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Cholecystokinin Potentiates the Rate-Decreasing Effects of Morphine on Schedule-Controlled Behavior in Rats

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WINSAUER, P. J. AND A. L. RILEY. *Cholecystokinin potentiates the rate-decreasing effects of morphine on schedule-controlled behavior in rats.* PHARMACOL BIOCHEM BEHAV **30**(3) 569–575, 1988.—In one component of a multiple schedule, responding (licking in rats) was reinforced under a fixed-ratio (FR 50) schedule of water presentation. In the other component, responding had no programmed consequences (timeout). Each session consisted of four 10-min timeout components alternating with four FR components. In general, increasing cumulative doses of morphine (3.2–18 mg/kg) produced a dose-dependent decrease in the overall rate of responding. In one subject, cholecystokinin (CCK) alone (10–32 μg/kg) produced dose-dependent decreases in rate in the first component, while in the other two subjects relatively little decrease in rate occurred. When these doses of CCK were given as a pretreatment before morphine, the decrease in overall response rate was greater than that found with morphine alone. This interaction was most noticeable at the lowest dose of morphine where CCK produced a dose-dependent "potentiation" of the rate-decreasing effects. Although the potentiation by CCK was not as evident at the intermediate doses of morphine, there were instances in which the rate-decreasing effects produced by the combination were greater than those expected from addition of the effects of CCK and morphine alone. In contrast, when naltrexone (1 mg/kg) was given as a pretreatment, little or no rate-decreasing effects were produced by the cumulative doses of morphine. Furthermore, pretreatment with naltrexone and the administration of a higher dose range of morphine indicated the dose-effect curve for morphine had shifted approximately 3/4 log-units to the right. The CCK-morphine potentiation found in the present study with schedule-controlled behavior is in contrast to the CCK-morphine antagonism previously reported using measures such as analgesia and feeding.

Operant licking Fixed ratio CCK Morphine Naltrexone Rats

CHOLECYSTOKININ (CCK) has been reported to interact in an antagonistic manner with both morphine and the morphine-like endogenous opioid β-endorphin across a wide range of measures. In the isolated guinea pig ileum preparation, for example, Zetler [32] found that administration of either morphine or β-endorphin antagonized the intestinal contracting actions produced by CCK. In a more recent study of opiate analgesia in rats, Faris *et al.* [7,8] reported that CCK (3–5 μg/kg, IP) attenuated opiate-mediated analgesia as measured by an increase in the latency to respond in the tail-flick test. In a similar study using the hot-plate test, Itoh *et al.* [18] reported that the antinociceptive effect of an intracerebroventricular injection of β-endorphin was antagonized by CCK, but not by the nonsulfated CCK octapeptide. Other behaviors in which CCK has been shown to antagonize or attenuate either morphine or β-endorphin include feeding [30], catalepsy [16] and body-shaking behavior [17].

Although the antagonistic interaction of CCK and morphine is well established for the aforementioned behaviors, the effects of these drugs in combination have not been investigated on schedule-controlled behavior. Schedule-controlled behavior, which can be remarkably stable and reproducible over long periods of time, has served as a sensitive baseline to study a variety of drug interactions (for review, see Woolverton [31]). Establishing a sensitive baseline is critical in an interaction study where the repeated assessment of the effects of two or more compounds, both alone and in combination, is required. Moreover, using schedule-controlled behavior should help to clarify whether the interaction of CCK and morphine is dependent on the specific characteristics of the response (e.g., measures such as feeding and analgesia), or is a result of a more general effect independent of the nature of the response.

The present experiment examined the interaction of CCK and morphine by administering both drugs alone and in combination to rats responding under a multiple schedule with alternating fixed-ratio (FR) and timeout components. Responding during the FR component consisted of licks on a dry tube. Responding was reinforced by water presentation on another tube after completion of the FR. A cumulative-dosing procedure was utilized to evaluate the effects of morphine. More specifically, increasing cumulative doses of morphine were administered before each FR component. To assess the interaction of CCK and morphine, cumulative doses of morphine were examined after pretreatment with CCK. Naltrexone, a prototype opioid antagonist, was also given as a pretreatment for comparison with the effects of CCK.

