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An Assessment of the Interaction Between Cholecystokinin and the Opiates Within a Drug Discrimination Procedure

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MELTON, P. M. AND A. L. RILEY. *An assessment of the interaction between cholecystokinin and the opiates within a drug discrimination procedure.* PHARMACOL BIOCHEM BEHAV 46(1) 237–242, 1993.—Recently, cholecystokinin (CCK) has been reported to antagonize a variety of opiate-induced effects, including nociception, body shaking, thermoregulation, and locomotion. Consistent with these results, a number of CCK antagonists potentiate the opiates in a range of behavioral and physiological assessments. The present study further examined the interaction between CCK and the opiates within the conditioned taste aversion baseline of drug discrimination learning, a design that utilizes the stimulus properties of the drug to control consummatory behavior. Specifically, animals injected with CCK prior to saccharin–LiCl pairings and the CCK vehicle prior to saccharin alone rapidly acquired the CCK–vehicle discrimination, avoiding saccharin consumption following the administration of CCK and consuming the same saccharin solution following the vehicle. Although the stimulus properties of CCK did not generalize to either naloxone or diprenorphine, morphine blocked and naloxone potentiated CCK's stimulus effects. These data are thus consistent with a physiological (rather than a pharmacological) interaction between CCK and the opiates.

CCK Opiates Drug discrimination learning Antagonism Potentiation

THE antagonistic effects of the sulfated form of the octapeptide cholecystokinin (CCK) on opioid-mediated analgesia are well established. For example, Faris (7) reported that the systemic administration of CCK attenuated analgesia produced by morphine and opioid-mediated front paw foot shock, but not that produced by nonopioid-mediated hind paw shock. In addition, O'Neill et al. (23) reported antagonism of analgesia induced by 8 mg/kg morphine in the rat paw pressure test. The antagonism is not limited to opiate-mediated analgesia, however, in that CCK has been reported to antagonize a variety of other opioid-induced effects, including nociception (7), body shaking (14), thermoregulation (16), locomotion (29,30), and disruption of maternal behavior (8). Consequently, it has been hypothesized that CCK acts as an endogenous antagonist of opioid action (7,10,23).

Consistent with these results, a number of CCK antagonists (e.g., the nonselective CCK antagonist proglumide and the selective CCKA antagonist devazepide) potentiate the opiates in a range of behavioral and physiological assessments (5,6,23,24,38,39). For example, Dourish et al. (4) reported that devazepide not only enhanced the analgesia induced by acute morphine treatment in the rat tail flick test, but in addition prevented the development of tolerance to morphine analgesia. Similarly, Hendrie et al. (11) demonstrated that devazepide enhanced, and modestly prolonged, morphine-induced and opioid-mediated social conflict analgesia, while it had no effect on nonopioid analgesia induced by defeat experience.

The present study extended this assessment of the interaction between CCK and the opiates by examining the effects of opiate agonists and antagonists on the stimulus properties of CCK within the conditioned taste aversion baseline of drug discrimination learning [(17,18,28,32); for general reviews of drug discrimination learning, see (12,15,26)]. Specifically, animals were injected with 13 μg/kg CCK prior to saccharin–LiCl pairings and the CCK vehicle prior to nonpoisoned exposures to the same saccharin solution. Upon acquisition of the CCK–vehicle discrimination (after subjects differentially consumed saccharin following the administration of CCK and the CCK vehicle), animals were administered various doses of the opiate antagonists, naloxone and diprenorphine, to assess their ability to substitute for the training dose of CCK, and the opiate agonist, morphine, to assess its ability to antagonize CCK's stimulus effects. Naloxone was also administered in combination with a lower dose of CCK to assess the ability of naloxone to potentiate the stimulus properties of CCK.

METHOD

Subjects

The subjects were 22 drug-naive, female rats of Long-Evans descent, approximately 270–310 g at the start of the

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experiment. They were housed in individual wire-mesh cages and were maintained on a 12L:12D cycle (lights on at 0800 h) and at an ambient temperature of 23°C for the duration of the experiment. Subjects received restricted access to fluid for the duration of the study, but were maintained on ad lib food.

