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Nicotine Can Attenuate the Disruptive Effects of Phencyclidine on Repeated Acquisition in Monkeys[1]

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THOMPSON, D. M. AND P. J. WINSAUER. *Nicotine can attenuate the disruptive effects of phencyclidine on repeated acquisition in monkeys.* PHARMACOL BIOCHEM BEHAV **25**(1) 185–190, 1986.—Patas monkeys acquired a different four-response chain each session by responding sequentially on three levers in the presence of four discriminative stimuli (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 nicotine was administered alone (IM) before the first session, the higher doses initially produced large decreases in overall response rate. Unlike phencyclidine, nicotine alone generally had no effect on percent errors. When intermediate or high doses of phencyclidine were administered after pretreatment with certain doses of nicotine, both the rate-decreasing and error-increasing effects were smaller than those produced by phencyclidine alone. This attenuation of the disruptive effects of phencyclidine on acquisition occurred at a time when nicotine alone had little or no behavioral effect.

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

PHENCYCLIDINE is frequently administered by adulteration of smoking materials, such as marijuana or tobacco, but the behavioral effects of these combinations have received little attention in laboratory studies [4]. In one such experiment, delta-9-tetrahydrocannabinol (THC) was found to potentiate the disruptive effects of phencyclidine on complex operant behavior in monkeys [14]. 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. 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. When phencyclidine was administered alone (IM), overall response rate decreased and percent errors increased with increasing cumulative doses. After pretreatment with orally administered THC 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.

In the present research, the repeated acquisition of response chains in patas monkeys served as a behavioral baseline to assess the effects of nicotine-phencyclidine combinations. In contrast to the THC-phencyclidine potentiation observed previously [14], there was reason to believe that nicotine might attenuate the behavioral effects of phencyclidine. Chaturvedi [6] recently reported that phencyclidine-induced locomotor activity in mice was attenuated by nicotine at doses that decreased activity when given alone. Whether such attenuation could be extended to the disruptive effects of phencyclidine on acquisition in monkeys was the main question examined in the present study.

METHOD

Subjects

Three adult male patas monkeys served. All subjects had experimental histories involving the repeated acquisition of

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response chains. The subjects were maintained at about 90% of their free-feeding weights (range 7.7 to 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 last session each day. Water was continuously available.

Apparatus

The subjects were housed individually in a primate cage (Research Equipment Co., model LC-1103) measuring 83.6 by 98.2 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 a correct response was made on any one of the three levers. 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 by 8 cm) that was located 3 cm to the left from the center of the 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. 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 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 associated numerals was always the same: 1,2,3,4 (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 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) 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) showed no systematic change from day to day. After baseline stabilization (four sessions per day for 7–10 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 M and N, 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, nicotine alone was tested. Nicotine hydrogen (+)-tartrate (dissolved in saline) or saline was injected IM 10 min before the first session. Several doses of nicotine were tested until the lowest effective dose for each subject was determined; this dose was defined as the lowest dose that had any effect on response rate and/or percent errors during the first session. The lowest effective dose of nicotine 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 nicotine alone was tested again. Next, using the same testing procedure, higher doses of nicotine (1 mg/kg for Monkey V; 1 mg/kg and then 3 mg/kg for Monkey M; 0.56 mg/kg and then 1 mg/kg for Monkey N) were administered alone and in combination with 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 (drug or saline) 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 nicotine alone was injected before the first session. On days when saline was injected (either before the first session or before all four sessions), the overall response rate for Monkeys V and N was relatively

