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Effects of Cholecystokinin on Morphine-Elicited Hyperactivity in Hamsters

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SCHNUR, P., S. S. CESAR, M. A. FODERARO AND P. J. KULKOSKY. *Effects of cholecystokinin on morphine-elicited hyperactivity in hamsters*. PHARMACOL BIOCHEM BEHAV **39**(3) 581–586, 1991.—The effects of the octapeptide cholecystokinin (CCK) on hamster locomotor activity were investigated in three experiments. In Experiment 1, the effect of CCK (25, 50, 75 μg/kg) on morphine (2.5 mg/kg)-elicited hyperactivity was studied. Results indicated that CCK antagonized morphine-elicited hyperactivity and that CCK alone elicited hypoactivity. There were no effects of dose of CCK. In Experiment 2, the effects of intraperitoneal (IP) and subcutaneous (SC) routes of administration of CCK (25 μg/kg) on locomotor activity were studied. Compared to saline controls, CCK induced hypoactivity that was of greater magnitude and of longer duration when administered IP than SC. Experiment 3 was designed to replicate the route of administration effect observed in Experiment 2 and to determine whether sensitization to CCK-induced hypoactivity develops over the course of a few injections. Results indicated that CCK-induced hypoactivity was greater after IP than SC administration but that sensitization was not detectable. It is concluded that CCK antagonizes morphine-elicited hyperactivity in the hamster by acting, in part, independently of morphine to produce opposite behavioral effects.

Cholecystokinin Morphine CCK Naloxone Hamster Locomotor activity Route of administration Neuropeptide

CHOLECYSTOKININ (CCK) is a gastrointestinal and brain octapeptide that exerts diverse behavioral effects (43,49). Moreover, several lines of evidence suggest that CCK may function as an endogenous antagonist of opiate actions: First, the distribution of CCK in brain overlaps that of the endogenous opiates (41). Second, the effects of CCK often are opposite those of the opiates: Food intake in rats, for example, is increased following the administration of opiates (1, 19, 20, 25, 26), but decreased following the administration of CCK (14, 38–40). Third, CCK has been shown to antagonize opiate-induced analgesia (12,13), feeding (25) and catalepsy (15). Moreover, morphine has been shown to antagonize the intestinal and analgesic effects of CCK (47,48). Finally, proglumide and L-364-718, CCK antagonists (3,43), potentiate morphine-induced analgesia (44,45) and hypoactivity (2), and prevent or reverse morphine tolerance (11, 16, 42, 45).

The purpose of the present study was to test the effects of CCK on morphine-elicited hyperactivity in the hamster. Previously (36), we demonstrated that CCK antagonizes morphine-elicited hyperactivity only at a relatively high dose of CCK (75 μg/kg). The earlier work, however, may not have been sensitive enough to observe low-dose CCK antagonism of morphine-elicited hyperactivity: at the 15-mg/kg dose of morphine used, hyperactivity did not occur for more than 90 min after the CCK injection. In the present study, a low dose of morphine (2.5 mg/kg) was used. At this dose, morphine-elicited hyperactivity is evident almost immediately (29), particularly if the animals are morphine tolerant (28,29). Thus any effects of an immediately preceding injection of CCK should be evident on hyperactivity elicited by a low dose of morphine.

The present study was designed also to compare the antagonistic effects of CCK with those of naloxone on morphine-elicited hyperactivity. Naloxone antagonizes morphine-elicited hyperactivity in hamsters (27, 30, 31, 33, 34) without itself affecting locomotor activity. To the extent that CCK acts as a pharmacological antagonist at opiate receptors (21), it too should antagonize morphine-elicited hyperactivity without affecting locomotor activity itself. On the other hand, if morphine and CCK produce antagonistic but independent behavioral effects, then: 1) CCK alone should elicit hypoactivity; 2) CCK should attenuate or block the effects of morphine; and 3) morphine should attenuate or block the effects of CCK.

EXPERIMENT 1

In the first experiment, the effects of naloxone (0.1, 1 and 10 mg/kg) and of CCK (25, 50 and 75 μg/kg) on morphine-elicited hyperactivity were tested.

