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Effects of μ- and δ-Opioid–Receptor Antagonists on the Stimulus Properties of Cholecystokinin

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RILEY, A. L. AND P. M. MELTON. *Effects of μ- and δ-opioid–receptor antagonists on the stimulus properties of cholecystokinin.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 57–62, 1997.—Melton and Riley recently reported that the relatively selective μ-opioid–antagonist naloxone potentiated the stimulus properties of the gut peptide cholecystokinin (CCK). To assess whether such opioid potentiation is limited to activity at the μ-receptor subtype, in the present experiment the effects of the highly selective δ-antagonist naltrindole on CCK's stimulus properties were examined. Because in the initial report of naloxone's potentiation of CCK a relatively high, nonphysiologic dose of CCK (i.e., 13 μg/kg) was used as the training drug, in the current analysis subjects were trained to discriminate 5.6 μg/kg CCK from its vehicle and the assessments and comparisons of the effects of naloxone and naltrindole were based on this dose. Specifically, rats were administered 5.6 μg/kg CCK before saccharin–LiCl pairings and the CCK vehicle before saccharin alone. With such training, they rapidly acquired the drug discrimination, avoiding saccharin consumption when it was preceded by CCK and consuming the same saccharin solution when it was preceded by its vehicle. In subsequent generalization tests, doses of CCK that were ineffective in suppressing saccharin consumption (i.e., did not substitute for the training dose of CCK) did result in the suppression of saccharin consumption when combined with doses of the μ antagonist naloxone that alone had no effect on saccharin intake. On the other hand, the highly selective δ-opioid–receptor antagonist naltrindole was ineffective in potentiating the effects of CCK. Specifically, when naltrindole was combined with ineffective doses of CCK, subjects drank at control levels. The ability of naloxone to potentiate CCK's stimulus effects is consistent with a range of other demonstrations of the role of the μ-opioid–receptor subtype in CCK–opioid interactions, although the specific basis for the interaction remains unknown. Given recent findings on the effects of δ agonists and antagonists on CCK-induced activity, the failure of naltrindole to potentiate CCK's stimulus effects may be due to the absence of δ activity within this preparation, rather than the absence of δ mediation of CCK–opioid interactions in general. © 1997 Elsevier Science Inc.

CCK Naloxone Naltrindole Drug discrimination learning Opioid antagonism μ δ

THE antagonistic effects of the sulfated form of the octapeptide cholecystokinin (CCK) on opioid-mediated analgesia is well established. For example, as early as 1985, CCK was reported to attenuate analgesia produced by morphine as well as by opioid-mediated front paw foot-shock (15). Subsequently, Dourish and colleagues reported that CCK antagonized analgesia induced by 8 mg/kg morphine in the rat paw pressure test (47) and the rat tail-flick test (12). These antagonist effects of CCK on the opioids are not limited to opiate-mediated analgesia, however. CCK has now been reported to antagonize a variety of other opioid-induced effects, including body shaking (24), disruption of maternal behavior (16), feeding (75), locomotion (62,63), and thermoregulation (26). Consequently, CCK has been hypothesized to act as an endogenous antagonist of opioid action (15,19,47).

Related to the findings that CCK functions as an opioid antagonist, Melton and Riley (37) recently demonstrated the potentiation of CCK's discriminative stimulus properties by the opioid antagonist naloxone, an effect consistent with the often reported finding that CCK antagonists potentiate the effects of opioid agonists within a variety of behavioral and physiologic preparations (12–14,20–22,28,47,48,55,72–74,78,79). In their assessment of the ability of naloxone to potentiate the stimulus effects of CCK, Melton and Riley used the condi-

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tioned taste aversion baseline of drug discrimination learning [(31,33,35); for reviews, see (57,58)], a preparation that uses the subjective effects of drugs to establish control over behavior [(25,50,66); for a bibliography, see (61)]. Specifically, Melton and Riley injected rats every fourth day with CCK (13 μg/kg) immediately before a pairing of a saccharin solution and an injection of the emetic LiCl. On intervening days, the subjects were injected with the CCK vehicle (i.e., distilled water) immediately before saccharin alone. Under these training conditions, discriminative control by the drug was reflected in different patterns of consumption of the saccharin solution following the drug and its vehicle. Specifically, subjects avoided the consumption of saccharin when it was preceded by CCK and drank the same saccharin solution when it was preceded by the CCK vehicle [see also (36,38)]. On subsequent tests, naloxone was given concurrently with doses of CCK that alone did not produce avoidance of saccharin. Under these conditions, CCK was now effective in suppressing saccharin consumption (i.e., naloxone potentiated the stimulus effects of CCK). This potentiation was evident even though naloxone alone had no effect on the consumption of saccharin.

