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Failure of Cholecystokinin to Precipitate Withdrawal in Morphine-Treated Rats

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POURNAGHASH, S. AND A. L. RILEY. *Failure of cholecystokinin to precipitate withdrawal in morphine-treated rats.* PHARMACOL BIOCHEM BEHAV **38**(3) 479–484, 1991.—In a test of the possible antagonistic interaction between cholecystokinin (CCK) and morphine, morphine-dependent rats were injected with one of three doses of CCK or with naloxone immediately following the consumption of a novel saccharin solution. Whereas opiate-dependent rats injected with the opiate antagonist naloxone acquired an aversion to the saccharin solution (and displayed a dramatic weight loss), CCK was without effect. These data were discussed in relation to the possible pharmacological antagonism between CCK and the opiates.

CCK Morphine dependence Antagonism Precipitated withdrawal Conditioned taste aversion

THE interaction of the gut peptide cholecystokinin (CCK) and both endogenous and exogenous opioids is well established within a variety of procedures. For example, Faris, Komisaruk, Watkins and Mayer (5) reported that analgesia classically conditioned to front paw shock in the rat (an opioid-mediated effect) was significantly antagonized by CCK-8 (3 μg/kg) administered intraperitoneally 30 min before the conditioned stimulus. Similarly, analgesia induced by the administration of morphine into the periaqueductal gray of the rat was blocked by CCK-8 (15). O'Neil, Dourish and Iversen (18) have also demonstrated that analgesia induced by morphine administration (8 mg/kg), as assessed in a rat paw pressure test, was abolished by CCK (4–16 μg/kg). Assessments of the interaction of CCK and morphine are not limited to nociception. Other opiate-mediated effects antagonized by CCK include hypothermia (14,35) and body shaking (13) [for failures to see such antagonism, see (3, 12, 14, 32, 33, 35, 36)].

Conversely, the CCK antagonist, proglumide, *potentiates* a range of opiate-mediated effects. For example, the onset and duration of opiate analgesia, as measured by tail-flick and paw-lick latency, are increased by proglumide (27,30). Other procedures in which proglumide potentiates morphine-induced analgesia include mouse hot plate (2), rat tail immersion (10) and rat paw pressure (10) tests.

The present study further examined the interaction of CCK and morphine, specifically the ability of CCK to precipitate withdrawal in opiate-dependent animals. In the present experiment, rats were rendered dependent by the administration of morphine for 21 consecutive days (8,34). They were then injected with either the opiate antagonist, naloxone, a compound that readily precipitates withdrawal in opiate-dependent subjects, or one of a range of doses of CCK (10, 20 and 40 μg/kg). Precipitated withdrawal was assessed by changes in body weight and the acquisition of an aversion to a solution given immediately prior to the drug challenge [see (22)]. Both body weight (6,8) and taste aversions (16, 20, 21, 29, 34) have been reported to be sensitive indices of precipitated and spontaneous withdrawal.

METHOD

Subjects

The subjects were 40 experimentally naive, female rats of Long-Evans descent, approximately 90 days of age at the beginning of the experiment. The subjects were housed in individual wire-mesh cages and were maintained on a 12-h light/12-h dark cycle (light on at 0800 h) with an ambient temperature of 25–26°C for the duration of the experiment.

Drugs

CCK (generously supplied by Squibb) was prepared as 1 μg/ml in distilled water. Naloxone hydrochloride (generously supplied by DuPont Pharmaceuticals) was prepared as 1 mg/ml in distilled water. Morphine sulfate (generously supplied by NIDA) was prepared as 10 mg/ml in distilled water.

Procedure

Phase I: Habituation. Following water deprivation, all 40 subjects were given 20-min access to water each day for 12 consecutive days. Typically, animals at this point were approaching and drinking from the tube within 2 s of its presentation.

