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Differential Interaction of Cholecystokinin With Morphine and Phencyclidine: Effects on Operant Behavior in Pigeons[1]

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WINSAUER, P. J. AND D. M. THOMPSON. *Differential interaction of cholecystokinin with morphine and phencyclidine: Effects on operant behavior in pigeons.* PHARMACOL BIOCHEM BEHAV **41**(1) 83–90, 1992.—To extend previous operant research in rats with morphine and cholecystokinin (CCK), these two substances were given alone and in combination to pigeons. In one component of a multiple schedule, responding of pigeons (key pecking) was reinforced under a fixed-ratio (FR 50) schedule of food presentation. In the other component, responding had no programmed consequence (timeout). Each session consisted of four 10-min timeout components alternating with four 5-min FR components. In Experiment 1, cumulative dose-effect curves for morphine were obtained by giving an IM injection before each of four FR components; successive injections increased the cumulative dose by ¼ log-unit steps. In general, as the cumulative dose of morphine increased, the overall response rate in each FR component decreased. Dose-dependent decreases in response rate also occurred when single noncumulative doses of CCK were administered alone 20 min prior to the start of the session. This effect of CCK alone diminished as the session progressed. When CCK was given as a pretreatment before cumulative doses of morphine, the morphine dose-effect curve for response rate shifted to the left. At intermediate doses of CCK, the "potentiation" was so complete that two of three subjects failed to respond during any of the four FR components (i.e., the dose-effect curve for morphine had shifted approximately 1 log-unit to the left). In order to evaluate the pharmacological specificity of this effect, cumulative doses of phencyclidine were administered in combination with CCK (Experiment 2). Unlike the interaction between morphine and CCK, the interaction between phencyclidine and CCK was reciprocal. After pretreatment with each dose of CCK, high doses of phencyclidine tended to produce smaller rate-decreasing effects than those obtained with phencyclidine alone. Moreover, low doses of phencyclidine attenuated the rate-decreasing effects of the higher doses of CCK in the initial FR components. The results of Experiment 1 extend the generality of previous findings in rats with morphine and CCK on schedule-controlled behavior, while the results of Experiment 2 indicate distinct differences in the way in which CCK interacts with morphine and phencyclidine.

Fixed-ratio schedule Cumulative dosing Morphine Phencyclidine Cholecystokinin Drug interaction Pigeons

A recent study by Winsauer and Riley (36) examined the interactive effects of cholecystokinin (CCK) and morphine on operant behavior in rodents. Both drugs were given alone and in combination to rats responding under a multiple-schedule baseline with alternating fixed-ratio (FR) and timeout components. More specifically, increasing cumulative doses of morphine were given before each of four FR components, and varying doses of CCK were administered as pretreatments before the start of the session. Naltrexone, a prototype opioid antagonist, was also given as a pretreatment for comparison purposes. When CCK and morphine were given in combination, CCK potentiated the rate-decreasing effects produced by the increasing cumulative doses of morphine. This unexpected interaction of CCK and morphine was remarkably different from that of naltrexone and morphine, and different from CCK-morphine interactions reported in other studies using measures such as analgesia [cf. (36)].

Although the basis of these CCK-morphine interactions remains largely unexplained, the further examination of these two drugs using schedule-controlled operant behavior is of particular interest. Whether or not the interaction of these drugs on operant behavior is a result of the characteristics of the specific behavioral response or a more general action of the drugs in any organism could be answered by attempting to replicate this interaction in another species. In general, species comparisons for drug interactions with CCK are particularly important in light of the already well-established species differences found for CCK on satiety [e.g., (21)]. As Morley et al. (21) point out, certain species appear to be resistant to the satiating effects of CCK. Furthermore, in those species in which CCK does produce an effect on satiety, this effect is mediated by a peripheral mechanism in some species and by a central mechanism in others.

Experiment 1 examined the interactive effects of CCK and morphine on operant behavior in pigeons to extend these effects

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in another species. In addition, the interaction of CCK with another centrally acting drug, phencyclidine, was also tested to examine the pharmacological specificity of these effects and possibly extend these findings to another drug (Experiment 2). Unlike both morphine and phencyclidine, relatively little is known about the effects of CCK on schedule-controlled behavior in pigeons. In rats, CCK alone has been shown to decrease response rates under several different simple schedules of food or water reinforcement (2, 6, 12, 20, 35). A cumulative dosing procedure was used for both comparisons 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 [e.g., (26, 36, 38)].

EXPERIMENT 1

METHOD

Subjects

Three adult male White Carneaux pigeons (P-197, P-3124 and P-624) maintained at approximately 80% of their free-feeding body weights (445 g, 465 g and 410 g) served as subjects. Food was earned during the experimental session, and if necessary, was provided after the session to maintain subjects at their 80% weight. Water and grit were always available in the home cages. All three subjects had a history of responding under FR schedules.