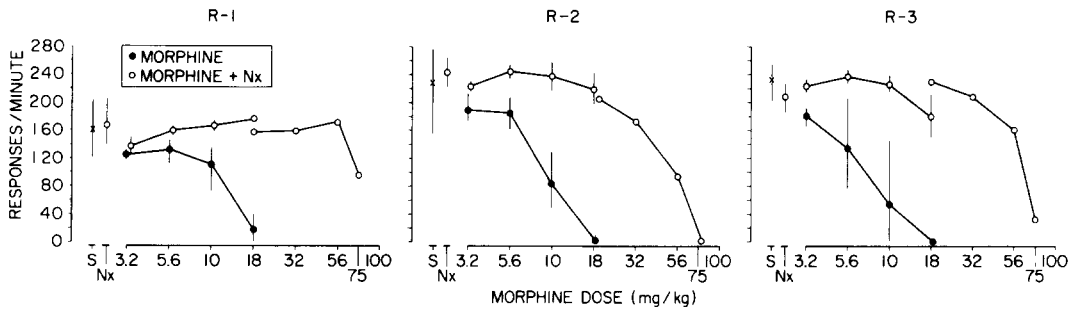

FIG. 1. Effects of cumulative doses of morphine, and morphine in combination with naltrexone, on overall response rate for each rat. The points and vertical lines at S indicate the mean and range for 5 or 6 saline (control) sessions. The filled points with vertical lines in the dose-effect data indicate the mean and range for three determinations of morphine alone. The open points and vertical lines at Nx and in the dose-effect data for the low dose range of morphine indicate the mean and range for two determinations for naltrexone, alone and in combination with morphine, respectively. Naltrexone in combination with the higher dose range of morphine was only determined one time for each rat; all other points without vertical lines indicate an instance in which the range is encompassed by the point.

METHOD

Subjects

Three adult male Long-Evans rats, maintained at approximately 80% of their free-feeding weight by restricting water in their individual home cages, served as subjects. Throughout the experiment, Purina Rat Chow was available ad lib in the home cages and subjects were weighed before and after each experimental session. Water was earned during the experimental session and, if necessary, was provided in the home cage for a brief period (approximately 10 min) after the session to maintain subjects at their 80% weight. On Sundays, when there was no experimental session, the subjects were given 20 min free access to water in their home cages. All three subjects had a history of operant licking.

Apparatus

The experimental space was a Plexiglas cage (29×18.5×12.5 cm), housed within a sound-attenuating chamber. The floor of the cage was made of 13 stainless-steel rods (19×0.5 cm) spaced 2 cm apart center to center. The front wall of the cage had three horizontally aligned concave-edged holes, 6 cm apart center to center and 4 cm above the floor. A configuration of three 20-gauge stainless-steel drinking tubes protruded through each of the holes. Each tube configuration was mounted through a Plexiglas block (6×1.2×4 cm) located directly behind the front wall and attached to two stainless-steel rods. The right tube configuration was attached to a Teflon solenoid valve (General Valve Corporation, Model No. 3) which in turn was attached to a fluid reservoir (30-cc syringe). Red and white lights, centered in each Plexiglas block above the configuration of tubes, served as stimuli. A green light located on the front wall 4 cm above the floor also served as a stimulus. Contact between the floor of the cage and the tube configuration completed a circuit and registered responses on a drinkometer (Lafayette, Model No. 58008). Electromechanical programming and recording equipment was used. A fan provided ventilation and masked extraneous noise.