Phase II: Drug exposure. On Day 1 of this phase, all subjects were again given 20-min access to water. Six h following fluid access, they were matched on water consumption and given either an intraperitoneal (IP) injection of morphine sulfate (80 mg/

kg, Group M; n=20) or the distilled water vehicle (Group W; n=20). This procedure was repeated for each group for 21 consecutive days.

Phase III: Precipitated withdrawal. On Day 1 of this phase, subjects in both Groups M and W were given access to saccharin in place of water during the 20-min drinking period. Immediately following saccharin consumption, subjects in Groups M were matched on saccharin consumption and given an IP injection of either naloxone hydrochloride (10 mg/kg), CCK (10, 20 or 40 μg/kg) or the distilled water vehicle, resulting in Groups MN, MC10, MC20, MC40 and MW, respectively (n=4 per group). Subjects in Group W were treated similarly, resulting in Groups WN, WC10, WC20, WC40 and WW, respectively (n=4 per group). Six hours following this injection, subjects were given their respective maintenance injections of morphine (Groups MN, MC10, MC20, MC40 and MW) or distilled water (Groups WN, WC10, WC20, WC40 and WW). On each of the following three recovery days, all subjects were given 20-min access to water followed 6 h later by an injection of either morphine or distilled water. This alternating cycle of conditioning/water recovery was repeated until all subjects had received four complete cycles. Following the last water-recovery cycle, all subjects were given 20-min access to saccharin in a final test of the aversion to saccharin. No injections followed this test.

Statistical Analyses

All determinations of statistical significance are based on a Kruskal-Wallis one-way analysis of variance test and the Friedman analysis of variance by rank. The Kruskal-Wallis one-way analysis of variance test was performed on all between-group comparisons of saccharin consumption and body weights. If an overall between-group comparison was significant, contrasts were subsequently run and individual group comparisons were based on these contrasts. The Friedman analysis of variance by rank was performed on all within-group comparisons of saccharin consumption and body weights over repeated conditioning trials. If an overall within-group comparison was significant, contrasts were subsequently run and individual trial comparisons were based on these contrasts. Statements of significance for both Kruskal-Wallis (H) and for the Friedman (χ_r^2) are based on $p<0.05$, one-tailed.

RESULTS

Phase I: Habituation

On the final three days of water habituation, all subjects drank a mean of approximately 12 ml. The mean body weight at this point was 215 g.

Phase II: Drug Exposure

Water consumption. There were no significant differences between groups in water consumption for the first two days of morphine and water injections, H(1)=2.46 and H(1)=0.77, respectively. By Day 3, subjects in Group M drank significantly less water than subjects in Group W, H(1)=5.86. This difference was maintained over the next 10 days, all H's(1)>3.79. From Days 14–21, there were no consistent significant differences in water consumption between the two groups (see Fig. 1).

Body weight. On the first day of morphine or distilled water injections, there were no significant differences in body weight between groups, H(1)=0.00, with subjects in each group weighing a mean of approximately 218 g. Although subjects in both groups gradually increased in body weight over this phase, the increase was significantly less for subjects in Group M. As illustrated in Fig. 2, on the final day of this phase the mean body weights for subjects in Groups W and M were 235 and 225 g, respectively. This difference between Groups W and M was significant as early as Day 10 of the injection period H(1)=4.28.