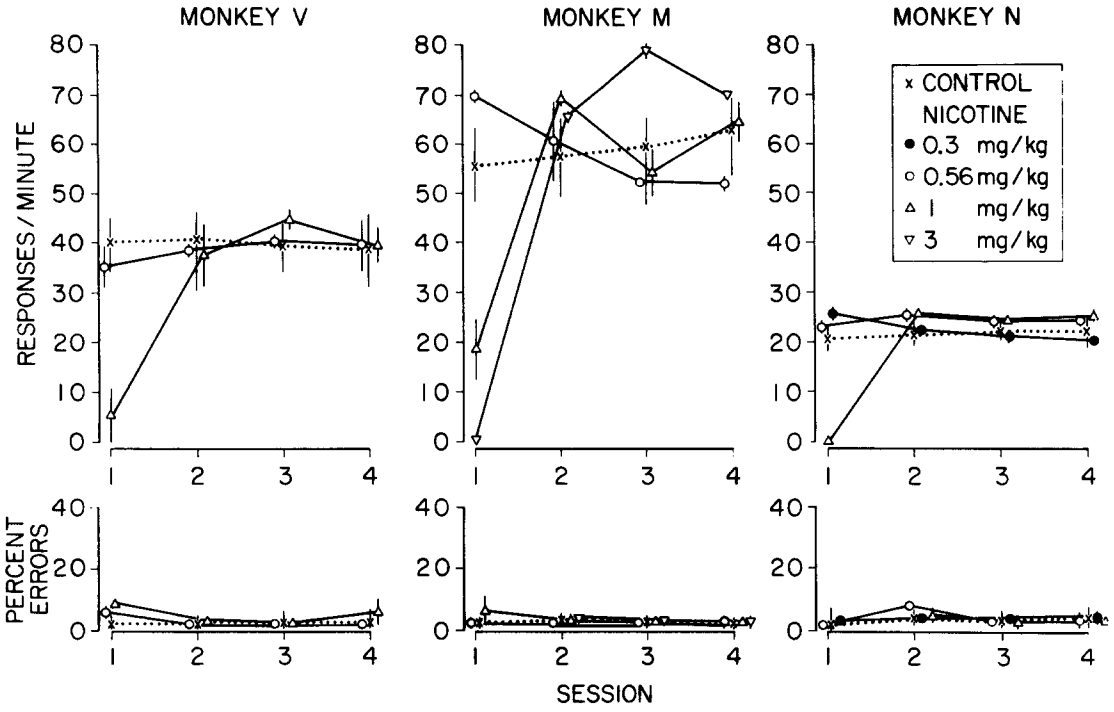

FIG. 1. Overall response rate and percent errors for each subject during the four sessions on control (saline) days and on days when nicotine hydrogen (+)-tartrate alone was injected before the first session. The points and vertical lines indicate the mean and range for 10 control days and for two determinations at each dose of nicotine. 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.

constant across the four sessions, though Monkey N responded at a lower rate. Monkey M responded at a higher control rate than the other two subjects and there was a slight upward trend in the mean overall response rate across the four control sessions, although the ranges of variability overlapped considerably. There were also individual differences in the effects of nicotine alone on response rate. Nicotine was considered to have an effect on the overall response rate during a given session to the extent that the data points for the drug fell outside of the control range for that session. In Monkey V, 0.56 mg/kg of nicotine had no effect on overall response rate during any of the four sessions, whereas in Monkey M, this dose increased response rate during the first session. A small but reliable rate-increasing effect was also seen in Monkey N during the first session at the lowest dose of nicotine (0.3 mg/kg). In all three subjects, however, 1 mg/kg of nicotine produced large decreases in overall response rate during the first session. The rate-decreasing effects of this dose were followed by small rate-increasing effects during the second session in two of the subjects (Monkeys M and N). The biphasic effects of nicotine on response rate (a decrease, then an increase) were even more pronounced at the 3 mg/kg dose in Monkey M. In this case, however, the maximal rate-increasing effect occurred during the third session. In contrast to its varied effects on overall response rate, nicotine generally had no effect on overall accuracy (percent errors). In the few cases where nicotine increased percent errors (e.g., Monkey V, session 1), the effects were relatively small.