Drugs

The drugs used in this study were morphine sulfate, naltrexone hydrochloride and sulphated cholecystokinin-octapeptide (CCK-8). All drugs were dissolved in 0.9% saline and administered IP. The volume for morphine and naltrexone injections, and their respective control injections, was 0.1 ml/100 g of body weight. Doses of morphine and naltrexone are expressed in terms of the salt of each drug. Doses of CCK were calculated from a 30 μg/kg stock solution, and control injections for CCK consisted of saline given in a volume equivalent to that of the largest dose of CCK.

Procedure

Baseline. Initially, responding in the presence of a white stimulus light over the center drinking tube was reinforced under a fixed-ratio (FR 1) schedule. Completion of the ratio turned off the white stimulus light over the center tube and turned on a red stimulus light over the right drinking tube for 5 sec, during which time water was continuously available at this tube. After 5 sec, the red stimulus light over the reinforcement tube was extinguished and the white stimulus light was again illuminated. When the behavior under the FR 1 schedule was stable, the ratio size was gradually increased until the rats reliably responded under an FR 35.

At this point, a two-component multiple schedule was introduced. Each session consisted of four 10-min components of responding under the FR 35 schedule of water presentation and four 10-min timeout components. Sessions began with a timeout component, which alternated with FR components where the stimulus conditions were identical with those during initial training. During the timeout components, the green stimulus light above the tube configurations was illuminated and responses were counted, but had no programmed consequences. Two final manipulations were made after the introduction of the multiple schedule to stabilize responding across the FR components. The FR was increased from 35 to 50, and the amount of time in which the reinforcer was available was shortened from 5 sec to 2.5 sec. The overall response rate (total responses/min, excluding reinforcement time) was calculated for each FR component. In addition, within-session changes in responding were monitored by a cumulative recorder.

Drug testing. The multiple-schedule baseline was considered stable when the response rate no longer showed systematic change from either component to component or session to session. When response rate was stable (45–50 ses-

sions), a cumulative-dosing procedure was initiated. Morphine sulfate was injected at the start of each timeout component, i.e., 10 min before each component of FR responding. More specifically, 3.2 mg/kg of morphine was administered before the first timeout component and 2.4, 4.4 and 8 mg/kg, respectively, were injected at the start of the remaining timeout components. Each successive injection increased the cumulative dose in 1/4 log-unit steps, yielding cumulative doses of 3.2, 5.6, 10 and 18 mg/kg.

Following the determination of a cumulative dose-effect curve for morphine, a single dose of naltrexone (1 mg/kg) was tested. Naltrexone was administered as a single injection and given immediately before the start of the session. After the determination of the effects of naltrexone alone, naltrexone was given as a pretreatment before the cumulative dose of morphine (3.2–18 mg/kg). The effects of naltrexone, both alone and in combination with this dose range of morphine, were redetermined before testing combinations of naltrexone with higher cumulative doses of morphine, i.e., cumulative doses of 18, 32, 56 and 75 mg/kg. The cumulative dose-effect curves established for morphine alone (i.e., 3.2–18 kg) were redetermined both during and after testing with naltrexone.

Next, single log doses of CCK (10, 18 and 32 μg/kg) were administered alone and in combination with the 3.2–18 mg/kg cumulative dose range of morphine. Doses of CCK were tested in quasi-random order, and each dose was given alone before being given in combination with morphine. Like naltrexone, CCK was administered IP just prior to the start of the first timeout component. The effects of a given dose and that dose in combination were redetermined before the next dose was given.

Throughout drug testing, saline was given either at the start of the first timeout, as a control for naltrexone and CCK, or at the beginning of each timeout as a control for morphine. Drug sessions were generally conducted on Tuesdays and Fridays, with control sessions occurring on Thursdays. No injections were given on Mondays, Wednesdays and Saturdays. At least one week intervened between the end of a series of injections with one drug or drug combination and the start of a series with another.