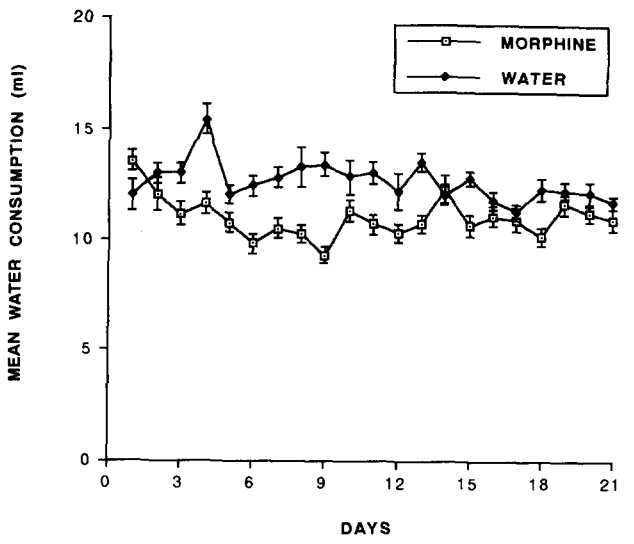

FIG. 1. Mean daily water consumption for groups injected with either morphine or the distilled water vehicle during Phase II: Drug Exposure. Bars above and below each point represent standard error of the mean (S.E.M.).

Phase III: Precipitated Withdrawal

Taste aversion conditioning. Figure 3 illustrates the percent shift in saccharin consumption from baseline for all morphine-injected groups over repeated conditioning trials. On the initial conditioning trial, subjects in all groups drank approximately 12 ml of saccharin with no differences among groups, H(4)=2.63. On

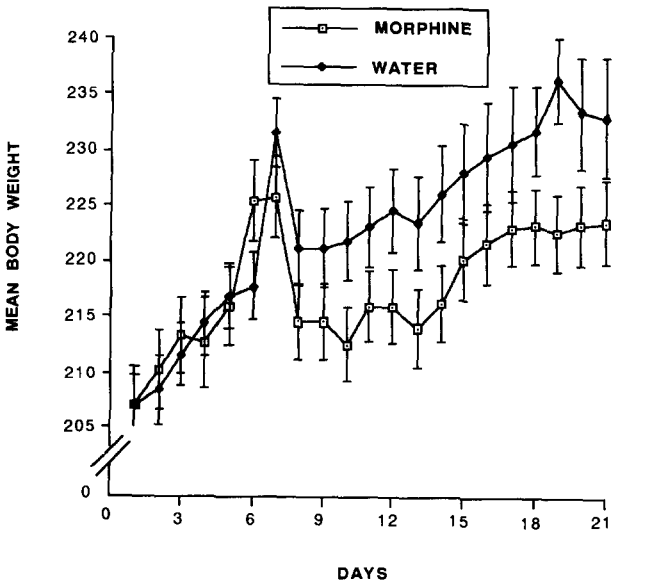

FIG. 2. Mean body weight for groups injected with either morphine or the distilled water vehicle during Phase II: Drug Exposure. Bars above and below each point represent S.E.M.

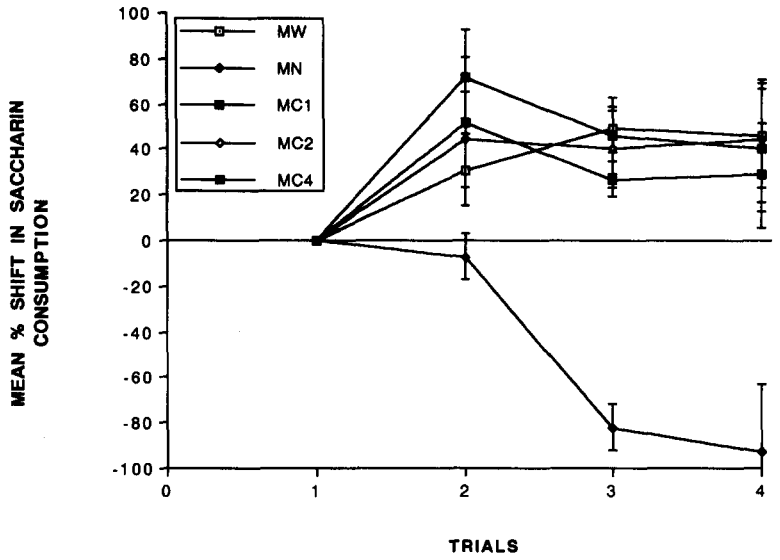

FIG. 3. Mean percent shift in saccharin consumption over repeated conditioning trials for morphine-maintained animals treated with vehicle (MW), naloxone (MN) and 10 (MC1), 20 (MC2) and 40 μg/kg (MC4) of cholecystokinin during conditioning (Phase III: Precipitated Withdrawal). The percent shift over conditioning reflects changes from the initial saccharin exposure (Trial 1). Bars above and below each point represent S.E.M.