METHOD

Subjects

Thirty-one female golden Syrian Hamsters (Sasco, Inc., Omaha, NE) with a mean weight of 103 grams were used. They were housed individually in stainless steel cages, maintained on a

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12:12 lighting cycle (lights on at 0700), and given free access to tap water and paper nesting materials. Hamsters were fed a daily ration of rodent lab chow (Purina, #5001) sufficient to maintain 90% of their ad lib weights, a regimen that we have found to encourage stable daily levels of running wheel activity (35).

Apparatus and Materials

The apparatus consisted of 31 identical activity wheels (Wahmann Co., Model LC-34) housed in plywood enclosures that isolated the wheels visually from one another. Noise from ventilator fans in each enclosure (approximately 70 dB re: 0.0002 dynes/cm^2) provided auditory masking. Movements of each wheel were detected by microswitches, transduced by an interface (Lafayette, Model 1180-01) and recorded on Apple II+ computers. The morphine injection (MOR) consisted of a 2.5-mg/kg dose of morphine sulfate diluted from a 15-mg/ml stock with 0.9% saline. Saline injections (SAL) were 0.9% filtered saline. Cholecystokinin injections (CCK), a gift from Squibb Institute for Medical Research (SQ 19,844; batch #NN025NC), consisted of one of three doses of CCK (25, 50 and 75 μg/kg) diluted with 0.9% saline. Naloxone injections (NLX) consisted of one of three doses of naloxone hydrochloride (Sigma, 0.1, 1 and 10 mg/kg) diluted with 0.9% saline. All injections were administered intraperitoneally (IP) in 1-ml/kg volumes.

Procedure

For the first eight days of the experiment, animals were assigned randomly to two groups: On each day, animals in Group MOR (n = 15) received an IP injection of morphine (2.5 mg/kg) 10 min before being placed in the running wheels for 3 h. Animals in Group SAL (n = 16) received a daily injection of saline before the 3-h running wheel session. These sessions were designed to ensure that morphine elicited hyperactivity compared to saline (28,29). For Days 9, 10 and 11, the groups were subdivided and animals were randomly assigned to one subgroup or another for the three test sessions: Animals in Group SAL/MOR (n = 5) were given the usual morphine injection preceded (10 min) by a saline injection; those in Group CCK/MOR (n = 5) were given morphine preceded by CCK; those in Group NLX/MOR (n = 5) were given morphine preceded by naloxone. Animals in Group SAL/SAL (n = 5) were given the usual saline injection preceded by a saline injection; those in Group CCK/SAL (n = 5) were given saline preceded by CCK; those in Group NLX/SAL (n = 6) were given saline preceded by naloxone. On each of the test days, animals in Groups CCK/SAL and CCK/MOR received one randomly chosen dose of CCK (25, 50, or 75 μg/kg). Similarly, animals in Groups NLX/SAL and NLX/MOR received one randomly chosen dose of NLX (0.1, 1 and 10 mg/kg) on each test day. Animals in Groups SAL/SAL and SAL/MOR also were tested on each day, but, of course, there was no dose manipulation of saline. Ten min after the second injection on each test day, animals were placed in the running wheels for a 3-h running wheel session. Locomotor activity was recorded every 20 min. In this and the following experiments, all testing was done between 1200 and 1800 h.

RESULTS

Locomotor activity on the test days was analyzed initially using a 3 (first injection: saline, naloxone, CCK) × 2 (second injection: morphine, saline) × 3 (dose of first injection) × 9 (20-min time blocks) mixed factorial analysis of variance (ANOVA). This analysis indicated that neither dose nor any of its first-order interactions was significant. The second-order interaction among first injection, dose and time was significant, $F(32,400) = 1.73$, $p<0.01$. However, since the dose of saline used in the first injection was not defined, and since there were no significant effects otherwise, the data were collapsed across dose and reanalyzed.