RESULTS

The effects on overall response rate when cumulative doses of morphine were given both alone and in combination with naltrexone are shown for each subject in Fig. 1. In all three subjects, cumulative doses of morphine administered alone produced a dose-dependent decrease in the overall rate of responding. The lowest dose generally had little or no effect, and the highest dose, 18 mg/kg, either substantially decreased the overall rate of responding or eliminated responding. In contrast, when these same doses of morphine were given in combination with a dose of naltrexone that was ineffective alone, there was little or no rate-decreasing effect. The only exception was at the highest dose for R-3, where there was a small decrease in rate. When naltrexone was given in combination with higher doses of morphine, dose-dependent decreases in response rate again occurred in all three subjects, although the rate decreasing effects in R-1 were somewhat less than those obtained in the other two subjects. Administration of the higher dose range indicated the dose-effect curve for morphine had shifted approximately 3/4 log-units to the right.

The within-session effects of cumulative doses of morphine alone and in combination with naltrexone are shown in

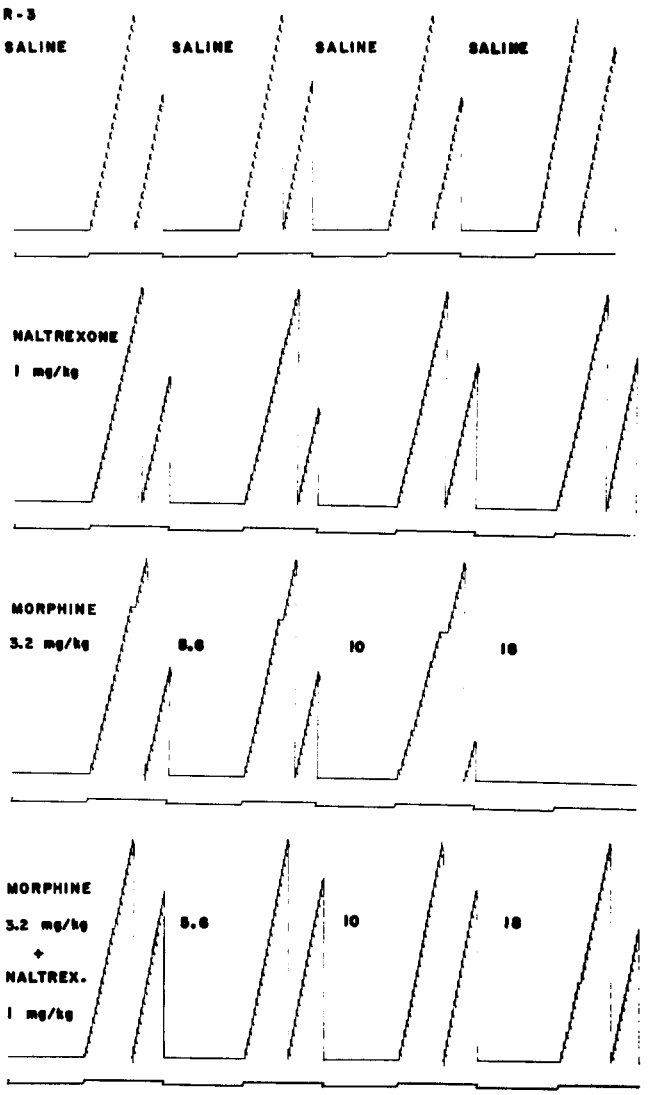

FIG. 2. Within-session effects of morphine, and morphine in combination with naltrexone, in R-3. The response pen stepped upward with each response and was deflected downward with each reinforcement. The event pen was deflected downward during timeout components. Components changed after 10 min. Each of the four cumulative records is from a different day. The top record shows a session in which each FR component was preceded by an injection of saline (administered at the start of the 10-min timeout component). The second record shows a session that was preceded by naltrexone alone (1 mg/kg), the third record shows a session with increasing cumulative doses of morphine alone (3.2–18 mg/kg), and the last record shows a session that was preceded by the cumulative doses of morphine in combination with 1 mg/kg of naltrexone (injected at the start of the session).