the second exposure to saccharin (the first exposure following conditioning), subjects in Group MN displayed a slight, but nonsignificant, decrease in saccharin consumption below their initial baseline, $\chi_r^2(3) = 1.33$. Subjects in Group MC1 and MC2 significantly increased saccharin consumption above their baselines, H's = 5.34, while the remaining groups showed no significant changes, all H's(4) < 1.33. There were no significant differences among groups in the percent shift on this exposure, H(4) = 6.16. With repeated conditioning trials, subjects in Group MN significantly decreased saccharin consumption, drinking less than 15% and 10% of their initial saccharin baseline on the third, $\chi_r^2(3) = 5.34$, and fourth conditioning trials, $\chi_r^2(3) = 5.34$, respectively. Subjects in the remaining groups continued to consume saccharin at high levels throughout conditioning, drinking between 25 to 35% above baseline on the final conditioning trial. Subjects in Group MN differed significantly from subjects in the remaining groups on the third, H(4) = 9.90 and fourth, H(4) = 9.75, conditioning trials. No other group differences were significant.

Figure 4 illustrates the percent shift in saccharin consumption from baseline for all morphine-naive groups. On the initial conditioning trial, subjects in all groups drank approximately 12 ml of saccharin with no differences among groups, H(4) = 0.13. On the second exposure to saccharin, subjects in Groups WW and WC2 displayed a significant increase in saccharin consumption above their initial baselines, $\chi_r^2(3) = 5.34$, while the remaining groups showed no significant changes, all χ_r^2's(3) < 1.33. There were no significant differences among groups in the percent shift on this exposure, H(4) = 2.42. With repeated conditioning trials, subjects in all groups continued to consume saccharin at high levels, drinking between 2% below and 19% above baseline on the final conditioning trial. There were no significant differences among groups in the percent shift in saccharin consumption on this exposure, H(4) = 3.32.

Body weight. Figure 5 illustrates the percent shift in body weight from baseline for all morphine-injected groups over conditioning. To determine this percent shift, body weight prior to receiving the injection on each conditioning trial was compared to the weight on the following day (i.e., 24 hours following the injection). As illustrated, subjects in Groups MN and MC4 displayed significant reductions in body weight following the first conditioning trial, both χ_r^2's(3) = 5.34, reducing body weight by approximately 6% and 1.3%, respectively. Subjects in the remaining groups displayed slight, but nonsignificant, changes following their respective injections, all χ_r^2's(3) < 3.00. On this day, there were significant differences in the percent shift in body weight between subjects in Group MN and subjects in the remaining groups, H(4) = 11.11. No other differences were significant.

Subjects in Group MN continued to reduce body weight by approximately 6.5% following each naloxone injection. Subjects in the remaining groups continued to display small changes in body weight with each injection, the only significant change occurring for subjects in Group MW on the third conditioning trial, $\chi_r^2(3) = 5.34$. Following the final injection, there were significant differences between subjects in Groups MN and subjects in the remaining groups, H(4) = 9.50. No other differences were significant.

Figure 6 illustrates the percent shift in body weight from baseline for all morphine-naive groups. With the single exception of subjects in Group WC4 on the second conditioning trial, $\chi_r^2(3) = 5.34$, there were no significant changes in body weight following the various injections at any point during conditioning for any group, all χ_r^2's(3) < 3.52. Further, there were no significant differences among groups following any injection, all H's(4) < 5.36.

DISCUSSION

As described, morphine-maintained subjects injected with 10 mg/kg naloxone displayed a significant reduction in body weight [cf. (6)] and acquired a robust aversion to the saccharin solution which immediately preceded the naloxone injection [cf. (16)].