Apparatus

The experimental space was a standard three-key pigeon chamber (BRS/LVE model SEC-002). The center key could be transilluminated by either of two Sylvania 24-ESB indicator lamps, one with a red plastic end cap and one with no cap. This translucent response key required a minimum force of 0.18 N for activation. Electromechanical programming and recording equipment was used. White noise was continuously present in the chamber to mask extraneous sounds, and a fan provided ventilation.

Procedure

Baseline. In one component of a multiple schedule, the center key was illuminated with white light, and responding on this key was reinforced under a fixed-ratio (FR 50) schedule of food presentation (5-s access to mixed grain). Presentation of the grain magazine was accompanied by the offset of the white key light and onset of the magazine light. During the other component, the key light was red and responding had no programmed consequences (timeout). Sessions began with a 10-min timeout component, which alternated with a 5-min FR component. Each session consisted of four timeout components and four FR components.

The data for the FR component were analyzed in terms of overall rate (responses/s). The data for each subject were analyzed by comparing the mean of several drug sessions at a given dose with the control range of variability. A drug was considered to have an effect to the extent that the dose data fell outside of the control range (23, 25, 26). In addition to these measures based on session totals, within-session changes in responding were monitored by a cumulative recorder.

Drug testing. Before drug testing began, the rate of responding under the multiple-schedule baseline was stabilized. The baseline was considered stable when the response rate no longer showed systematic change from either component to component or session to session. After the baseline had stabilized (approximately 10 sessions), cumulative dose-effect data were obtained for morphine sulfate. Doses of morphine were dissolved in saline (0.9%) and injected IM at the start of each timeout component, i.e., 10 min before each FR component. In two subjects (P-197 and P-624), 0.56 mg/kg of morphine was administered before the first timeout component, and 0.44, 0.8, and 1.4 mg/kg, respectively, were injected at the start of the remaining timeout components. Each successive injection increased the dose of morphine in ¼ log-unit steps, yielding cumulative doses of 0.56, 1, 1.8 and 3.2 mg/kg. A similar regimen for injections was used with P-3124 except that the cumulative dose range was slightly lower (i.e., 0.32–1.8 mg/kg).

Next, single log doses of sulfated cholecystokinin-octapeptide (CCK-8) dissolved in a vehicle of saline and a small amount of 1-M sodium bicarbonate were administered. CCK (5.6–32 μg/kg, IM) was first given alone 20 min before the start of the session, and then as a pretreatment, 20 min before the administration of the first dose of morphine. Doses of CCK were tested in a mixed order, and each dose was given alone before being given as a pretreatment with morphine. Each dose and dose combination were redetermined before the next dose was tested. Finally, after all the dose combinations had been tested, the cumulative dose-effect curves for morphine alone were redetermined. Throughout testing, injections of vehicle were given either alone at the start of the session, as a control for CCK, or in combination with four saline injections as a control for CCK and morphine combinations. Saline alone, given at the start of each timeout component, served as a control for morphine alone. The volume for morphine injections and the saline control injections was 0.1 ml/100 g of body weight. Doses of CCK were calculated from a 50-μg/ml stock solution, and control injections for CCK consisted of vehicle given in a volume comparable to that for a high dose of CCK (e.g., the volume for the 32-mg/kg dose for P-3124 was 0.3 ml). Drug sessions were usually conducted on Tuesdays and Fridays, with control sessions occurring on Thursdays, and baseline sessions (no injections) on Mondays and Wednesdays.

RESULTS

The upper panel of Fig. 1 shows the rate of responding across all four FR components on control days, and on days when CCK was given alone 20 min before the start of the session. During control sessions, responding was relatively constant across the four FR components for all three subjects, although P-3124 did show a small increase in rate across successive FR components. In comparison with the ranges of control variability, CCK produced dose-dependent decreases in the rate of responding in all three subjects. In general, the low dose for each subject had little or no effect on response rate, while the intermediate dose produced a decrease in response rate in the first component in two of three subjects. The only notable exception occurred in P-624 at the 18-μg/kg dose, where a small decrease in response rate was also evident in the second component. The highest dose of CCK generally decreased the rate of responding for the first two components (approximately 30 min) in all three subjects. This can clearly be seen in P-3124 and P-624 at the 32-μg/kg dose, where the decrease in response rate was graded across the first two FR components. Although the rate-decreasing effects for P-197 in the second component were not as large as those for the other two subjects, both determinations did produce a