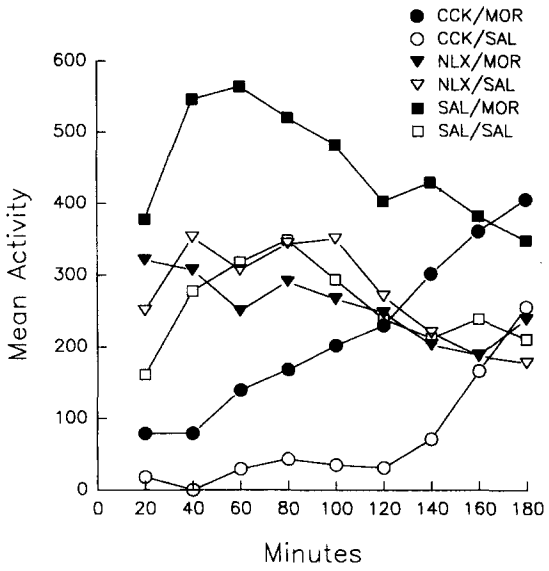

FIG. 1. Mean running wheel activity as a function of minutes of the test sessions for all groups in Experiment 1, collapsed over dose of the first injection.

Figure 1 shows mean locomotor activity during the 3-h test session for all groups collapsed across dose. Several effects are evident. First, compared with saline controls (Group SAL/SAL), morphine at a dose of 2.5 mg/kg (Group SAL/MOR) elicited hyperactivity that was antagonized by naloxone (Group NLX/MOR), whereas naloxone itself had no effect on activity (Group NLX/SAL). This pattern of findings is entirely consistent with previously reported results from our laboratory (27, 29–31). Second, CCK elicited hypoactivity: Compared with Group SAL/SAL, Group CCK/SAL was hypoactive for most of the test session. Third, CCK and morphine were mutually antagonistic: Group CCK/MOR was neither as hyperactive as Group SAL/MOR nor as hypoactive as Group CCK/SAL.

These conclusions are corroborated by a 3 (first injection) × 2 (second injection) × 9 (time blocks) mixed factorial ANOVA. The effect of the first injection was significant, $F(2,25) = 4.53$, $p<0.025$, but neither the effect of the second injection, $F(1,25) = 3.76$, $p = 0.064$, nor the interaction between these factors, $F(2,25) = 1.35$, $p<0.05$, was significant. In addition, the interaction between the first injection and time was significant, $F(16,200) = 3.41$, $p<0.001$. Post hoc comparisons using Fisher's LSD test indicated that Group SAL/MOR was hyperactive compared with Group SAL/SAL between 20 and 100 min and again after 140 min (p's<0.05). Group CCK/SAL was hypoactive compared with Group SAL/SAL between 40 and 120 min (p's<0.05). Group CCK/MOR was less active than Group SAL/SAL after 40 min and more active than CCK/SAL between 120 and 160 min (p's<0.05).

DISCUSSION

The results of this experiment are consistent with previously published investigations of the effects of morphine and CCK on

locomotor activity in the hamster (29, 30, 36). First, low doses of morphine have been shown to elicit naloxone-reversible hyperactivity in the hamster, as in several other species (30,31). The present results confirm this finding in the performances of Group SAL/MOR and Group NLX/MOR. Second, CCK has been shown to antagonize morphine-elicited hyperactivity in the hamster (36), and that finding is replicated here, in the performance of Group CCK/MOR.

The present results also indicate that CCK itself has a robust effect on locomotor activity in hamsters: Compared with saline controls, Group CCK/SAL was hypoactive during most of the test session. Our previous work (36) gave some suggestion of CCK-elicited hypoactivity, but the effect was transient and occurred only at a high CCK dose (75 μg/kg). In the present study, the effect was large and long lasting. Indeed, the failure to demonstrate an effect of CCK dose on activity was due to the fact that all doses of CCK produced maximal hypoactivity during the test session. One possible reason for the difference in the magnitude of effect between the two experiments might be route of administration, IP here, SC previously.

EXPERIMENT 2

The purpose of Experiment 2 was to compare directly the effects of IP and SC routes of CCK administration on locomotor activity in the hamster. In Experiment 1, IP administration of CCK at doses ranging from 25–75 μg/kg elicited hypoactivity that was both robust and durable, whereas, in previous work in our laboratory (36), SC administration of a 75-μg/kg dose of CCK elicited hypoactivity that was weak and transient. Since the interpretation of CCK's antagonism of morphine-elicited hyperactivity rests upon whether CCK itself elicits hypoactivity, it is important to determine whether CCK-elicited hypoactivity depends upon route of administration. The present experiment employed a 25-μg/kg dose of CCK.