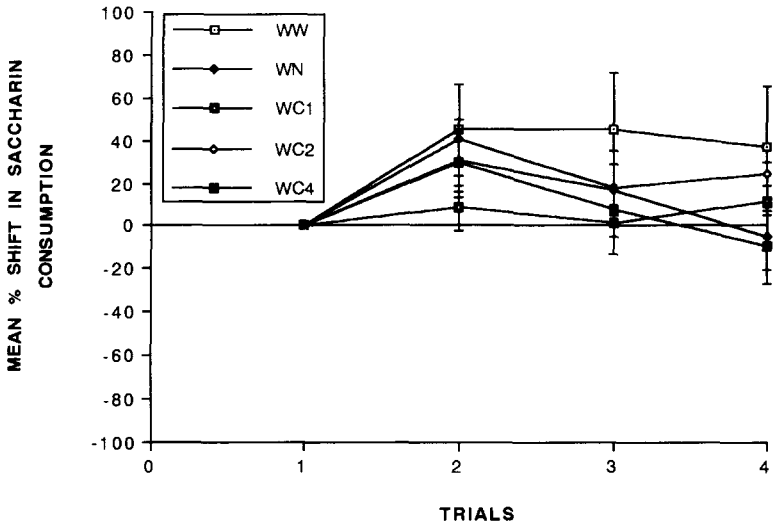

FIG. 4. Mean percent shift in saccharin consumption over repeated conditioning trials for water-maintained animals treated with vehicle (WW), naloxone (WN) and 10 (WC1), 20 (WC2) and 40 μg/kg (WC4) of cholecystokinin during conditioning (Phase III: Precipitated Withdrawal). The percent shift over conditioning reflects changes from the initial saccharin exposure (Trial 1). Bars above and below each point represent S.E.M.

Thus the specific injection schedule (i.e., 80 mg/kg of morphine/day for 21 consecutive days) was effective in inducing dependence in these animals. Interestingly, CCK neither affected body weight nor induced a taste aversion in the morphine-dependent subjects at any of three doses tested. Given the aforementioned well-documented interaction of CCK and the opiates, these findings are somewhat surprising.

One possible basis for the differences between the present findings and those reporting an effect of CCK on opiate-mediated behaviors concerns the specific doses used in the assessment of precipitated withdrawal. That is, it is possible that the doses of CCK may have been too low to precipitate withdrawal. Accordingly, if the dose had been increased, an effect comparable to that produced by naloxone might have occurred. Although possible, it should be noted that relative to other reports on the antagonistic interaction between CCK and the opiates, the doses used in the present experiment were high. For example, Faris et al. (5) have reported that doses as low as 3 μg/kg produce antagonism. Conversely, it might be argued that the doses in the present study were too high. For example, Faris et al. noted that although low doses of CCK (3 μg/kg) antagonized morphine-induced analge-

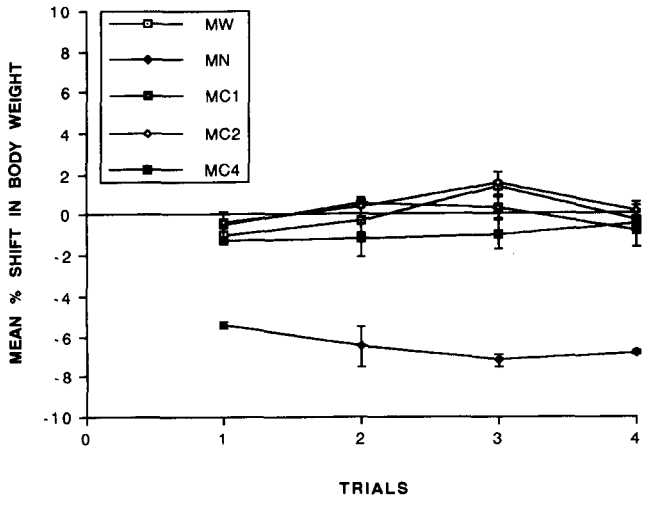

FIG. 5. Mean percent shift in body weight over repeated conditioning trials for morphine-maintained animals treated with vehicle (MW), naloxone (MN) and 10 (MC1), 20 (MC2) and 40 μg/kg (MC4) of cholecystokinin during conditioning (Phase III: Precipitated Withdrawal). For any specific trial, the percent shift reflects changes from the preceding day's weight. Bars above and below each point represent S.E.M.