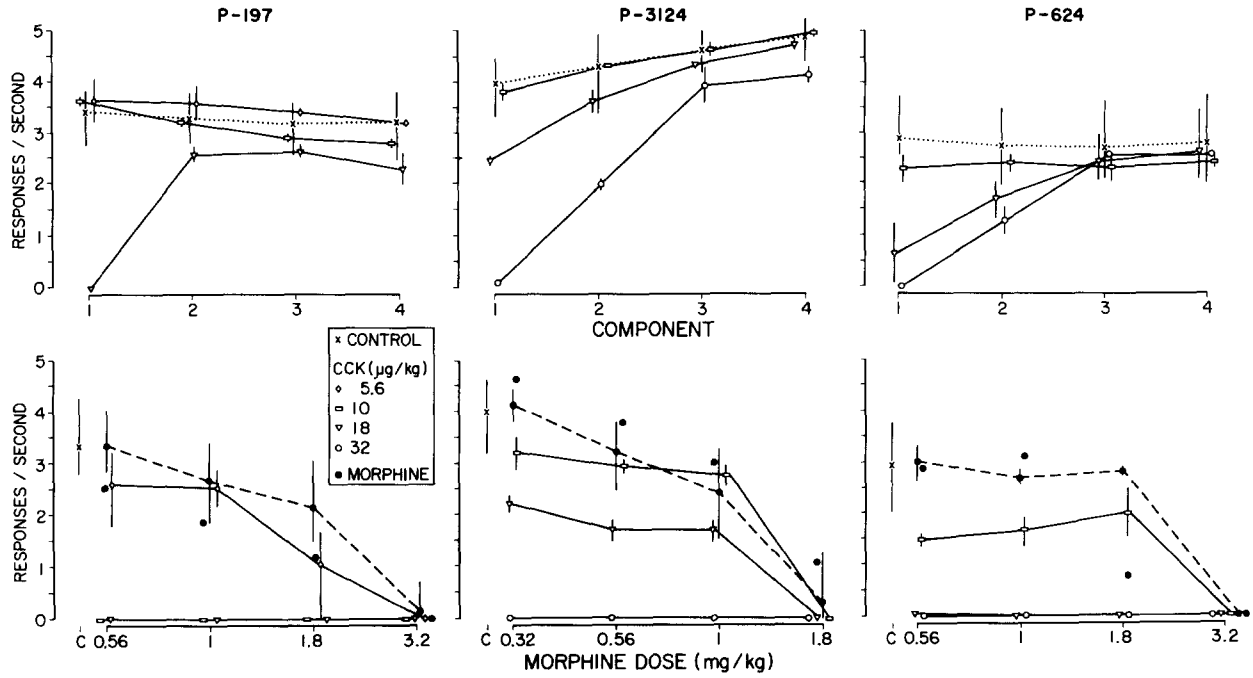

FIG. 1. The upper panels show the overall response rate for all three subjects during the four FR components on control (vehicle) days and on days when cholecystokinin (CCK) alone was injected before the start of the session. The points and vertical lines indicate the mean and range for 10 control days and for 2 or 3 determinations at each dose of CCK. The points without vertical lines indicate an instance in which the range is encompassed by the point. The lower panels show the effects of cumulative doses of morphine, alone and in combination with CCK. The points and vertical lines at (C) indicate the mean and range for 12–14 control (saline or vehicle and saline) days. The points and vertical lines in the dose-effect curves for each combination indicate the mean and range for 2 or 3 determinations, and the connected filled circles represent 3 or 4 determinations for morphine alone. The points in the dose-effect data without vertical lines indicate an instance in which the range is encompassed by the point. The unconnected filled circles show a redetermination of the dose-effect data for morphine alone after morphine was tested in combination with CCK.

small rate-decreasing effect.

The lower panel of Fig. 1 shows the dose-effect data for morphine alone and for morphine in combination with CCK. In general, when morphine was administered alone, the overall response rate decreased with increasing doses in all three subjects. When morphine was given in combination with CCK, the rate-decreasing effects were generally greater than those obtained with morphine alone. This interaction, which produced greater rate-decreasing effects than expected from the simple addition of the effects of each drug alone, was most evident at the highest dose of CCK where responding was virtually eliminated at each dose of morphine in all three subjects. In two of three subjects, responding was also eliminated at an intermediate dose of CCK in combination with each of the doses of morphine. Although the rate-decreasing effects for P-3124 at the intermediate dose of CCK were not as large as those seen for the other two subjects, the effects were still greater than those seen with morphine alone (e.g., 0.56 mg/kg). This was also true for P-624 at the lowest dose of CCK in combination with morphine. In P-197 and P-3124, the effects at the lowest dose of CCK closely approximated the effects of morphine alone.

