) was less than additive.

Returning to Fig. 1, it can be seen that the mean response rates of Monkey M after 10 mg/kg of THC alone were consistently below (by about 5–9 responses/min) the mean control rates. Although the ranges overlap, one could argue that the reliable differences between the means indicate a drug effect, and this should be taken into account in the calculation of additivity. If this were done for Monkey M, the effects on rate produced by phencyclidine in combination with 10 mg/kg of THC would be approximately additive, as in Monkey B (Fig. 2).

Figure 3 shows the within-session effects of cumulative doses of phencyclidine, alone and in combination with THC, in Monkey V. 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 3–5 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 two lower doses (0.03 and 0.056 mg/kg) were ineffective; the pattern of responding during these sessions was similar to that seen in the saline sessions. The third injection of phencyclidine (a cumulative dose of 0.1 mg/kg) produced a large decrease in the rate of correct responding and a substantial increase in errors, though acquisition (within-session error reduction) still occurred. After the fourth injection of phencyclidine (a cumulative dose of 0.17 mg/kg), there was virtually no responding during the session.

The third row of records in Fig. 3 shows four sessions that were preceded by increasing cumulative doses of phency-

clidine in combination with 5.6 mg/kg of THC (administered before the first session). After pretreatment with this dose of THC, which was ineffective when given alone (Fig. 1), a cumulative dose of 0.056 mg/kg of phencyclidine (second session) now produced a noticeable decrease in the rate of correct responding and a small increase in errors. When the cumulative dose of phencyclidine was then increased to 0.1 mg/kg, there was greater disruption of the pattern of responding than after this dose of phencyclidine alone, as indicated by the lower rate of correct responding and the larger increase in the relative frequency of errors with little acquisition. The bottom row of records shows four sessions that were preceded by increasing cumulative doses of phencyclidine in combination with 10 mg/kg of THC (administered before the first session). After pretreatment with this higher dose of THC, which was still ineffective in Monkey V when given alone (Fig. 1), there was even greater disruption of the pattern of responding during the second and third sessions than that produced by 5.6 mg/kg of THC in combination with phencyclidine. In fact, the disruptive effects on rate and accuracy at 0.056 mg/kg of phencyclidine in combination with 10 mg/kg of THC resemble the effects seen at 0.1 mg/kg of phencyclidine alone. Moreover, it should be noted that the very large disruptive effects seen at 0.1 mg/kg of phencyclidine in combination with 10 mg/kg of THC (i.e., long pausing and no acquisition) were not produced by phencyclidine alone until the cumulative dose was increased to 0.17 mg/kg. In general, the within-session effects of phencyclidine, alone and in combination with THC, in Monkey V were replicated with the other two subjects, although the particular doses and the magnitude of the effects varied.

DISCUSSION

The rate-decreasing effects found with phencyclidine alone (Figs. 2 and 3) 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 [17]. The error-increasing effects found with phencyclidine alone (Figs. 2 and 3) 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 [11] 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.

In contrast to the disruptive effects obtained with phencyclidine alone, the repeated-acquisition baseline was relatively insensitive to THC alone (Fig. 1). Although THC produced dose-related decreases in overall response rate in one subject (Monkey B), it had little or no effect on accuracy (percent errors) in this subject and had virtually no effect on rate or accuracy in the other two subjects at any of the doses tested (5.6–17 mg/kg). While the individual differences here may be related to several variables (e.g., female vs. male; behavioral and drug history), it should be noted that marked inter-subject variability is not unusual in studies of the behavioral effects of THC in monkeys [3, 5, 9]. For example, Elsmore [5] found a large difference between two male rhesus monkeys in their sensitivity to the rate-decreasing effects of orally administered THC (4–16 mg/kg) in a temporal-discrimination task. Considerable variability was also seen between the first and second determinations at a given dose, as in the present study (Fig. 1, Monkey B, 17 mg/kg). It was suggested that such variability may reflect differences in absorption time, depending on the degree to which the fruit containing the THC was masticated before being swallowed. Alternatively, the marked variability between the first and second determinations at 17 mg/kg in Monkey B may reflect the development of tolerance to THC since the rate-decreasing effects were generally smaller during the second determination. As McMillan [10] has pointed out, tolerance to THC can develop even when the drug is administered only once a week.

The present finding that THC alone had little or no effect on accuracy is in contrast to the dose-related decrements in accuracy obtained in the Elsmore [5] study. Disruption of accuracy by orally administered THC has also been found in rhesus monkeys during discrimination reversals [7], in rhesus monkeys responding in a delayed oddity-discrimination task [18], and in chimpanzees responding in a delayed matching-to-sample task [6]. Moreover, in squirrel monkeys trained to press either two or five differently colored keys sequentially (regardless of key position), THC (administered IM) reduced accuracy in a dose-related fashion [3]. On the other hand, under different experimental conditions, THC has been reported to have little or no effect on discrimination accuracy, as in the present study. For example, it has been shown that orally administered THC does not disrupt the acquisition of a simultaneous color discrimination in rhesus monkeys [7], the performance of a simultaneous oddity discrimination in rhesus monkeys [18], nor the performance of zero-delay matching to sample in chimpanzees [6]. Also, in pigeons responding in a delayed matching-to-sample task, THC (administered IM) had little effect on accuracy even at doses that greatly decreased response rate [11]. In short, the extent to which THC disrupts discrimination accuracy seems to be task-dependent, though the critical variables involved have not yet been isolated.

Despite the fact that the repeated-acquisition baseline was relatively insensitive to THC alone, THC did alter the behavioral effects of phencyclidine in all three subjects. When phencyclidine was administered after pretreatment with THC, the phencyclidine dose-effect curves for both rate and accuracy tended to shift to the left as the dose of THC was increased (Fig. 2). The shift to the left in the dose-effect curves cannot 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 THC-phencyclidine combinations were tested. Probably the most reasonable interpretation of the shift in the phencyclidine dose-effect curves is that THC "potentiated" the disruptive effects of phencyclidine (cf., [8]). The present results with monkeys responding in a complex operant task (repeated acquisition) thus extend the generality of previous findings suggesting that THC potentiates the disruptive effect of phencyclidine on simple schedule-controlled performance in rats [12]. It should be noted, however, that in the present study when THC alone did decrease response rate (Monkey B, 10 mg/kg), the effects of the combination were generally

predictable from the individual actions of the two drugs; i.e., the effects on rate were additive, except at the lowest dose of phencyclidine. Such additive effects are in contrast to the supra-additive effects produced by pentobarbital-phencyclidine combinations in patas monkeys responding in the same behavioral task [14], thereby indicating that the repeated-acquisition baseline can differentiate the interactions between phencyclidine and other prototype drugs of abuse.

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