Drugs

The sulfated form of cholecystokinin octapeptide (generously supplied by the Squibb Institute) was prepared at a concentration of 2 or 10 μg/ml and was injected in a volume of 0.18 and 1.8 ml/kg, respectively. Naloxone hydrochloride (generously supplied by DuPont Pharmaceuticals) was prepared at concentrations of 0.56–5.6 mg/ml and injected in a volume of 0.31–1.8 ml/kg. Morphine sulfate and diprenorphine hydrochloride (generously supplied by the National Institute on Drug Abuse) were prepared at concentrations of 1.0–5.6 mg/ml and 1.8–5.6 mg/ml, respectively, and injected in a volume of 0.31–1.8 ml/kg. All drugs were prepared in distilled water.

Procedure

Phase I: Acquisition. Every fourth day, subjects (n = 22) were given an intraperitoneal (IP) injection of CCK (13 μg/kg) 5 min prior to 5-min access to saccharin (0.1% w/v, Sodium Saccharin Salt, Sigma Pharmaceuticals). Immediately following saccharin access, subjects in Group L (n = 12) were given an IP injection of 1.8 mEq, 0.15 M LiCl (76.8 mg/kg), while subjects in Group W (n = 10) were given an equivolume injection of the distilled water vehicle. On the intervening 3 days, all subjects were injected with distilled water (1 ml/kg) prior to saccharin access. No injections were given following saccharin access on these recovery days. This alternating procedure of conditioning (CCK–saccharin–LiCl or CCK–saccharin–distilled water) and recovery (distilled water–saccharin) was repeated for each experimental subject until it consumed at least 50% less than the mean of the control subjects for three consecutive conditioning trials (no more than 15 conditioning/recovery cycles).

Phase II: Generalization. The procedure during this phase was identical with that described for Phase I with the following exception. On the second recovery day following conditioning, seven animals in Group L (those acquiring the CCK–distilled water discrimination within 15 trials) and nine animals in Group W were injected with one of a range of doses of CCK (5.0–18.0 μg/kg), naloxone (0.32–3.2 mg/kg), or diprenorphine (1.8–5.6 mg/kg) 5–15 min prior to saccharin access. On any specific probe day, individual subjects in Group L were given an injection only if they had consumed at least 50% less than the *mean* of the control subjects on the immediately preceding conditioning trial. Doses were administered in a mixed pattern. No injections followed saccharin access on these probe sessions.

Phase III: Antagonism. The procedure during this phase was identical with that described for Phase II with the exception that on the second recovery day following conditioning one of a range of doses of morphine (0–5.6 mg/kg) was administered 15 min prior to the training dose of CCK (13 μg/kg), which in turn was administered 5 min prior to saccharin access. To assess the effects of morphine alone on saccharin consumption, each dose of morphine was also administered 20 min prior to saccharin access with no intervening CCK injection. Doses of morphine were administered in a mixed pattern. No injections followed saccharin access on these antagonism sessions.

Phase IV: Potentiation. The procedure during this phase was identical with that described for Phase II with the exception that on the second recovery day following conditioning one of a range of doses of naloxone (0–3.2 mg/kg) was administered 10 min prior to CCK, which in turn was administered 5 min prior to saccharin access. To determine the specific dose of CCK used in this assessment, dose-response functions for CCK were reestablished in individual experimental subjects. The minimal effective dose necessary to reduce consumption to *less* than 50% of the mean of the control subjects was determined. The dose of CCK administered in combination with naloxone was one-quarter log dose less than this dose. Doses of naloxone were administered in a mixed pattern. No injections followed saccharin access on these potentiation sessions.

Statistical Analysis

A two-tailed Mann-Whitney U-test was performed on all between-group comparisons of saccharin consumption. Absolute probabilities are presented for all comparisons.

RESULTS

Phase I: Acquisition

Under the terminal dose and temporal parameters (13 μg/kg CCK administered 5 min prior to 5-min saccharin access), seven of the 12 experimental subjects acquired the CCK discrimination (i.e., drinking less than 50% of the mean of the control subjects for three consecutive conditioning trials within 15 trials). On the final conditioning trial, consumption for these subjects ranged from 0 to 1.75 ml (mean consumption of 0.25 ml), while the mean consumption for subjects in Group W was 8.3 ml.