Figure 2 shows cumulative records from four different sessions for P-3124 that illustrate some of the within-session effects of both morphine and CCK alone, and morphine after pretreatment with CCK. A representative control session is shown at the top. As shown in this record, the pattern and rate of responding were consistent from component to component; responding occurred at a high rate, and brief pauses followed reinforcement and preceded each run of responses. After 32 μg/kg of CCK alone (second record), responding was almost eliminated in the first component and was substantially decreased in the second component. During the third and fourth components, however, the rate of responding approximated that for a control session. With increasing doses of morphine (third record), the pattern of responding showed greater disruption with each successive FR component; i.e., longer pauses occurred after reinforcement, and fewer ratios were completed during the 5-min component. The bottom record shows a session in which morphine was given after pretreatment with 32 μg/kg of CCK. As can be seen, responding during this session was virtually eliminated.

DISCUSSION

In the present study, CCK in combination with morphine produced dose-dependent rate-decreasing effects. In all three subjects, these effects were substantially larger than those obtained with the cumulative doses of morphine alone. Although CCK alone also produced dose-dependent rate-decreasing effects, these effects were generally not large enough to account for the extensive rate-decreasing effects obtained across all four FR components after the administration of the combination. Not only was responding virtually eliminated at the highest dose of CCK in combination with morphine in all three subjects, it was also eliminated at an intermediate dose of CCK in two of three subjects. The large effects produced by the combination, there-

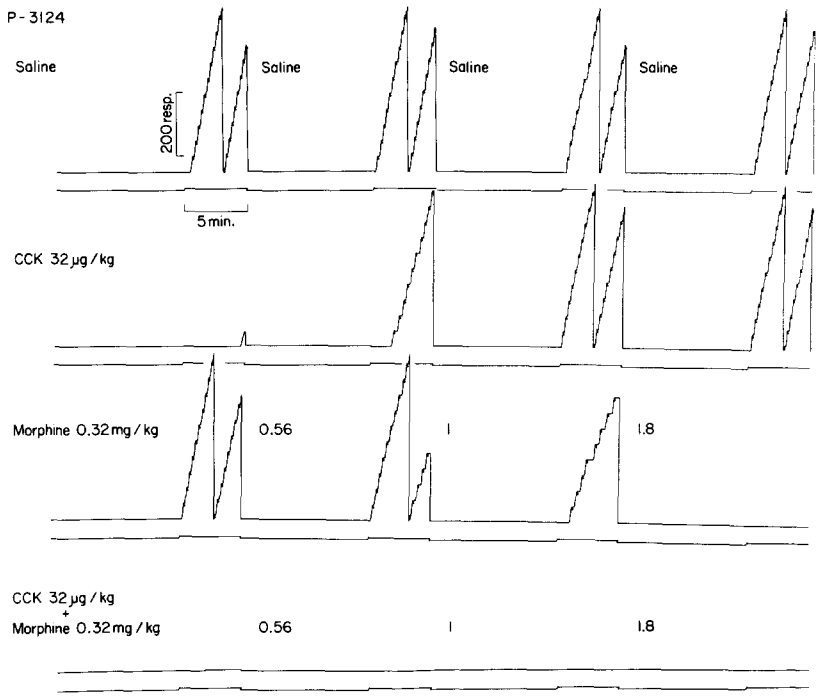

FIG. 2. Within-session effects of cholecystokinin (CCK) alone, cumulative doses of morphine alone, and morphine in combination with CCK in P-3124. In the 5-min FR components, the response pen stepped upward with each response and was deflected downward with each reinforcement. The event pen was deflected downward during the 10-min timeout components. Each of the four cumulative records is from a different day. The top record shows a control session in which saline was injected at the start of each timeout component. The second record shows a session in which CCK was given alone 20 min before the start of the session, and the third record shows a session where increasing cumulative doses of morphine alone (0.32–1.8 mg/kg) preceded each FR component. The bottom record shows a session where cumulative doses of morphine were given after pretreatment with 32 µg/kg of CCK.

fore, cannot solely be explained as the summation of the rate-decreasing effects produced by each drug alone. These effects also cannot be attributed to the development of "supersensitivity" to morphine (i.e., an increased sensitivity due to repeated drug administration) since the effects of morphine alone were generally replicated after the CCK-morphine combinations were tested. Probably the most reasonable interpretation of the large rate-decreasing effects produced by the combination is that CCK "potentiated" the effects of morphine [cf. (26, 27, 36)].

The effects obtained in the present study with morphine and CCK in pigeons are similar to those reported for rats responding under an FR schedule. Winsauer and Riley (36) found that pretreatment with a similar range of doses of CCK potentiated the rate-decreasing effects of cumulative doses of morphine. In that study, as in the present study, the dose-effect curve for morphine tended to shift to the left after CCK pretreatment, and there were similar instances where the rate-decreasing effects produced by the combination were greater than those expected from the summation of the effects of CCK and morphine alone. Although the rate-decreasing effects of CCK alone were smaller in the rat study, and the interaction obtained was less complete (i.e., rate-decreasing effects occurred at fewer doses of morphine), the effects of the combination in pigeons were qualitatively similar to the effects of the combination in rats. Thus the present research in pigeons extends the generality of the effects for both CCK alone and CCK in combination with morphine on operant behavior across species (36).