METHOD

Subjects

Sixteen female golden Syrian hamsters (Sasco, Inc., Omaha, NE) with a mean weight of 100 grams were used. Eleven of these animals were experimentally naive; five had served in Experiment 1 in Groups NLX/SAL (n=2), SAL/SAL (n=2) and CCK/SAL (n=1). Conditions of housing and maintenance were identical to those described above.

Apparatus and Materials

The apparatus was identical to that used in Experiment 1. Saline injections (SAL) were 0.9% filtered saline. CCK injections consisted of 25-μg/kg doses of CCK diluted with 0.9% saline. All injections were administered in 1-ml/kg volumes.

Procedure

Animals were assigned randomly to one of two routes of administration groups: Group IP received intraperitoneal injections, and Group SC received subcutaneous injections in the dorsal surface of the neck. The first three days of the experiment comprised baseline training. On each day, animals were given an injection of saline 10 min before being placed in the running wheel for a 3-h baseline session. On the fourth day, a randomly selected half of each route of administration group was given an injection of CCK (25 μg/kg), and half was given an injection of saline 10 min before being placed in the running wheels for a 3-h test session. During the next three days, saline baseline sessions again were conducted. The purpose of these sessions was to minimize drug carry-over effects from one test session to the next. On the eighth day, each route of administration group was tested with the drug they had not received on Day 4 (i.e., saline or CCK). The number of wheel revolutions every 20 min was recorded.

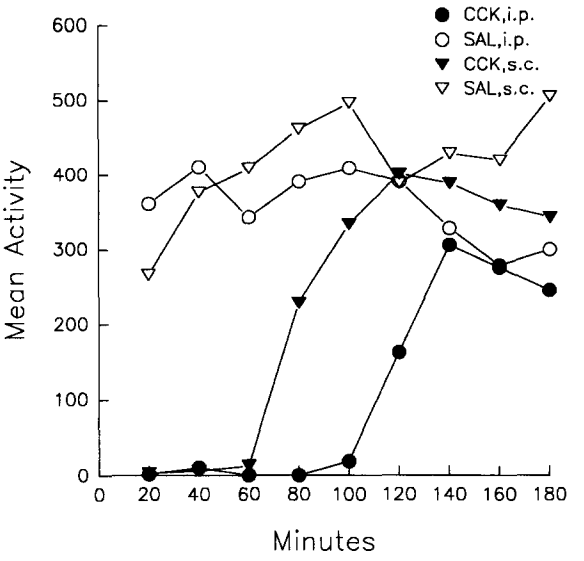

FIG. 2. Mean running wheel activity as a function of minutes of the test sessions in Experiment 2.

RESULTS

Figure 2 shows mean activity as a function of time for all groups in Experiment 2. Compared with saline controls, CCK produced a robust suppression of locomotor activity, whether administered intraperitoneally or subcutaneously, although the IP route of administration appears to have produced a longer lasting hypoactivity than the SC route.

These findings are corroborated by a 2 (route) × 2 (drug) × 9 (time blocks) mixed factorial ANOVA, which indicated that the effects of drug, $F(1,13)=9.11$, $p<0.01$, and time, $F(8,104)=8.70$, $p<0.001$, were significant. In addition, the interactions between route and time, $F(8,104)=2.44$, $p<0.025$, as well as drug and time, $F(8,104)=5.87$, $p<0.001$, were significant. Post hoc analyses using Fisher's LSD test ($p<0.05$) indicated that Group IP/CCK was hypoactive compared to Group IP/SAL between 20 and 120 min, whereas Group SC/CCK was hypoactive compared to Group SC/SAL only between 20 and 80 min.