Phase II: Generalization

Figure 1 presents the mean amount (±SEM) of saccharin consumed for the seven subjects in Groups L who acquired the CCK discrimination and for nine subjects in Group W following various doses of CCK (one of the original 10 subjects in Group W died during the acquisition phase). As illustrated, for subjects in Group L there was an inverse relation-

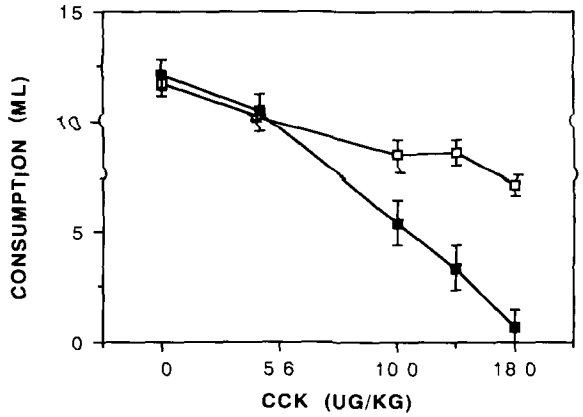

FIG. 1. The mean amount (±SEM) of saccharin consumed for subjects in Groups L (filled squares) and W (open squares) following various doses of CCK (0.0 – 18.0 μg/kg) during generalization testing

ship between the dose of CCK and the amount of saccharin consumed. Consumption of saccharin for subjects in Group W also decreased as the dose of CCK increased, although this decrease was not as dramatic as that for subjects in Group L. At the lower doses of CCK (0 and 5.0 μg/kg), consumption for subjects in Group L did not differ from that for subjects in Group W (U = 27, 36, p = 0.63 and U = 25, 38, p = 0.49, respectively). At 10, 13, and 18 μg/kg, subjects in Group L drank significantly less saccharin than subjects in Group W (U = 13, 50, p = 0.044; U = 6, 57, p = 0.007; and U = 0, 63, p = 0.0008, respectively).

Figure 2 presents the mean amount (±SEM) of saccharin consumed for six subjects in Group L and nine subjects in Group W following the administration of various doses of naloxone and diprenorphine (one subject in Group L did not maintain discriminative control during this phase; see criterion for generalization testing). As illustrated in the left panel of Fig. 2, subjects in both groups displayed little change in consumption of saccharin over the increasing doses of naloxone. There were no significant differences in saccharin consumption between Groups L and W at any dose of naloxone tested (all ps > 0.09). There was an inverse dose-response function following injections of diprenorphine with both groups decreasing saccharin consumption as the dose of diprenorphine increased (see right panel of Fig. 2). There were no significant differences in saccharin consumption between Groups L and W at any dose of diprenorphine tested (all ps > 0.27).

Phase III: Antagonism

Figure 3 presents the mean amount (±SEM) of saccharin consumed for six subjects in Group L and seven subjects in Group W following the administration of various doses of morphine administered alone or prior to the training dose of CCK (13 μg/kg) (during this phase one subject in Group L did not maintain discriminative control and two subjects in Group W became ill and were not subsequently tested). As illustrated, when the morphine vehicle (0 mg/kg) was administered prior to the training dose of CCK, subjects in Group L totally avoided saccharin consumption. As the dose of morphine increased, saccharin consumption increased (i.e., morphine antagonized the stimulus properties of CCK). There was

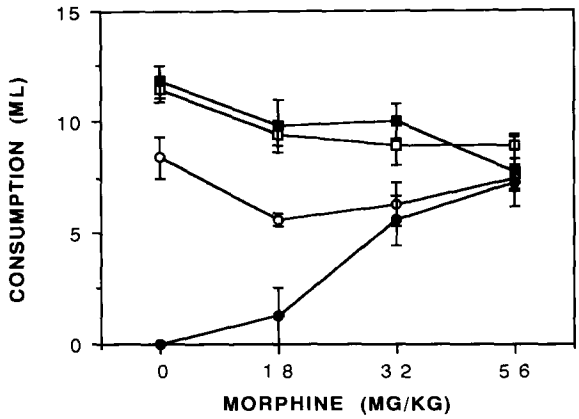

FIG. 3. The mean amount (±SEM) of saccharin consumed for subjects in Groups L (filled symbols) and W (open symbols) following various doses of morphine (0.0 – 5.6 mg/kg) administered alone (squares) or in combination with 13 ug/kg CCK (circles).

no systematic change in saccharin consumption for subjects in Group W over the increasing doses of morphine administered prior to CCK. Consumption was significantly different between Groups L and W at 0 and 1.8 mg/kg morphine (U = 0, 42, p = 0.002 and U = 6, 36, p = 0.03, respectively). There were no significant differences in saccharin consumption at 3.2 and 5.6 mg/kg morphine (U = 18, 24, p = 0.62 and U = 20, 22, p = 0.83, respectively). There was a slight decreasing trend in saccharin consumption for both groups following increasing doses of morphine administered alone. There were no significant differences between groups at any dose of morphine when it was tested alone (all ps > 0.39).