Given naloxone's relative affinity for the μ-receptor subtype of the opiate receptor (30,32,34,77), it was concluded that the potentiating effects of naloxone on CCK's stimulus properties were likely mediated by the μ receptor (a conclusion consistent with a range of other reports demonstrating the role of the receptor subtype in CCK–opioid interactions) (3,9,43,44,70). Such a conclusion, however, does not preclude the possibility that opioids with activity at other subtypes of the opiate receptor also influence CCK's stimulus effects. To assess this possibility, in the present experiment the effects of the highly selective δ-antagonist naltrindole (6,29,45,60,65) on CCK's stimulus properties were evaluated and compared with those produced by the relatively selective μ antagonist naloxone. Naltrindole was selected for analysis because of recent evidence implicating this receptor subtype in opioid–CCK interactions (8,23,49,53,64) as well as the recent demonstration by Roques et al. (7) that the suppressant effects of the CCK_A agonist Boc-Tyr-Lys-(CONH-*o*-tolyl)-Asp-Phe-NH_2 on opiate-mediated hyperlocomotion were potentiated by the highly selective δ-opioid antagonist naltrindole (in the presence of the enkephalin-degrading enzyme inhibitor RB101). In the original report assessing the effects of naloxone on the stimulus properties of CCK (37), a relatively high, nonphysiologic dose of CCK (i.e., 13 μg/kg) was used in training the discrimination. Because 13 μg/kg is outside the range of doses used in many other assessments of the effects of CCK on behavior [for a discussion, see (36)], it is not known to what extent the results from assessments of opioid–CCK interactions with this dose generalize to baselines using smaller and more physiologic doses of CCK. Accordingly, in the present experiment subjects were trained to discriminate 5.6 μg/kg CCK from its vehicle and the assessments and comparisons of the effects of naloxone and naltrindole were based on this dose.

METHOD

Subjects

The subjects were 24 experimentally naive, female rats of Long–Evans descent, approximately 300 g at the start of the experiment. They were housed in individual wire-mesh cages and were maintained on a 12 L:12 D 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 food ad lib.

Drugs

The sulfated form of CCK octapeptide (generously supplied by the Squibb Institute) was prepared at a concentration of 10 μg/ml distilled water and injected at doses of 5.6 μg/kg (conditioning) and 1.8 μg/kg (potentiation). Naloxone hydrochloride (generously supplied by DuPont Pharmaceuticals) and naltrindole (generously supplied by the National Institute on Drug Abuse, Bethesda, MD) were prepared at concentrations of 0.056–3.2 and 0.56–5.6 mg/ml distilled water. Naloxone was injected at doses ranging from 0 to 3.2 mg/kg (generalization) and 0 to 0.56 mg/kg (potentiation). Naltrindole was injected at doses ranging from 0 to 3.2 mg/kg (generalization) and 0 to 5.6 mg/kg (potentiation). For both naloxone and naltrindole, concentration varied with dose to control for volume injected (0.1 × body wt.). The doses of naloxone used in the present study have previously been reported to antagonize opioid activity (51,52) as well as potentiate CCK's stimulus effects (37). The doses of naltrindole used in the present study have previously been reported to antagonize opioid (10,69) and cocaine-mediated effects (39,54,67,68) as well as potentiate CCK's suppression of opioid-mediated hyperlocomotion (7). Further, the pretreatment times used to assess the ability of naloxone and naltrindole to substitute for or potentiate CCK's stimulus effects are within the temporal window during which the general efficacy of these compounds has been reported (7–10,49,51,54).