Fig. 2. The cumulative record in the top row shows the pattern of responding during a representative control session in which saline was administered before each FR component to R-3. The pattern of responding was similar across all four FR components; i.e., responding occurred at a high rate and brief pauses followed reinforcement and preceded each run of responses. The record in the second row of this figure shows a similar pattern of responding for a session that followed

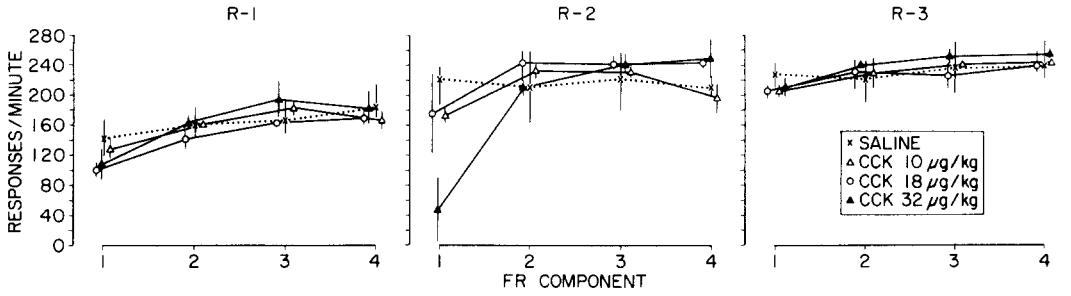

FIG. 3. Overall response rate for each rat during the four FR components on saline (control) days and on days when cholecystokinin (CCK) alone was injected before the first component. The points and vertical lines indicate the mean and range for 4 or 5 control sessions and for two or three determinations at each dose of CCK.

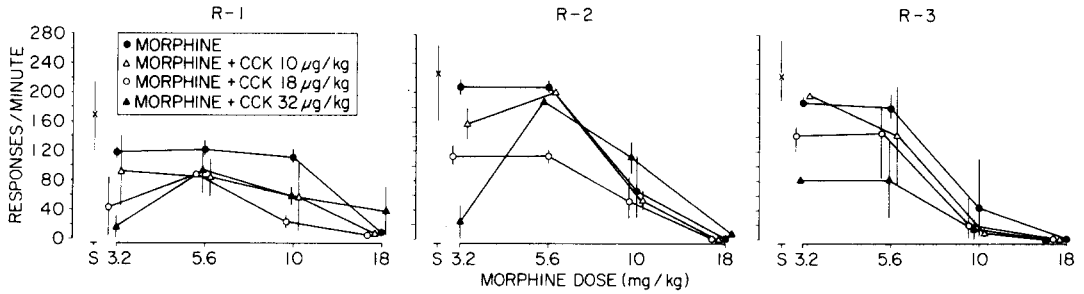

FIG. 4. Effects of cumulative doses of morphine, alone and in combination with CCK, on the overall response rate for each rat. The points and vertical lines at S indicate the mean and range for 5 or 6 saline control sessions. The points and vertical lines in the dose-effect data indicate the mean and range for two or three determinations.

naltrexone pretreatment. The record in the third row shows four FR components that were preceded by increasing cumulative doses of morphine. Lower cumulative doses of morphine (3.2 and 5.6 mg/kg) tested alone had little or no effect on response rate (see Fig. 1). Although the overall pattern of responding was similar to that seen in the saline session, fewer ratios were completed during the 10-min components. The third injection of morphine (a cumulative dose of 10 mg/kg) produced a large decrement in responding. Longer pauses occurred between reinforcers and only four ratios were completed during the second excursion of the 10-min component. Following the highest dose of morphine administered alone, all responding was eliminated. The record in the bottom row shows the pattern of responding when cumulative doses of morphine were given in combination with a 1 mg/kg dose of naltrexone. As can be seen, responding during the four FR components was similar to that of the control session.