Phase IV: Potentiation

Figure 4 presents the amount of saccharin consumed by five *individual* subjects in Group L following the combination of various doses of naloxone (0–3.2 mg/kg) and a dose of CCK that, on immediately preceding generalization tests, did

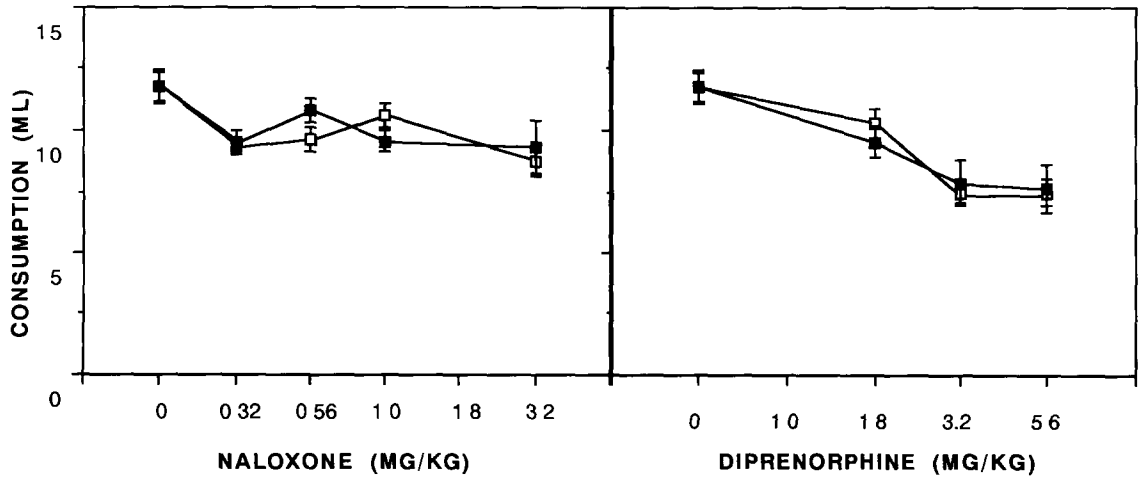

FIG. 2. The mean amount (±SEM) of saccharin consumed for subjects in Groups L (filled squares) and W (open squares) following various doses of naloxone (0.0 – 3.2 mg/kg) and diprenorphine (0.0 – 5.6 mg/kg) during generalization testing.