Procedure

During the light phase, subjects were given restricted access to water for 30 consecutive days. Over this period, the duration of restricted access decreased from 20 to 10 min, to the terminal value of 5 min. On days 31–33, a novel saccharin solution (0.1% w/v, sodium saccharin salt; Sigma Pharmaceuticals) replaced water during the 5-min access period (saccharin habituation) and was preceded on the last 2 days of saccharin habituation by an intraperitoneal (IP) injection of distilled water (0.56 ml/kg). On day 34, all subjects were given an IP injection of 5.6 μg/kg CCK 5 min before 5-min saccharin access. Immediately following saccharin access on this day, subjects were rank ordered according to saccharin consumption and assigned (ABBA sequence) to one of two groups (L or W). 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 = 12) were given an equivolume injection of the distilled water vehicle. On the following 3 days, all subjects were injected with distilled water (0.56 ml/kg) before 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 individual experimental subjects until discriminative control had been established (i.e., consumption by individual experimental subjects was at least 50% less than the mean of the control subjects for three consecutive conditioning trials).

The procedure following the acquisition of the CCK discrimination was identical with that described above with the following exceptions. Specifically, on the second recovery day following each conditioning trial, one of a range of doses of naloxone (six subjects each from Groups L and W) or naltrindole (the remaining six subjects from Groups L and W) was administered either alone 20 min before access to saccharin or 15 min before CCK (which in turn was adminis-

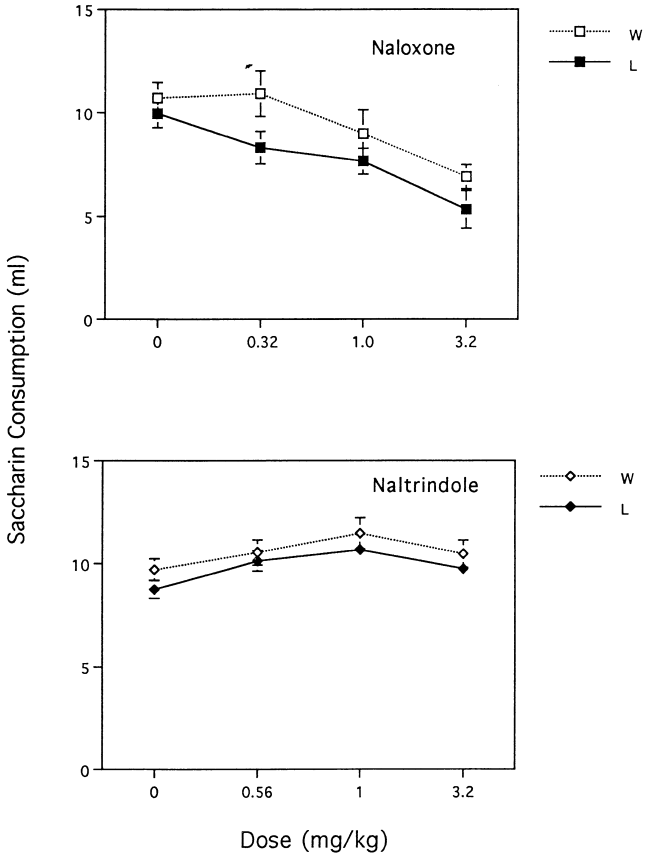

FIG. 1. Mean (±SEM) consumption of saccharin by subjects in Group W (□) and Group L (■) following various doses of naloxone (top panel) and naltrindole (bottom panel) alone.