Figure 3 shows the effects of CCK alone on overall response rate across all four FR components. Under control conditions, the overall response rate for each subject was relatively constant during each of the four components, although R-1 did show a small increase in rate across the components. Unlike naltrexone, the effects of CCK on FR responding were more variable among subjects. In R-1 and R-3, CCK produced only small rate-decreasing effects in the first component; however, it produced a substantial rate-decreasing effect in the first FR component for R-2. Moreover, in R-2, the 18 and 32 μg/kg doses of CCK produced small rate-increasing effects in the fourth FR component which were not seen in the other two subjects.

The data in Fig. 4 show the effects on overall response rate for each subject when varying doses of CCK were administered in combination with cumulative doses of morphine. Also shown are the effects of cumulative doses of morphine when given alone. Similar to the previous administration of morphine alone, dose-dependent decreases in the overall rate of responding were evident in all three subjects. Lower doses generally produced little or no rate-decreasing effects, whereas higher doses either substantially decreased the overall response rate or eliminated responding entirely. CCK in combination with morphine, on the other hand, produced completely different effects from those obtained with either morphine alone or morphine in combination with naltrexone. The rate-decreasing effects of morphine in combination with CCK were greater in all three subjects than the effects of morphine alone, i.e., the dose-effect curve for morphine tended to shift to the left. This was particularly evident at the lowest dose of morphine which had little or no effect when given alone, but when given in combination with CCK produced a large dose-dependent decrease in response rate. This interaction was least apparent in R-2 because of the large rate-decreasing effects obtained with CCK alone (Fig. 3). Although the rate-decreasing effects produced with CCK were not dose dependent at the intermediate doses of morphine (5.6 and 10 mg/kg), the decreases in response rate were generally larger than those found with CCK alone in all three subjects. The effects of CCK in combination with the highest dose of morphine were similar to those for morphine alone. In both instances responding was virtually eliminated, although some responding did occur in R-1 when the high dose of morphine was combined with 32 μg/kg of CCK.