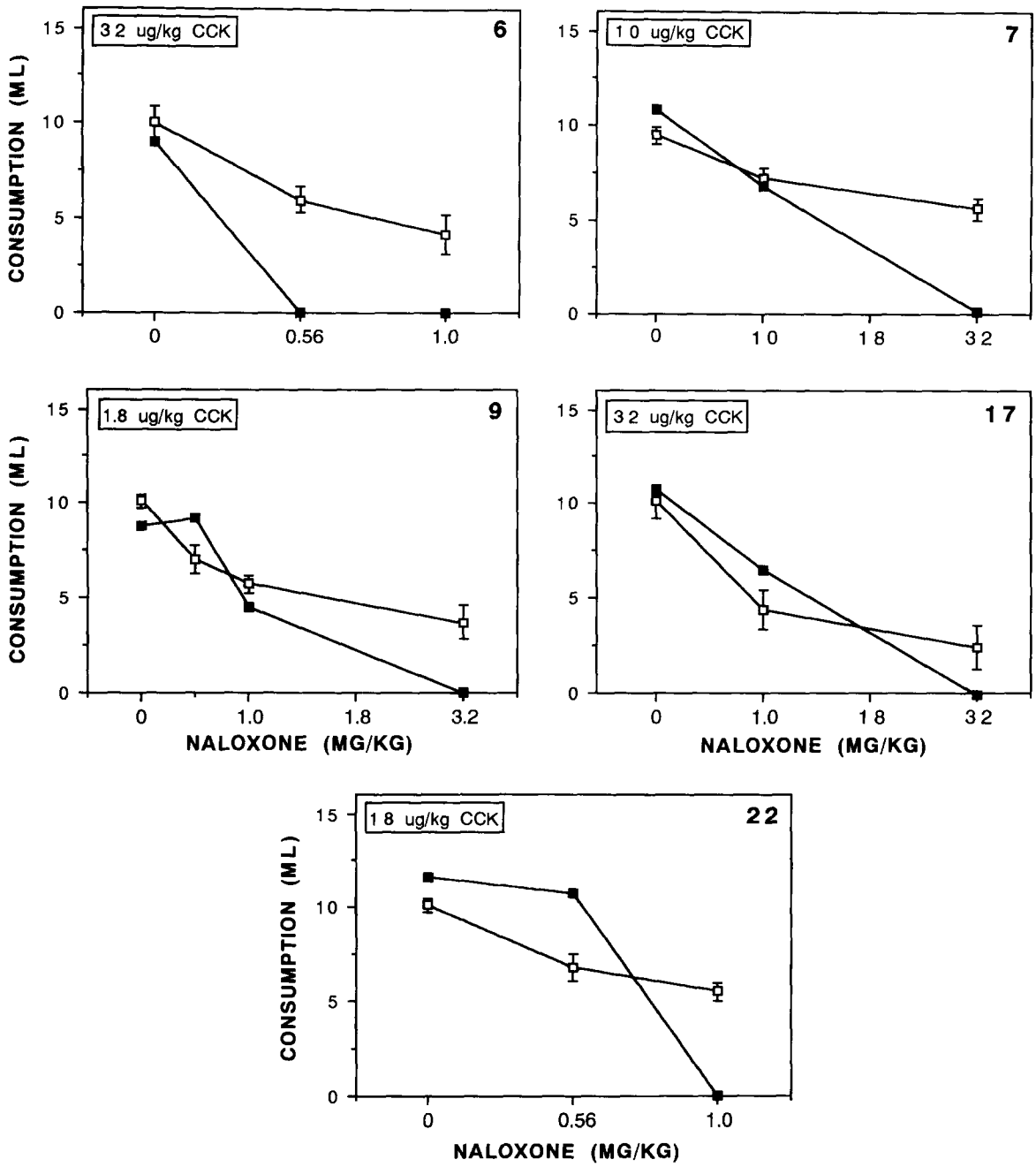

FIG. 4. Saccharin consumption for individual subjects in Group L (filled squares) following various doses of naloxone (0.0 – 3.2 mg/kg) administered in combination with a dose of CCK (noted in insert) ineffective in producing saccharin avoidance when administered alone. The mean amount (± SEM) of saccharin consumed for subjects in Group W is represented by open squares.

not substitute for the training dose of CCK (two subjects in Group L did not maintain discriminative control during this phase). As illustrated, when the naloxone vehicle (0 mg/kg) was administered prior to the probe dose of CCK, all subjects drank at control levels (i.e., there was no evidence of stimulus control at this probe dose of CCK). As the dose of naloxone increased for individual subjects, consumption decreased. All subjects eventually avoided saccharin consumption completely when naloxone preceded the ineffective dose of CCK, although the dose of naloxone at which this occurred varied for individual subjects. Consumption for subjects in Group W also decreased with increasing doses of naloxone, although it was not as dramatic as that for subjects in Group L.

DISCUSSION

As described, animals injected with CCK prior to the presentation of saccharin-LiCl pairings and with the CCK vehicle

prior to saccharin alone acquired the CCK-vehicle discrimination, avoiding saccharin following the administration of CCK and consuming the same saccharin solution following its vehicle [see also (18)]. Consistent with the aforementioned interactions between CCK and the opiates [for a review, see (3)], morphine blocked the stimulus properties of CCK (i.e., animals injected with morphine prior to an injection of the training dose of CCK consumed saccharin at control levels), while the opiate antagonist naloxone potentiated CCK's stimulus properties (i.e., animals injected with naloxone prior to an ineffective dose of CCK avoided the saccharin solution). That these results are likely due to a physiological interaction between CCK and the opiates (as opposed to a pharmacological one) is supported by the fact that neither naloxone nor diprenorphine substituted for CCK in generalization tests [see also (3,27,29,30,35,39,40)]. Given that compounds with similar receptor activity typically generalize to each other within drug discrimination learning (1,9,25), the present data provide no support for the position that CCK and the opiates act at the same receptor site to effect their antagonism (or potentiation).