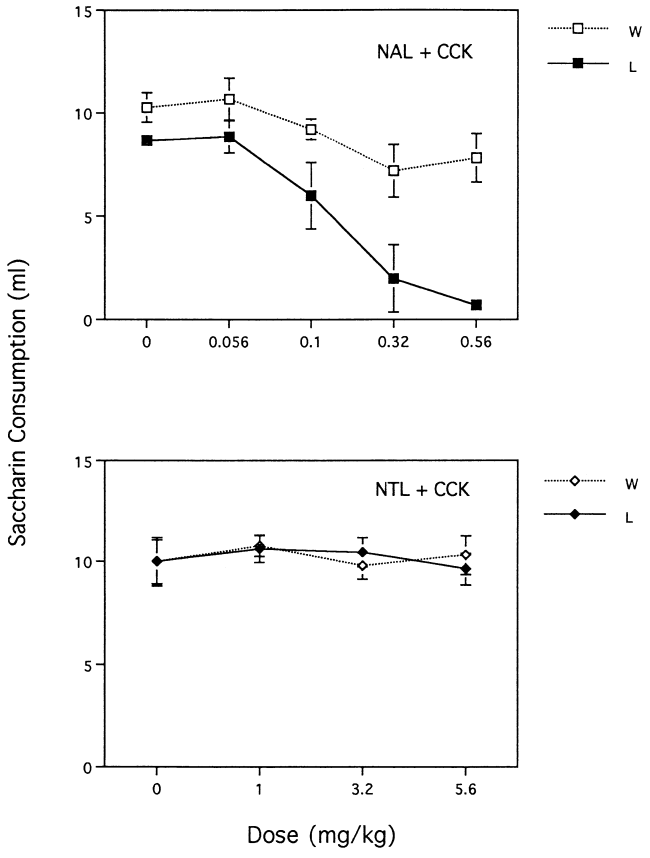

FIG. 2. Mean (±SEM) consumption of saccharin by subjects in Group W (□) and Group L (■) following various doses of naloxone (top panel) and naltrindole (bottom panel) in combination with CCK (1.8 μg/kg).

tered 5 min before saccharin access). No injections followed saccharin access on these probe sessions. Throughout these probes, doses of the antagonists were administered in a mixed pattern with the pattern consistent across all subjects within each group. To determine the specific dose of CCK used in combination with the opioid antagonists, dose–response functions for CCK were established in individual experimental subjects. The maximum dose producing no suppression of saccharin consumption was then used in combination with naloxone and naltrindole. On any specific probe day, individual subjects in Group L were given injections only if they had consumed at least 50% less than the mean of the control subjects on the immediately preceding conditioning trial.

RESULTS

All subjects in Group L acquired the CCK discrimination (i.e., drinking < 50% of the mean of the control subjects for three consecutive conditioning trials, within 15 conditioning trials). On the conditioning trial immediately preceding the initiation of the subsequent phases of this experiment, consumption for subjects in Group L ranged from 0 to 2.75 ml, while the mean consumption for subjects in Group W was 8.3 ml.

Figure 1 presents the mean amount (±SEM) of saccharin consumed for subjects in Groups L and W following the administration of various doses of naloxone (top panel) or naltrindole (bottom panel) alone. As illustrated, saccharin consumption decreased with increasing doses of naloxone for subjects in both Groups L and W. There was no systematic change in the difference in mean saccharin consumption between Groups L and W across the various doses of naloxone (Spearman rank-order correlation coefficient, $r_s = 0.4$; $p > 0.05$). Saccharin consumption was stable and high for subjects in Groups L and W over the increasing doses of naltrindole. Further, there was no systematic change in the difference in mean saccharin consumption between Groups L and W across the various doses of naloxone (Spearman rank-order correlation coefficient, $r_s = 0.4$; $p > 0.05$).

The top panel of Fig. 2 presents the mean amount (±SEM) of saccharin consumed by subjects in Groups L and W following the combination of various doses of naloxone (0–0.56 mg/kg) with a dose of CCK that on immediately preceding generalization tests did not substitute for the training dose of CCK (for subjects in Group L). As illustrated, when the naloxone vehicle (0 mg/kg) was administered before the probe dose of CCK (1.8 μg/kg), all subjects in Group L drank at control levels (i.e., there was no evidence of stimulus control at this probe dose of CCK). The difference in the mean amount of saccharin consumed between Groups W and L, however, increased monotonically over the increasing doses of naloxone (Spearman rank-order correlation coefficient, $r_s = 1.0$; $p < 0.01$), indicating that naloxone was potentiating the stimulus

effects of CCK as the dose of naloxone increased. The bottom panel of Fig. 2 presents similar data for subjects in Groups L and W following the combination of various doses of naltrindole (0–5.6 mg/kg) with a dose of CCK that on immediately preceding generalization tests did not substitute for the training dose of CCK (for subjects in Group L). As illustrated, when the naltrindole vehicle (0 mg/kg) was administered before the probe dose of CCK (1.8 μg/kg), all subjects in Group L drank at control levels (i.e., there was no evidence of stimulus control at this probe dose of CCK). Further, there was no systematic change in the difference in the mean saccharin consumption between Groups L and W over the various doses of naltrindole (Spearman rank-order correlation coefficient, $r_s = -0.4$; $p > 0.05$); that is, naltrindole did not potentiate the effects of CCK.