DISCUSSION

The results of this experiment replicate the finding that CCK elicits robust and durable hypoactivity in the hamster. Moreover, the hypoactivity occurred following IP as well as SC routes of administration, indicating that the failure to observe such an effect in our earlier work (36) was not due entirely to administering CCK by the SC route. Some effect of route of administration, however, is indicated by the present finding that longer-lasting hypoactivity was elicited following IP than SC CCK.

The relatively potent effect of CCK on hypoactivity in the

present experiments might be due to sensitization as a result of repeated exposure to CCK and/or to the testing procedures. That is, in Experiment 1, animals were treated with different doses of CCK on three successive test days and, in Experiment 2, several subjects with prior exposure to the experimental procedures were used. By contrast, in our previous research (36), experimentally naive animals were tested only once with CCK. Although an examination of the data from Experiment 1 revealed no effect of repeated exposure to CCK on CCK-elicited hypoactivity, we decided to evaluate the sensitization hypothesis in an independent experiment.

EXPERIMENT 3

The purpose of Experiment 3 was to investigate whether sensitization to CCK-induced hypoactivity develops over the course of a few injections. In addition, Experiment 3 served as an independent replication of CCK-induced hypoactivity in hamsters, while replicating the route of administration effect in naive animals. Finally, in Experiment 3, animals were maintained on ad lib food, but under a reversed lighting cycle. We have found that this lighting and feeding regimen produces stable rates of activity in the running wheel while obviating the need to maintain animals on a restrictive diet.

METHOD

Subjects

Sixteen female golden Syrian hamsters (Sasco, Inc., Omaha, NE) with a mean weight of 118 grams were housed individually in stainless steel cages, given free access to food and water and maintained on a reversed 12:12 lighting cycle (lights off at 0800).

Apparatus and Materials

The apparatus and materials were identical to those described in Experiment 2.

Procedure

Animals were assigned randomly to one of two routes of administration groups: Group IP received intraperitoneal injections, and Group SC received subcutaneous injections in the dorsal surface of the neck. The first three days of the experiment comprised saline baseline training conducted exactly as in Experiment 2. Tests on Days 4 and 5 evaluated the effect of route of administration on CCK-elicited hypoactivity. On Day 4, half of each route of administration group was randomly selected to be given an injection of CCK (25 μg/kg) and half, an injection of saline 10 min before being placed in the running wheel for a 3-h test session. On Day 5, each route of administration group was tested with the alternate drug (saline or CCK). Thus the drug was manipulated within groups, and the order of the test was counterbalanced across days.

To investigate whether sensitization occurs to CCK-elicited hypoactivity, two assessments were conducted: First, on Days 6–8, half of each route of administration group (equated for having been tested with CCK on Day 4 or 5) received CCK and half received saline 10 min before a 3-h running wheel session. Second, on Day 9, all animals received an injection of CCK 10 min before a 3-h test session. Thus sensitization should be apparent in: 1) an increase in CCK-elicited hypoactivity on Days 6–8; and/or 2) a difference on Day 9 between those animals treated with CCK and those treated with saline on Days 6–8.

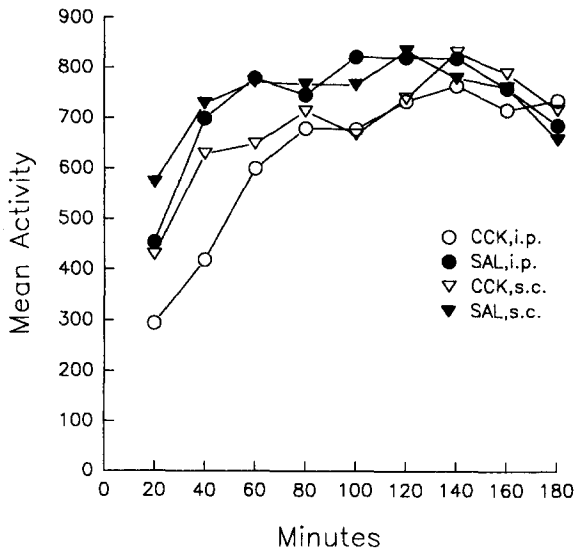

FIG. 3. Mean running wheel activity as a function of minutes of the test sessions in Experiment 3.