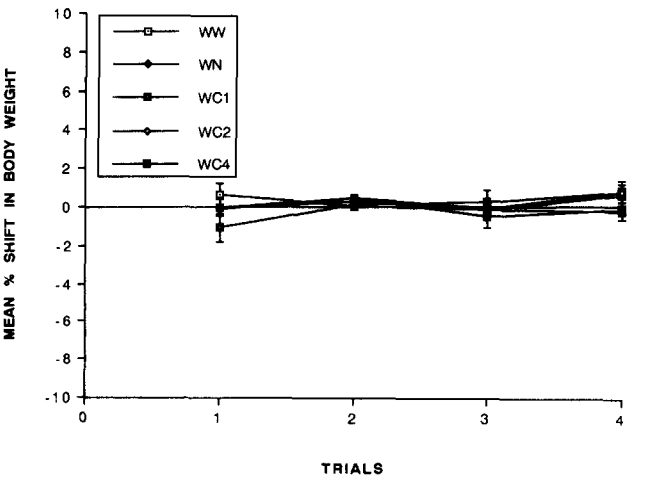

FIG. 6. Mean percent shift in body weight over repeated conditioning trials for water-maintained animals treated with vehicle (WW), naloxone (WN) and 10 (WC1), 20 (WC2) and 40 μg/kg (WC4) of cholecystokinin during conditioning (Phase III: Precipitated Withdrawal). For any specific trial, the percent shift reflects changes from the preceding day's weight. Bars above and below each point represent S.E.M.

sia, higher doses of CCK (30 μg/kg) had no such effect [see also (9)]. Although higher doses of CCK in those reports were ineffective, a number of studies have reported antagonism of opiate-induced effects by CCK at high doses. For example, O'Neil et al. (18) have reported that an IP injection of CCK at a dose of 16 μg/kg blocked morphine-induced analgesia in the paw pressure test in the rat. Also, Schnur, Raigoza, Sanchez and Kulkosky (24) have shown that doses as high as 75 μg/kg of CCK blocked morphine-induced hyperactivity in the hamster. Further, in unpublished work from this lab we have determined that 20 and 40 μg/kg of CCK are equally effective to 10 mg/kg of naloxone in the suppression of food consumption. Specifically, 20 and 40 μg/kg of CCK and 10 mg/kg of naloxone suppressed 1-h food consumption in mildly food-deprived rats (6-h deprivation) by approximately 40, 50 and 50%, respectively. Thus the doses of CCK used in the present experiment were in the range of those affecting opiate-mediated behaviors and were equieffective to naloxone in other assessments.

As a second possibility, Mucha (17) has reported recently that opiate dependence (and physiological withdrawal) are centrally mediated. Using a conditioned taste aversion design to assess physiological withdrawal, Mucha assessed the ability of intracerebroventricular (ICV) and subcutaneous (SC) injections of naltrexone, methylnaltrexone and diallylnormorphine to condition taste aversions in opiate-dependent rats. Interestingly, neither SC methylnaltrexone nor SC diallylnormorphine (two opiate antagonists which do not cross the blood-brain barrier) conditioned a greater taste aversion in opiate-dependent animals than in opiate-naive animals, i.e., there was no potentiation of the taste aversion in dependent rats. Subcutaneous naltrexone, which does cross the blood-brain barrier, did condition a greater taste aversion in dependent subjects. Each of the three compounds potentiated a taste aversion in dependent subjects when given ICV. Because only compounds which crossed the blood-brain barrier were able to produce a greater taste aversion in dependent rats, an effect presumably mediated by the precipitated withdrawal, Mucha concluded that dependence and withdrawal were centrally mediated.