Figure 2 shows the effects of cumulative doses of phencyclidine, alone and in combination with nicotine, 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 0.56 mg/kg (Monkeys V and M) or 0.3 mg/kg (Monkey N) of nicotine, which were the lowest effective doses when given alone (Fig. 1), the effects on rate and accuracy were generally similar to those produced by phencyclidine alone. The only notable exception was the small increase in response rate (above the control range) in Monkey V at the lowest dose of phencyclidine. When phencyclidine was administered in combination with higher doses of nicotine, however, the dose-effect curves for response rate tended to shift in a complex manner. At the lowest dose of phencyclidine in combination with either 1 mg/kg (Monkeys V and N) or 3 mg/kg (Monkey M) of nicotine, the overall response rate was virtually zero; this effect is essentially the same as that produced by these doses of nicotine alone during the *first* session (Fig. 1). Of greater interest is the finding obtained when the highest dose of phencyclidine was administered after pretreatment with either 1 mg/kg (Monkey V) or 3 mg/kg (Monkey M) of nicotine, namely, the rate-decreasing effects were substantially smaller than those produced by phencyclidine alone. To a lesser extent, a similar attenuation of the rate-decreasing effect of phencyclidine was seen in Monkey N at the 0.17 mg/kg dose after pretreatment with 0.56 mg/kg of nicotine. This subject, like Monkey V, also showed a small rate-increasing effect at this dose of nicotine when given in combination with the lowest dose of phencyclidine. Additionally, it should be noted that when the lowest dose of phencyclidine was combined with 1 mg/kg of