RESULTS

Figure 3 shows mean activity as a function of time for groups given CCK or saline via IP or SC routes on Test Days 4 and 5. In a replication of Experiments 1 and 2, CCK, administered IP or SC, elicited hypoactivity, although the magnitude of CCK-elicited hypoactivity was smaller here than in the first two experiments. Moreover, it appears that, once again, CCK administered intraperitoneally elicited more hypoactivity than CCK administered subcutaneously.

A 2 (route) × 2 (drug) × 9 (time blocks) mixed factorial ANOVA indicated that the effect of drug, $F(1,14)=7.07$, $p<0.025$, and the effect of time blocks, $F(8,112)=23.45$, $p<0.001$, were significant. In addition, the interaction between drug and time blocks, $F(8,112)=5.16$, $p<0.001$, was significant. No other main effects or interactions were significant. Although the route of administration effect was not significant and did not interact significantly with other variables, post hoc analyses using Fisher's LSD test ($p<0.05$) indicated that, for the first 40 min of the test session, Group IP/CCK was more hypoactive than Group SC/CCK.

There was no evidence of sensitization to CCK-induced hypoactivity on Days 6–8. On the contrary, the effect of CCK on activity was greatly diminished on these days. A 2 (route) × 2 (drug) × 3 (days) × 9 (time blocks) mixed factorial ANOVA indicated that neither the effect of drug nor route of administration nor any of their interactions was significant on Days 6–8. The effect of time, $F(8,96)=12.68$, $p<0.001$, the effect of days, $F(2,24)=6.45$, $p<0.005$, and the interaction between days and time, $F(16,192)=1.79$, $p<0.05$, were significant. These significant effects reflect: 1) the increase in activity from the beginning to the end of the test sessions; and 2) the higher levels of activity on Day 8 than on Days 6 and 7, particularly during the last 2 h of the test sessions. The effect of days, however, did not interact significantly with that of drug. Similarly, there was no evidence of sensitization to CCK on Day 9, when all animals were challenged with CCK. The effect of this challenge dose was the same whether animals had received CCK or saline repeatedly on Days 6–8. A 2 (route) × 2 (drug) × 9 (time blocks) mixed factorial ANOVA indicated that only the effect of time,

$F(8,96) = 14.21$, $p<0.001$, was significant on Day 9, reflecting the increasing amount of activity during the course of the test session.

DISCUSSION

The results of Experiment 3 confirm the effects reported in the first two experiments: CCK elicits hypoactivity in hamsters, and the magnitude of the effect is greater when CCK is administered intraperitoneally than subcutaneously. Moreover, Experiment 3 indicates that the hypoactivity observed in Experiments 1 and 2 is not likely the result of sensitization to CCK: In Experiment 3, CCK produced hypoactivity in experimentally naive animals. In addition, repeated exposure to CCK gave no evidence of sensitization; on the contrary, CCK-induced hypoactivity was attenuated with repeated exposure to CCK.

CCK-elicited hypoactivity was of smaller magnitude and of shorter duration in Experiment 3 than in Experiments 1 and 2. Similarly, the route of administration effect was of smaller magnitude in Experiment 3 than in Experiments 1 and 2. Although comparisons between experiments can only be suggestive and must be made cautiously, an explanation for the magnitude of effect difference between Experiment 3 and the first two experiments might be found in the higher levels of baseline activity seen in Experiment 3. That is, the mean level of activity of saline controls (Group SAL/SAL in Experiment 1; Groups SAL/IP and SAL/SC in Experiment 2) was lower in Experiments 1 and 2 than in Experiment 3. As an empirical generalization, then one might propose that CCK-induced hypoactivity is an inverse function of baseline activity levels. We have observed a similar effect of baseline activity levels in regard to morphine-induced hypoactivity in hamsters (unpublished observations).

Moreover, the higher baseline activity levels in Experiment 3 might be due to a change in housing conditions in our laboratory that was made between Experiments 2 and 3. That is, whereas animals in Experiments 1 and 2 were maintained on a normal lighting cycle and tested during the light phase, animals in Experiment 3 were maintained on a reverse lighting cycle and tested during the dark phase. It is plausible that running wheel activity levels would be higher in a nocturnal rodent like the hamster during the dark phase of the day-night cycle (23). Whether activity level itself modulates CCK-induced hypoactivity or whether some aspect of the circadian rhythm of the hamster modulates both activity level and the effects of CCK is not known at the present time. Future research is planned to explore the relationships among activity, circadian rhythm and the effects of CCK in the hamster.