Considerable evidence exists which suggests that when administered peripherally, CCK does not cross the blood-brain barrier (1). Further, complete vagotomies block the behavioral effects of peripherally administered CCK, again indicating that the actions of CCK are peripheral and the central effects of CCK are mediated via the vagus and are not a function of its direct action on the CNS (25). Accordingly, the failure of CCK to precipitate withdrawal in dependent rats (as indexed by the acquisition of taste aversions or changes in body weight) may be a function of the inability of CCK to cross the blood-brain barrier (see above). Although possible, recent work from Hommer and his colleagues [see (11)] has suggested that peripherally administered CCK can enter the CNS to effect some physiological changes. Specifically, peripherally administered CCK has two effects on the firing rate of cells in the substantia nigra. One of these effects appears to be mediated by the vagus, i.e., when the vagus is cut there is a dramatic decrease in CCK-induced activity in the substantia nigra. However, CCK is not without effect on the substantia nigra in vagotomized animals. Because of this residual activity, Hommer et al. have concluded that peripherally administered CCK has a direct action on dopamine neurons in the substantia nigra. The relation between CCK's ability to enter the CNS and its failure to precipitate withdrawal thus remains unknown. An assessment of the ability of ICV administered CCK to precipitate withdrawal in dependent subjects is needed to address this relationship directly.

Although the antagonistic interaction between CCK and the opiates is well established (see Introduction), the failure of such an interaction in the present report is consistent with several reports on the absence of an effect of CCK antagonists on opiate dependence. For example, the development of dependence (as measured by withdrawal) is not prevented by chronic treatment with the CCK antagonists, L-364,718 and proglumide, although similar treatment prevents the development of tolerance to analgesia in the same subjects (4,7). Further, Panerai, Rovati, Cocco, Sacerdote and Mantegazza (19) have shown that the development of tolerance to morphine-induced analgesia is prevented by the CCK antagonists, proglumide and benzotript, although dependence is unaffected. The basis for the inability of CCK to induce withdrawal in the present study and of the CCK antagonists to affect dependence may be related to the fact that precipitated withdrawal is a receptor-mediated event, and although nonsulphated CCK has been reported to bind to the opiate receptor (23), no such evidence exists for the active sulphated form of CCK (26,28).

The failure of CCK to affect the opiates is not limited to dependence or withdrawal. For example, Kapas, Benedek and Penek (14) reported that CCK had no effect on morphine-induced hyperthermia in freely moving rats. CCK also failed to antagonize the onset of beta-endorphin-induced catalepsy (12), and morphine had no effect on CCK-suppressed feeding (32). Interestingly, CCK potentiates the rate-decreasing effects of morphine on schedule-controlled behavior (33) and the CCK-like peptide, caerulein, potentiates morphine-induced thermoregulatory changes (35).

The absence of an interaction in measures such as feeding, hyperthermia, catalepsy and schedule-controlled behavior and the presence of such interactions in pain [see (18)] might indicate that an interaction between CCK and the opiates could be dependent upon the specific response system examined. However, although CCK generally antagonizes the effects of morphine within assays of pain, even here such antagonism is not always reported. For example, Barbaz, Hall and Liebman (3) have noted that morphine-induced tail-flick analgesia was not antagonized by CCK-8 at doses ranging from 1.25 to 30 μg/kg. Further, Weller and Blass (31) reported that CCK did not antagonize the effects of morphine on either distress vocalization or pain threshold in acutely isolated rat pups.

Together, these findings suggest that the interaction of CCK and the opiates is a function of both the response system examined and the specific assay used. The basis for the effects of CCK on the opiates remains unknown.

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