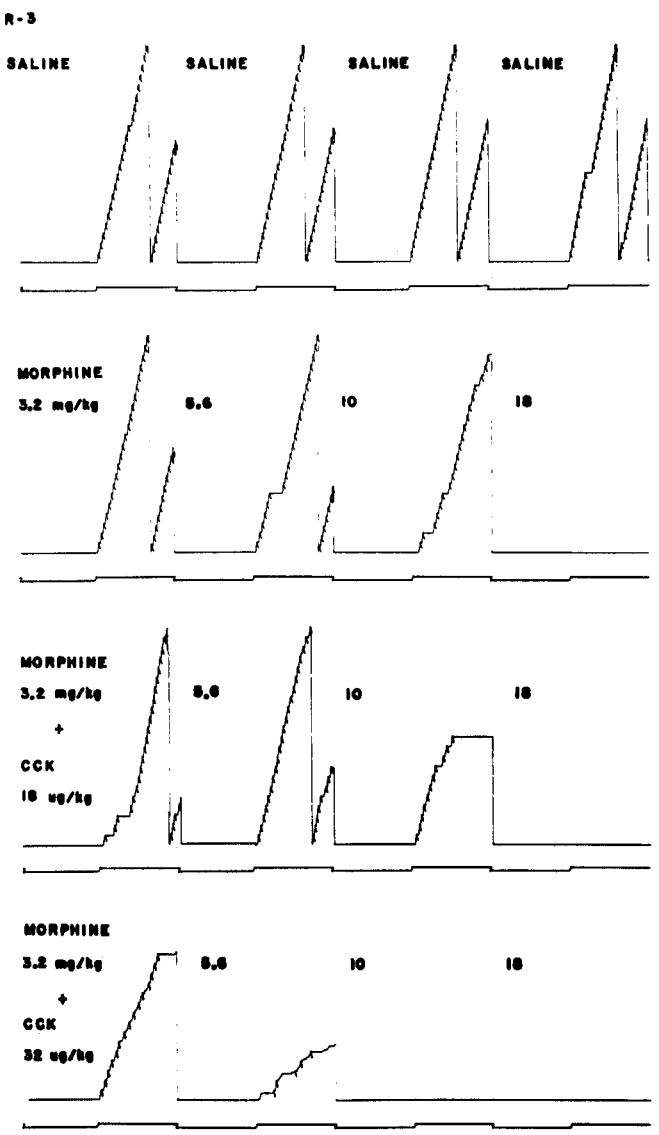

FIG. 5. Within-session effects of cumulative doses of morphine, alone and in combination with CCK, in R-3. Each cumulative record is from a different day. The top record shows a control session in which each FR component was preceded by an injection of saline. The second record shows a session with increasing cumulative doses of morphine alone (3.2–18 mg/kg). The third and fourth records show sessions that were preceded by the cumulative doses of morphine in combination with 18 or 32 μg/kg of CCK (injected at the start of the session). For other details, see legend for Fig. 2.

Within-session effects for morphine, both alone and in combination with CCK, are shown for R-3 in Fig. 5. The record in the top row shows a representative control session in which saline was administered before each FR component. The pattern and rate of responding during the control session were consistent from component to component. The record in the second row shows a session in which increasing cumulative doses of morphine were administered before each FR component. With increasing doses of morphine the pattern of responding indicated greater disruption (i.e., more pausing occurred and fewer ratios were completed) with each successive component. The highest cumulative dose of morphine eliminated all responding. A session in which 18 μg/kg of CCK was given with the cumulative doses of morphine is shown in the third row. Unlike the pattern of responding that occurred after the low dose of morphine alone, CCK in combination with the low dose produced more pausing during the first few minutes of the component and there were fewer completed ratios. Although overall responding during the second FR component was comparable to responding at the 5.6 mg/kg dose of morphine alone, a notable difference did occur during the third component where pausing occurred for a majority of the component when morphine was given with CCK. All responding was again eliminated at the highest dose. The bottom row shows a session in which cumulative doses of morphine were given in combination with a 32 μg/kg dose of CCK. Here, the effects on responding were greater than those obtained with the lower dose of CCK in combination with morphine. The pattern of responding was greatly disrupted during the first component, where the effects were similar to those seen when 10 mg/kg of morphine was given alone. When this dose of CCK was given in combination with 5.6 mg/kg of morphine, very few ratios were completed and the local pattern of responding was disrupted. Responding during the rest of the session was eliminated.

DISCUSSION

The present finding of antagonism with morphine and naltrexone is well established for schedule-controlled behavior (e.g., [10,12]). The interaction of CCK and morphine, however, was very different from the antagonistic interaction of CCK and morphine in previous studies using other measures such as analgesia [7,8] and feeding [30]. Although the basis for these differences are not known, the morphine-CCK interaction obtained in the present study is consistent with an earlier report on the interaction of morphine and a peptide related to CCK. Zetler [34] reported that caerulein potentiated morphine's effect on rectal temperature in mice. This, along with other reports indicating that both morphine and CCK alone can decrease operant responding (e.g., [1, 4, 11, 22, 24]), suggest that the combined effects of morphine and CCK on schedule-controlled behavior may simply reflect a threshold phenomenon; e.g., the effects of two subthreshold doses may summate to produce an effect. Such an interpretation is complicated, however, by the fact that similar results to those in the present study have not been reported for the combination of CCK and morphine on measures of analgesia in which CCK and morphine interact antagonistically but produce similar effects when given alone (cf. [7, 8, 33]).