GENERAL DISCUSSION

The present findings may be summarized as follows: 1) CCK antagonizes morphine-elicited hyperactivity in the hamster; 2) CCK itself induces hypoactivity in the hamster; 3) CCK-induced hypoactivity is of greater magnitude when administered IP than SC; 4) Little or no sensitization occurs to CCK-induced hypoactivity under the conditions of the present experiments.

It appears that CCK and naloxone antagonism of morphine-elicited hyperactivity are mediated, to some extent, by different mechanisms. As evident in Fig. 1, naloxone blocks morphine-elicited hyperactivity (Group NLX/MOR), but by itself (Group NLX/SAL) has no effect on locomotor activity in the hamster. By contrast, CCK itself elicits hypoactivity (Group CCK/SAL), while CCK and morphine are mutually antagonistic (Group CCK/MOR). Thus, whereas naloxone is known to act as a pharmacological antagonist at morphine receptors (21), it is likely that CCK antagonizes morphine's actions, in part, by acting independently to produce opposite behavioral effects.

The mechanism by which CCK elicits hypoactivity is not addressed in the present experiments, but there are several possibilities. CCK may be acting centrally to reduce locomotion. It has been reported (46) that, at a dose of 10.2 μg, CCK inhibited rearing and locomotion when microinjected into the ventral tegmental area. Although most studies have found no locomotor effect of CCK alone when injected directly into the rat brain (6), CCK is colocalized in dopaminergic neurons, and centrally administered CCK has been found to modulate the effects of dopamine agonists on activity (4–10). Nevertheless, there are no studies of the effects of intracerebrally administered CCK on locomotion in the hamster. Since there are known species differences in the behavioral effects (22,24) and in the neuroanatomical distribution of CCK (6), further tests of the locomotor effects of intracerebral administration of CCK in the hamster are warranted. Alternatively, and more plausibly, given CCK's limited ability to penetrate the blood-brain barrier (4,6), CCK may be acting peripherally by activating vagal afferents (4, 9, 10, 38–40) to reduce locomotion. Systemic administration of CCK in doses of 5 and 10 μg/kg has been reported to reduce exploratory behavior in rats and mice in a manner suggestive of mediation by cues similar to those accompanying food intake (5,7). Since CCK can support taste aversion learning under some conditions (18), it also is arguable that CCK elicits hypoactivity by producing malaise.

The results of Experiments 2 and 3 indicate that intraperitoneal CCK elicits more hypoactivity than does subcutaneous CCK. An explanation for this route of administration effect may be found in the pharmacokinetics of systemically administered CCK, but at the present time, the relevant data are not available. Another possibility is that the IP route of administration is more stressful than the SC route for the hamster. Previously, we demonstrated that stress can potentiate morphine-induced hypoactivity in the hamster (32). Thus perhaps CCK-induced hypoactivity also is potentiated by the stress resulting from drug administration, with greater potentiation produced by IP than SC routes.

Finally, the possibility that CCK-induced hypoactivity is subject to modulation by circadian rhythm and/or baseline levels of activity appears to provide an explanation for the robust effects of CCK in the present work compared with its transient effects in our previous study (36). That is, CCK-induced hypoactivity was of smaller magnitude and shorter duration in Experiment 3, where baseline levels of activity were relatively high, than in Experiments 1 and 2, where baseline levels of activity were relatively low. Similarly, in our previous work (36), baseline levels of activity were relatively high, and the effects of CCK on activity were correspondingly weak and transient. Rate-dependent effects of drugs have been noted before (17). For example, the effects of amphetamine depend upon the behavioral baseline: At the same dose, amphetamine decreases responding when the baseline is high but increases responding when the baseline is low (37). Additional research will be necessary to fully explicate the relationship between level of baseline activity and CCK-induced hypoactivity.

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