The underlying basis for the physiological interaction between CCK and the opiates in the present experiment is unknown, although several possibilities exist. For example, Wang and Han (37) have suggested that CCK may affect the binding of opiates to mu and kappa subtypes of the opiate receptor by way of an allosteric interaction. Specifically, they reported that CCK suppressed the binding in rat brain homogenates of [^{3}H]DAGO (a selective mu agonist) and [^{3}H]U69,593 (a selective kappa agonist) but left [^{3}H]DPDPE (a selective delta agonist) binding unaffected [for other analysis of the effects of CCK on opiate binding, see (13,31,36)]. If the opiates affect CCK binding in a complementary manner, the present data could be accounted for by such an allosteric interaction. Until the effects of opiates on CCK binding have been assessed, however, it is not clear if this type of receptor interaction underlies the present demonstration of antagonism (or potentiation).

Several reports have also noted that morphine inhibits the release of CCK (or CCK-like material) in vitro. For example, Micevych et al. (22) reported that both the mu agonist morphine and the delta agonist DADLE inhibited the in vitro K^+-stimulated release of CCK from hypothalamic (but not cortical) tissue (19–21). In relation to the present data, it is possible that such an inhibition underlies the ability of morphine to block the stimulus properties of CCK; however, changes in the endogenous release of CCK seem an unlikely explanation for the antagonism of exogenously administered CCK. In addition, it should be noted that the inhibitory effects of the opiates on CCK release are dose, drug, and preparation specific. For example, Benoliel et al. (2) have reported that while both the mu agonist DAGO and the delta agonist DTLET inhibited the K^+-stimulated release of CCK from slices of the dorsal zone of the rat lumbar enlargement, morphine and higher doses of DTLET enhanced CCK release. Further, both morphine and β-endorphin consistently induce the release of CCK from the spinal cord (33–35). Thus, it is unclear to what extent the effects of opiates on CCK release mediate the ability of opiates to block (or potentiate) the stimulus properties of CCK.

In a general review of the possible mechanism underlying CCK/opiate interactions on analgesic responsivity, Dourish (3) has suggested that the interaction of CCK and the opiates is mediated by the differential effects of CCK and the opiates on K^+ conductance. Specifically, he argues that opioid and CCK neurons converge upon a common system but have opposite effects upon this system (e.g., increases and decreases in K^+ conductance, respectively, via separate K^+ channels located on the same neuronal terminals). Accordingly, CCK antagonizes morphine analgesia by causing a reduction in K^+ efflux in opposition to the opiate-mediated increase in K^+ efflux. In relation to the present data, such a mechanism could underlie the noted antagonism if one assumes that morphine's effects on K^+ oppose those induced by CCK. Specifically, if the stimulus properties of CCK are based on K^+ activity, then morphine's effects on K^+ at the same system would oppose CCK's inhibition of K^+ efflux and consequently its stimulus properties. Similarly, the opiate antagonist naloxone might be expected to block endogenous opiate activity at the opiate receptor and thereby reduce the effects of endogenous opiates on K^+ activity, thereby amplifying the effects of CCK on K^+ efflux and consequently CCK's stimulus properties. Finally, the failure of the opiate antagonists naloxone and diprenorphine to generalize to CCK might be expected if the abovementioned effects on K^+ conductance produced by the blocking of endogenous opiates was insufficient to mimic the direct effects of CCK administration. Although the model proposed by Dourish could account for the present data, it should be noted that his model is based on activity at the dorsal horn and was developed to account for the effects of CCK on opiate-induced analgesia. It is simply unknown if the stimulus properties of CCK assessed within this drug discrimination design are related to CCK's effects on analgesic responsivity. Further, although the stimulus properties of CCK are affected by the opiates within this design, it is not known what specific opiate system (e.g., dorsal horn, periaqueductal gray, ventral tegmentum) or which specific opiate (or CCK) receptor subtype is involved.

In summary, the present study demonstrates that CCK can serve as a discriminative stimulus and that its stimulus properties can be modulated by the opiates. The interaction between CCK and the opiates appears physiological in nature, although the basis for this physiological interaction remains unknown. Further assessments of the receptor mediation of CCK's stimulus properties (e.g., CCK_A or CCK_B) as well as the specific opiate receptor subtype and system involved may provide insight into the mechanism underlying the ability of the opiates to modulate CCK.

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