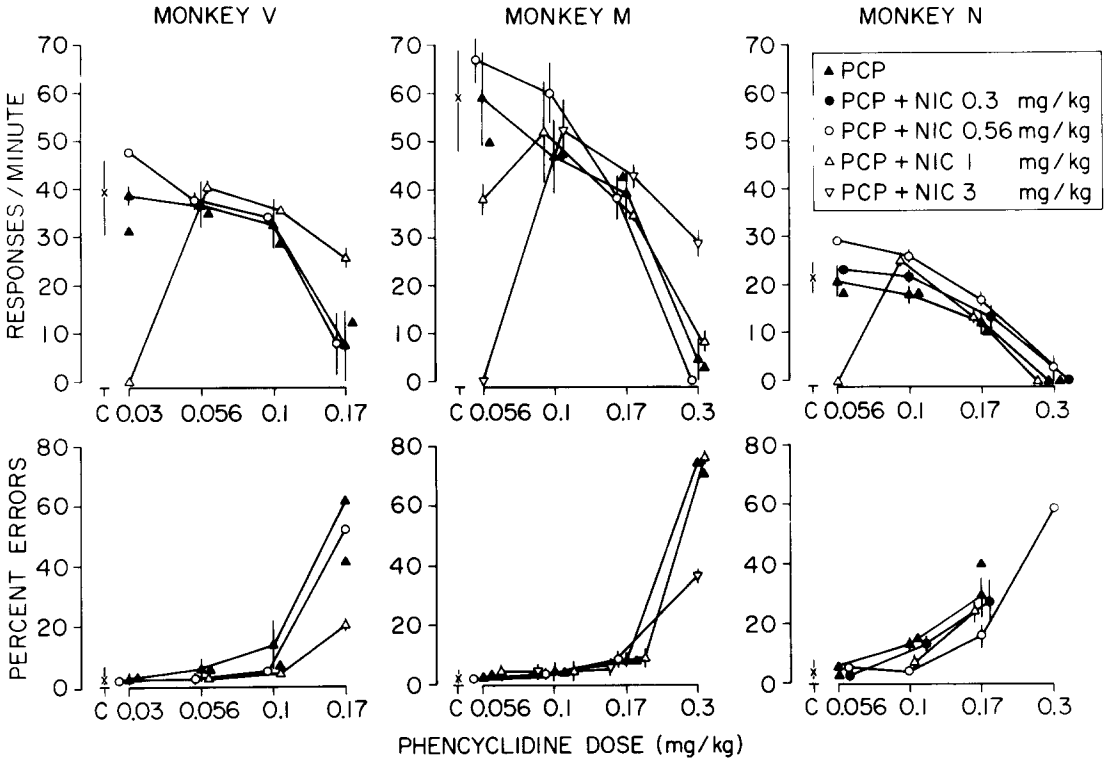

FIG. 2. Effects of cumulative doses of phencyclidine (PCP) hydrochloride, alone and in combination with nicotine (NIC) hydrogen(+)-tartrate, on the overall response rate and percent errors for each subject. The points and vertical lines at C indicate the mean and range for 40 control (saline) sessions. 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 nicotine.

nicotine in Monkey M, the rate-decreasing effect was considerably smaller than that produced by this dose of nicotine alone (compare Figs. 1 and 2).

With regard to overall accuracy, the main finding was that certain doses of nicotine attenuated the error-increasing effects of phencyclidine (Fig. 2, lower panels). Such attenuation was most evident at the highest dose of phencyclidine in Monkey V (with 1 mg/kg of nicotine) and Monkey M (with 3 mg/kg of nicotine) and at the intermediate doses of phencyclidine in Monkey N (with 0.56 mg/kg of nicotine). In general, the effects of phencyclidine alone on both rate and accuracy were replicated after the nicotine-phencyclidine combinations were tested (see the unconnected triangles).

Figure 3 shows some within-session effects of phencyclidine, alone and after pretreatment with nicotine, for each subject. As can be seen in the representative control records (top row), there were marked individual differences in the rate of correct responding, with Monkey M responding at the highest rate and Monkey N at the lowest rate. In each case, however, errors decreased in frequency as the session progressed; i.e., acquisition occurred. After the first 2–3 min of each saline session, relatively few errors were made and there were frequent runs of correct responses separated by brief periods of pausing; this break-and-run pattern of responding was especially noticeable in Monkey N. The second row of records shows the corresponding sessions for intermediate and high doses of nicotine alone. However, these sessions began either 85 min (Monkeys V and M) or 60 min (Monkey N) after nicotine was injected. By that time, the rate-decreasing and error-increasing effects of these doses of nicotine in Monkeys V and M (see Fig. 1) were no longer evident; the only noticeable effect was a slight increase in the rate of correct responding in Monkey M, in comparison to control. In contrast, after the higher doses of phencyclidine alone (third row), there was a relatively low rate of correct responding in each subject, increased pausing, and errors occurred throughout most of the session, with no sign of acquisition. The bottom row of records shows that these large disruptive effects of phencyclidine were attenuated after pretreatment with nicotine (at the same doses and presession injection times as in the second row). In each subject, there was an increase in the rate of correct responding compared to phencyclidine alone, though the rate was still well below control. In Monkeys V and M, there was also a run of correct responses after the first 5 min of the session, a sign of acquisition that was not seen after phencyclidine alone. In Monkey N, it is clear that the response chain was acquired approximately halfway through the session, in marked contrast to phencyclidine alone, where acquisition did not occur. Finally, it should be pointed out that the doses of nicotine that attenuated the disruptive effects of phencyclidine on acquisition usually produced a brief period of vomiting (which ended before the first session) in Monkeys V and M, but not in Monkey N.