Identifying the possible mechanisms for a threshold phenomena is difficult given the uncertainty surrounding the site of interaction for peripherally administered CCK (cf. [5, 20, 21, 25]) and peripherally administered morphine. Morphine, for example, crosses the blood-brain barrier and interacts with receptors within the central nervous system. CCK, however, was found to be more effective in decreasing water-reinforced operant responding after systemic administration than central administration [4]. This finding along with the fact that the satiety effects of CCK are substantially reduced by complete abdominal vagotomy [24,25], other evidence demonstrating the limited uptake of peptides by the brain [23] and differences in central and peripheral CCK receptors [9], suggest a peripheral activation of the vagus is responsible for the central effects of CCK. This would limit any direct interaction between CCK and morphine in the central nervous system. Nevertheless, central mediation of the effects of CCK on schedule-controlled be-

havior cannot be ruled out since relatively high intraventricular doses (20 and 50 μg) of CCK alone decrease the rate of responding of schedule-controlled behavior (e.g., [4]).

Given the evidence for the coexistence of CCK and dopamine in several brain areas (e.g., [14]), one could speculate on the involvement of the dopaminergic system for the present finding of potentiation. That CCK is capable of directly influencing this system has been shown by Hsaio *et al.* [15], who demonstrated that altered responding to both CCK and a dopaminergic agonist occurred in rats after chemical denervation of dopamine terminals by 6-hydroxydopamine. Moreover, CCK is thought to affect the availability of dopamine by influencing both the presynaptic release of dopamine [2] and postsynaptic receptor systems (e.g., [29]). In reference to the effect CCK has on dopamine-induced hyperlocomotion, Crawley *et al.* [5] have postulated a "low affinity binding site, or a binding site for CCK that is linked to the dopamine receptor." CCK, therefore, could potentiate the effects of another drug that also decreases the functional availability of dopamine. Combined injections of CCK and haloperidol (a drug which blocks dopamine receptors), for example, were reported by Cohen *et al.* [3] to reduce conditioned-avoidance behavior significantly more than either drug alone. A similar interpretation for the potentiation found in the present study is questionable, however, since the effects of morphine on the release or blockade of dopamine in the brain are still unclear. For example, in different experimental situations morphine has been shown to increase, decrease and have no effect on the release of dopamine in the rat brain (cf. [28]).

Another problem with relating the changes in dopamine to the changes in behavior becomes evident if the effects of CCK and cocaine are compared. The potentiating effect with CCK in the present experiment parallels the effect found on a similar baseline with cocaine in a study involving cocaine-phencyclidine combinations in patas monkeys [27]. In that study, cocaine potentiated the effects of cumulative doses of phencyclidine on rate of responding under a second-order FR schedule. More specifically, when cumulative doses of phencyclidine were given after pretreatment with doses of cocaine that either decreased responding initially or had no effect when given alone, the dose-effect curve for phencyclidine shifted to the left. Although CCK and cocaine potentiate the rate-decreasing effects of morphine and PCP, respectively, they affect the availability of dopamine differently. Unlike CCK, which is probably decreasing the amount of available dopamine, cocaine tends to increase the availability of dopamine by blocking reuptake (cf. [6]). That both an increase and a decrease in dopamine yields the potentiation of rate-decreasing effects needs to be investigated further.

Finally, it is possible that CCK may have potentiated the rate-decreasing effects of morphine by releasing endogenous opioids. This mechanism of action for CCK has been suggested by several studies in which the antinociceptive effects of CCK (sulphated) were antagonized by naloxone (e.g., [13, 19, 33]). If CCK does decrease the rate of responding through the indirect release of endogenous opioids, the present findings could reflect a threshold phenomena. However, further study of how CCK decreases response rate is needed since it is also clear from previous studies, using measures other than nociception, that direct interaction of CCK with opioid receptors is questionable. CCK has not only been shown to antagonize varying effects produced by both endogenously and exogenously administered opioids, but to have effects that are not sensitive to naloxone reversal as well. Van Ree *et al.* [29], for example, reported the inability of naloxone to reverse CCK-induced inhibition of hypermotility elicited by low doses of apomorphine. CCK, therefore, could either potentiate the rate-decreasing effects of morphine by releasing endogenous opioids, or by affecting the function of dopaminergic neurons through nonopioid or unknown opioid mechanisms.

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