Several possible mechanisms for this type of interaction have been suggested [cf. (36)]; however, the lack of research using operant behavior makes it difficult to compare previous findings with CCK and morphine to the present finding. This is especially true since the effects of CCK and morphine in combination on operant behavior are in contrast to the antagonistic effects reported previously for CCK and opiate combinations on such measures as analgesia and feeding [e.g., (10, 32, 35)]. Generally, it has been argued that the observed interactions were related to the differing effects each drug alone had on the dopaminergic system. Given the evidence for the coexistence of CCK and dopamine in certain brain areas and neurons (4,13), and the evidence that morphine (30) can influence the functional availability of dopamine, the involvement of this neurotransmitter system is implicated. The ability of CCK to influence the dopaminergic system and behavior has been shown by Hsaio et al. (14), who demonstrated altered responding (locomotor activity) with both CCK and a dopaminergic agonist after chemical denervation of dopamine terminals by 6-hydroxydopamine. CCK can also decrease the availability of dopamine by influencing both presynaptic release (5) and postsynaptic receptor sites (31). All of these data, however, have not led to a greater understanding of how CCK and morphine act on this system in combina-

tion. Interpreting the CCK-morphine interaction is complicated by research with rats indicating that morphine can increase, decrease, or have no effect on the actions of dopamine (30). CCK alone has produced conflicting results that often depend on the specific brain region examined and the route of administration [cf. (22)]. Until these apparent discrepancies in the literature are resolved, and more is known about the central actions of both drugs, further speculation about the dopaminergic mechanism(s) underlying their interaction would be premature.

EXPERIMENT 2

Two important reasons for specifically studying cholecystokinin and phencyclidine stem from the fact that both substances have been thought to play a role in schizophrenia [e.g., (8,9)], and recent biochemical data have shown that phencyclidine can dose-dependently inhibit the potassium-induced release of endogenous CCK in several regions of the brain (1). Unlike CCK, the effects of phencyclidine on schedule-controlled behavior in pigeons are well established. Under FR schedules, for example, Wenger (33) reported that phencyclidine dose-dependently decreased the overall rate of responding. This finding is consistent with numerous other reports on the effects of phencyclidine on responding in pigeons under both simple (17, 33, 34) and second-order (29,37) FR schedules of food presentation. Similar rate-decreasing effects under FR schedules have also been reported for phencyclidine when it was given in combination with other drugs. In pigeons responding under a second-order FR schedule, Thompson and Moerschbaecher (24) found that pentobarbital potentiated the rate-decreasing effects of phencyclidine (i.e., the phencyclidine dose-effect curves for response rate shifted to the left as the dose of pentobarbital increased). Although other drugs [e.g., *d*-amphetamine (25), cocaine (26), and delta-9-tetrahydrocannabinol (27)] have been reported to potentiate the rate-decreasing effects of phencyclidine on schedule-controlled behavior, these interaction studies were conducted with monkeys. Whether or not cholecystokinin (CCK) produces the same behavioral effects as these CNS drugs when combined with phencyclidine in pigeons needs to be investigated.

Experiment 2 examined the behavioral interaction of phencyclidine and CCK in pigeons. The multiple-schedule baseline was the same as that used in Experiment 1. A cumulative dosing procedure was utilized to evaluate the effects of phencyclidine alone and phencyclidine in combination with CCK. To assess the interaction of phencyclidine and CCK, cumulative doses of phencyclidine were administered after pretreatment with varying doses of CCK.

METHOD

Three adult male White Carneaux pigeons (P-3933, P-3124 and P-1754) maintained at approximately 80% of their free-feeding body weights (435 g, 465 g and 437 g) served as subjects. The apparatus and behavioral conditions in this experiment were identical to those in Experiment 1. Doses of phencyclidine were dissolved in saline (0.9%) and injected similarly to morphine (i.e., 10 min before each FR component). Successive injections increased the cumulative dose in ¼ log-unit steps, yielding cumulative doses of 0.18, 0.32, 0.56 and 1 mg/kg for subjects P-3933 and P-3124, and cumulative doses of 0.32, 0.56, 1 and 1.8 mg/kg for subject P-1754. As in Experiment 1, doses of CCK were tested in a mixed order, and each dose was given alone before being given as a pretreatment with phencyclidine. Each dose and dose combination were redetermined before the next dose was tested. Cumulative dose-effect curves for phencyclidine alone were redetermined after all CCK-phencyclidine combinations had been tested.