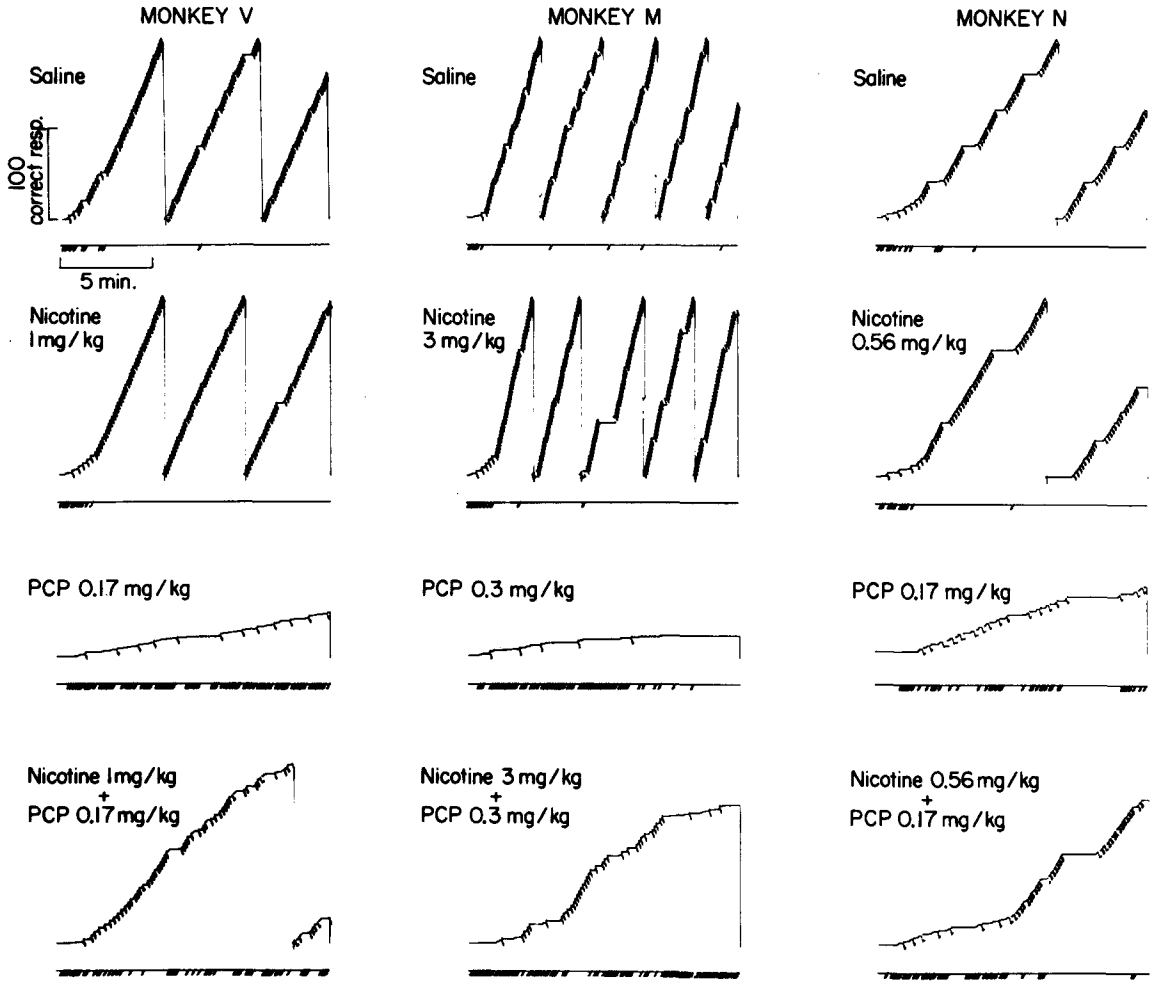

FIG. 3. Within-session effects of phencyclidine (PCP) hydrochloride, alone and after pretreatment with nicotine hydrogen(+)-tartrate, for each subject. Each day there were four 15-min sessions, with a 10-min intersession interval. Each row of cumulative records shows the fourth session for Monkeys V and M and the third session for Monkey N. Saline (top row) and phencyclidine (third and fourth rows) were injected 10 min before the sessions shown, whereas nicotine (second and fourth rows) was injected either 85 min (Monkeys V and M) or 60 min (Monkey N) before the sessions shown. 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.