RESULTS

The upper panel of Fig. 3 shows the rate of responding for all three subjects across all four FR components on control days, and on days when CCK was given alone 20 min before the start of the session. For two of three subjects (P-3933 and P-3124), control responding was relatively constant across the four FR components. For subject P-1754, however, control responding did show a small increase in rate across successive FR components. In contrast, CCK produced dose-dependent decreases in the rate of responding in all three subjects. Although the doses of CCK administered to each subject varied, these doses did produce comparable rate-decreasing effects. The lowest dose generally had little or no effect, while intermediate doses tended to produce a rate-decreasing effect in the first and second FR components. The highest dose of CCK alone produced even larger rate-decreasing effects in all three subjects. In subjects P-3124 and P-1754, for example, the response rates were similar to that during control sessions only in the fourth FR component.

The lower panel of Fig. 3 shows the dose-effect data for phencyclidine alone and for phencyclidine in combination with CCK. In general, as the cumulative dose of phencyclidine increased, the overall response rate decreased. Note that the highest dose of phencyclidine alone eliminated responding in all three subjects. When phencyclidine was given in combination with CCK, the dose-effect curve shifted in a complex manner. At the lowest dose of phencyclidine, the rate-decreasing effects of higher doses of CCK were attenuated. In subjects P-3933 and P-1754, for example, 0.18 mg/kg of phencyclidine in combination with the highest dose of CCK given to each bird produced only small rate-decreasing effects. These effects are in marked contrast to the large rate-decreasing effects seen with these doses of CCK alone (see upper panel). Although the attenuation of the effect of CCK by the low dose of phencyclidine was not as marked for P-3124 at the highest dose of CCK (56 μg/kg), a notable attenuation was evident when 32 μg/kg of CCK was given in combination with phencyclidine. At the two intermediate doses of phencyclidine, the pretreatment with CCK produced effects similar to those produced by phencyclidine alone, i.e., the combination data generally cluster around the dashed line (representing phencyclidine alone), and the ranges of variability tend to overlap. A notable exception occurred in P-1754 at the 1-mg/kg dose of phencyclidine in combination with 18 μg/kg of CCK where the effect of the combination was less than that for phencyclidine alone. Interestingly, this attenuation of phencyclidine's rate-decreasing effects by CCK was also noted in P-3933 and P-3124 at the highest dose of phencyclidine. Note that in both these subjects, the data for CCK in combination with the 1-mg/kg dose of phencyclidine generally fall to the right of the dashed line. This shift to the right is most evident in P-3933 where the data for phencyclidine in combination with the 32- and 100-μg/kg doses of CCK is shifted approximately ¼ log-unit.

Figure 4 shows cumulative records from four different sessions for P-3124 that illustrate some of the within-session effects of both phencyclidine and CCK alone, and phencyclidine after pretreatment with CCK. A representative control session is shown at the top. As shown in this record, the pattern and rate of responding were consistent from component to component. When 56 μg/kg of CCK was given alone 20 min before the start of the session (second record), responding was eliminated in the

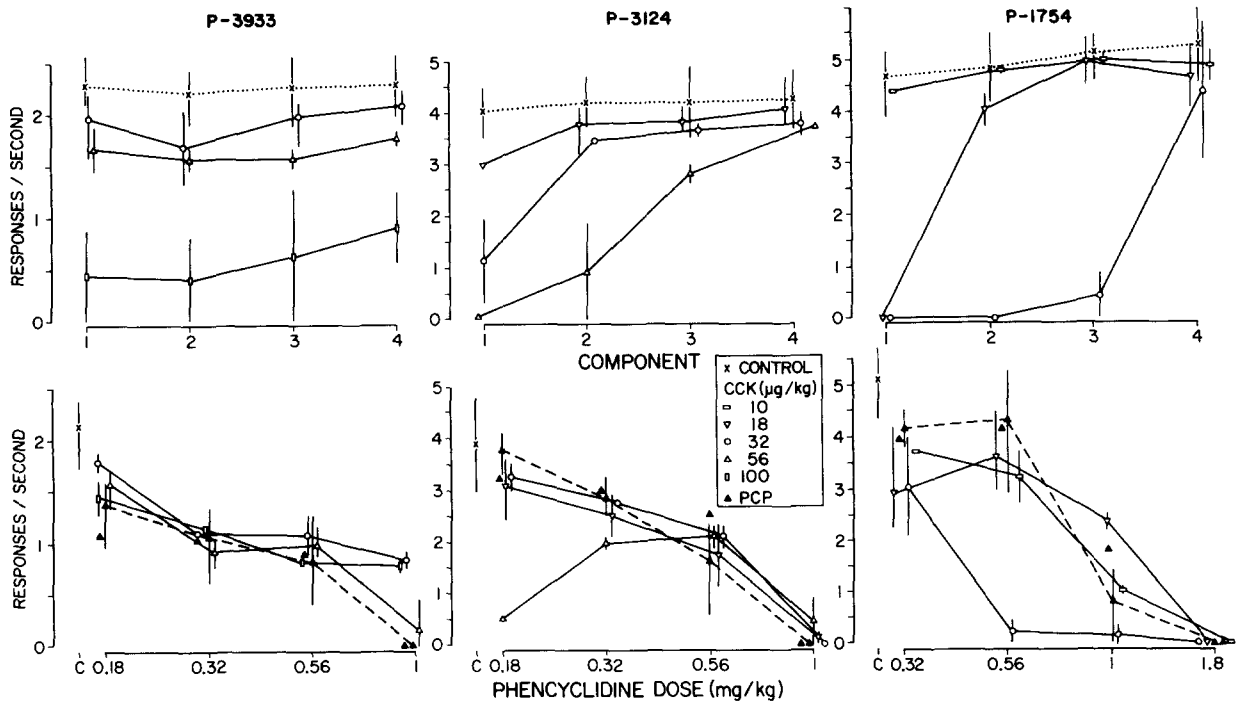

FIG. 3. The upper panels show the overall response rate for all three subjects during the four FR components on control (vehicle) days and on days when CCK alone was injected before the start of the session. The points and vertical lines indicate the mean and range for 6–11 control days and for 2 or 3 determinations at each dose of CCK. The points without vertical lines indicate an instance in which the range is encompassed by the point. The lower panels show the effects of cumulative doses of phencyclidine (PCP), alone and in combination with CCK. The points and vertical lines at (C) indicate the mean and range for 3–15 control (saline or vehicle and saline) days. The points and vertical lines in the dose-effect curves for each combination indicate the mean and range for 2 or 3 determinations, and the connected filled triangles represent 5 determinations for phencyclidine alone. At least two of these five determinations were given in combination with a single vehicle injection which was given at the start of the session, similar to the pretreatment with CCK. The points in the dose-effect data without vertical lines indicate an instance in which the range is encompassed by the point. The unconnected filled triangles show a redetermination of the dose-effect data for phencyclidine alone after phencyclidine was tested in combination with CCK.

first component and was substantially decreased in the second component. Only small rate-decreasing effects occurred in the third component, and by the fourth component, responding approximated that for a control session. With increasing doses of phencyclidine (third record), the pattern of responding showed greater disruption with each successive component (i.e., longer pauses occurred after reinforcement and fewer ratios were completed during the 5-min component). The bottom record shows a session in which phencyclidine was given after pretreatment with 56 µg/kg of CCK. Note that the rate-decreasing effect produced with the combination in the first component was less than that seen with CCK alone, and the rate-decreasing effect in the last component was less than that seen with phencyclidine alone.

DISCUSSION

In both experiments, CCK alone produced dose-dependent rate-decreasing effects on responding under an FR schedule in pigeons. This finding in pigeons extends the generality of previous observations in rats where CCK has been shown to decrease the rate of FR responding in a dose-dependent manner (2, 6, 12, 20, 35, 36). The potentiation obtained in Experiment 1 with CCK and morphine was also comparable to that found in a previous study involving rats (36). The reciprocal interaction with CCK and phencyclidine (i.e., the attenuation of the effects of high doses of CCK by low doses of phencyclidine and attenuation of the effects of high doses of phencyclidine by varying doses of CCK), however, was unexpectedly different from the interaction obtained with CCK and morphine. That CCK interacted differently with phencylidine and morphine is interesting because all three drugs alone produced similar rate-decreasing effects. Moreover, the dose-dependent rate-decreasing effects found with phencyclidine alone were comparable to those found in previous studies using pigeons with both cumulative and noncumulative dosing procedures (17, 29, 33, 34, 37). Given the similarity between the effects of phencyclidine in this study and those in other operant studies involving pigeons, and the similarities of all three drugs on FR responding in the present study, it is difficult to explain how CCK differentially interacted with morphine and phencyclidine.

The complex drug interaction observed with CCK and phencyclidine is different from the interactions reported for a variety of other drugs when tested in combination with phencyclidine. In one of the few phencyclidine interaction studies involving pigeons (24), pentobarbital potentiated the rate-decreasing effects of phencyclidine under a second-order FR schedule. In addition, *d*-amphetamine (25), cocaine (26), delta-9-tetrahydrocannabinol (27), and pentobarbital (23) have all been found to potentiate the rate-decreasing effects of phencyclidine in monkeys. Although limited success in attenuating the rate-decreasing effects of phencyclidine has been reported in some species [e.g., by