DISCUSSION

When nicotine was administered alone, the higher doses produced large decreases in overall response rate during the first session (Fig. 1). This finding in patas monkeys is consistent with the results of previous studies in squirrel monkeys [7, 10, 12] in which nicotine decreased response rate under FR schedules of food presentation in a dose-dependent manner. A similar decrease in the rate of FR responding after high doses of nicotine was recently reported for rhesus monkeys in a drug-discrimination task [8]. In the present study, the rate-decreasing effects of nicotine were followed by small rate-increasing effects in two of the three subjects. Such biphasic effects with nicotine, though unusual under an FR schedule, have been obtained at high doses in squirrel monkeys responding under an FI schedule [12]. With regard to overall accuracy during acquisition, nicotine alone had little or no effect on percent errors even at doses that decreased response rate substantially. In this respect, nicotine was similar to THC, which was previously tested in patas monkeys responding in the same type of repeated-acquisition task [14].

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 [3]. 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 [15]. The error-increasing

effects found with phencyclidine alone (Figs. 2 and 3) complement the results obtained with other discrimination techniques. For example, in an oddity-discrimination task with rhesus monkeys, phencyclidine decreased the rate of correct responding in a dose-dependent manner and, at higher doses, increased errors [5].

Unlike the THC-phencyclidine potentiation observed previously [14], certain doses of nicotine were found to attenuate both the rate-decreasing and error-increasing effects of phencyclidine (Figs. 2 and 3). Given the effects of nicotine alone on repeated acquisition, this finding was unexpected. On the other hand, the finding might have been predicted on the basis of Chaturvedi's recent study [6] showing that nicotine attenuated a behavioral effect of phencyclidine (increased locomotor activity) in mice. One could argue, however, that the attenuation observed in that study was not surprising because it occurred at doses of nicotine that decreased activity when given alone. In contrast, in the present study, the attenuation occurred at a time when nicotine alone had little or no behavioral effect (e.g., see Fig. 3). In any case, the present results extend the generality of Chaturvedi's finding across species (mice and monkeys) and the type of behavioral effect of phencyclidine that was attenuated by nicotine (increased activity and disruption of complex schedule-controlled behavior).

In discussing the nicotine-phencyclidine attenuation observed, Chaturvedi [6] suggested that this drug interaction "could be associated with the action of PCP at the nicotinic ACh receptor-ion channel complex" (p. 564). Although Albuquerque *et al.* [1] have obtained data from rat brain synaptosomes that are consistent with this interpretation, the relevance of such data to the behavioral effects of phencyclidine in primates remains to be determined. Of course, the present finding that nicotine attenuated the behavioral effects of phencyclidine does not necessarily mean that the two drugs were interacting at the receptor level. Alternatively, it is possible that the attenuation occurred because the repeated nicotine pretreatment increased the metabolism of phencyclidine. There are at least three lines of evidence that are relevant to this explanation. First, according to a recent review of phencyclidine biotransformation [9], phencyclidine itself, and not its metabolites, seems to be primarily responsible for its behavioral effects. Second, it has been shown that the microsomal cytochrome P-450 enzymatic system is of major importance in the biotransformation of phencyclidine; e.g., pretreatment with phenobarbital, which is known to stimulate the synthesis of cytochrome P-450, was found to attenuate the effects of phencyclidine in a behavioral test measuring ataxia [9]. Finally, there is some evidence indicating that chronic administration of nicotine can also cause this type of enzyme induction, at least in rats [2,11]. Additional research is needed to determine whether the nicotine dosing regimen used in the present study produces enzyme induction in primates and, if so, whether this can fully explain the nicotine-phencyclidine interaction observed. Although the attenuation of phencyclidine's disruptive behavioral effects by nicotine probably has limited practical significance because of the nicotine-induced vomiting, it nevertheless is interesting in terms of the mechanism involved and deserves further study.

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