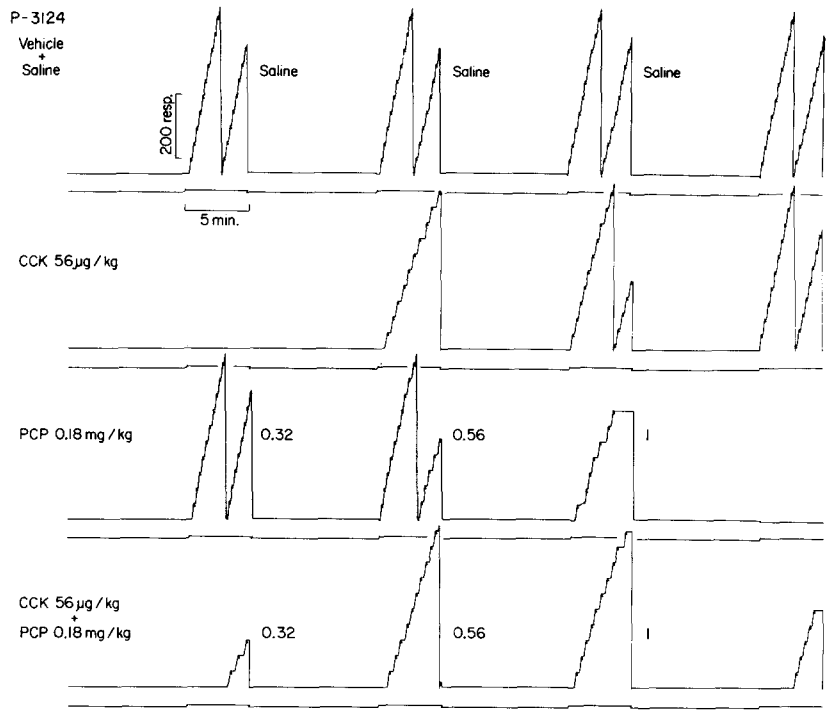

FIG. 4. Within-session effects of CCK (56 µg/kg), cumulative doses of PCP alone (0.18–1 mg/kg), and PCP in combination with CCK in P-3124. For other details, see legend for Fig. 2.

nicotine in monkeys (28), by yohimbine and prazosin in rats (3)], this research has not yet been extended to schedule-controlled behavior in pigeons. The potential problems with doing this are evident in several reports. Metaphit, for example, which has been shown to antagonize phencyclidine-induced stereotypy and ataxia in rats, fails to antagonize either measure in pigeons (16). In fact, Koek (16) found that after IM administration in the pigeon, metaphit produced phencyclidine-appropriate responding in a drug discrimination task. A related issue is the degree and selectivity of antagonism within a given species. Yohimbine and prazosin in the rat, for example, partially reverse the rate-decreasing effects of phencyclidine, but not its discriminative stimulus properties (3). Whether or not CCK can attenuate the discriminative stimulus properties of phencyclidine in the pigeon remains to be investigated.

Since phencyclidine has been reported to increase the availability of dopamine by stimulating release and inhibiting reuptake (7), it is possible that the observed attenuation again reflects the extent to which each drug opposes the effect of the other on the dopaminergic system. This interpretation for the CCK-phencyclidine interaction is complicated, however, by the finding that haloperidol, a dopamine antagonist, fails to attenuate the rate-decreasing effects of phencyclidine in pigeons (15) and by the lack of consistent data on the central actions of CCK following peripheral administration [e.g., (6,22)].

Interestingly, one of the more plausible biochemical explanations of CCK's ability to attenuate the effects of phencyclidine involves this peptide's possible interaction with the NMDA receptor channel complex. Specifically, in vitro results using striatal membranes have shown that CCK can produce marked downregulation of [^{3}H]glutamate binding sites (11). Given the reported location of the phencyclidine receptor inside the NMDA receptor channel complex [see (18) for review], the broader ramification of this finding is that CCK could be limiting the binding of phencyclidine to its receptor by decreasing the number of open NMDA channels. In fact, phencyclidine binding has already been shown to depend often on the presence of excitatory amino acid receptor agonists (18,19). In the present experiment, CCK was given as a pretreatment 20-min presession, and phencyclidine was given in increasing cumulative doses as the session progressed. If CCK had decreased excitatory amino acid binding in vivo (and thereby effectively decreased the number of available phencyclidine receptors), one would have expected phencyclidine to have less of an effect after each cumulative dose just as it appeared to in two of three subjects.

Although this explanation clearly would not account for phencyclidine's attenuation of CCK's effects, it does seem to be a plausible explanation for at least part of the reciprocal interaction found in the present experiment. Allard et al. (1) has shown that phencyclidine can inhibit the release of CCK from several regions of the rat brain which have high concentrations of endogenous CCK. However, to our knowledge, it has not been shown that peripherally administered exogenous CCK produces its central effects by releasing centrally located stores of endogenous CCK. If this were the case, it could explain phencyclidine's ability to attenuate CCK's effects. Although this explanation is highly speculative, it clearly exemplifies the need for future research with these substances in pigeons as well as other species. In particular, future research with these substances seems especially critical, since both substances have been closely tied to psychotic behaviors in humans often resembling schizophrenia [e.g., (8,9)].

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