DISCUSSION

As described [and similar to earlier findings from this lab using a higher dose of CCK as the training drug, i.e., 13 μg/kg (37)], naloxone potentiated the stimulus properties of CCK within the taste aversion baseline of drug discrimination learning. Specifically, doses of CCK ineffective in suppressing saccharin consumption completely suppressed consumption when combined with naloxone. This potentiation by naloxone was evident at doses of naloxone which had no effect on saccharin consumption when given alone. Although the μ antagonist naloxone potentiated CCK's stimulus properties, the selective δ antagonist naltrindole had no such effect. In fact, when naltrindole (up to 5.6 mg/kg) was combined with ineffective doses of CCK, consumption remained at control levels. Thus, the discriminative stimulus effects of CCK appear to be modulated selectively by the μ-, but not δ-, opiate receptor subtype.

That naloxone was effective in modulating the stimulus properties of CCK is consistent with work assessing the interaction of CCK and μ opiate receptors within a variety of preparations. For example, in one of the initial analyses of the effects of CCK on opioid binding, Wang and Han (71) reported that CCK reduced the number of μ opioid-binding sites (although affinity of μ agonists at these sites was unaffected). Also, the acute administration of μ opioid agonists blocks CCK release (3), while their chronic administration upregulates CCK activity (78). Further, Micevych and colleagues (40–42) reported that morphine inhibits the in vitro K^+-stimulated release of CCK from hypothalamic tissue [see also (3) for similar inhibition of K^+-mediated CCK release from slices of the dorsal horn of the rat lumbar enlargement by the selective μ agonist DAMGO].

Although the effects of naloxone within the present design are consistent with other work on CCK–μ interactions, the failure to potentiate CCK's stimulus properties by naltrindole is somewhat surprising given the growing evidence of the involvement of the δ-pioid receptor subtype in CCK–opioid interactions. For example, naltrindole blocks the enhancement of morphine nociception by the CCK_B antagonist L365,260 [(8); see also (49)]. Further, selective δ agonists (like selective μ agonists) block the K^+-stimulated release of CCK in several in vitro preparations (3,40–42). Finally, and more relevant to the present findings, naltrindole has been reported to potentiate the effects of CCK_A agonists on endorphin-mediated hyperlocomotion (7). Thus, within a number of preparations δ receptor activity appears to play a role in CCK–opioid interactions. The failure of naltrindole to affect the stimulus properties of CCK within the present experiment may thus speak more to the fact that different biochemical systems mediate different response preparations than the general absence of δ involvement in CCK-mediated activity.

Although the present experiment (as well as the majority of other work assessing opioid–CCK interactions) focused on the effects of μ- and/or δ-opioid agonists and antagonists on CCK-mediated effects, other opioid receptor subtypes may also be involved—for example, κ. In one of the few assessments of the effects of κ involvement with CCK, Wang and Han (70,71) reported that CCK reduced the affinity of κ agonists at the κ-opioid receptor without reducing the number of κ receptors, an effect opposite that reported with the μ receptor (see above). Assessments of the involvement of κ receptors in CCK–opioid interactions are limited, however, a limitation likely due to the absence of selective short-acting, reversible κ antagonists (80). The shorter-acting, reversible κ antagonists such as MR2266 are not selective, binding with near equal affinity to μ and κ subtypes [and to a reduced degree, to the δ subtype (5,32,77); for a recent discussion, see (51,59)]. Although its binding affinity is nonselective, MR2266 is effective as a κ antagonist (1,4,27,46,76). It is interesting in this context that MR2266 potentiates CCK activity in a manner very similar to that reported with naloxone (unpublished data from this laboratory). As noted, however, because of its nonselective binding profiles, it is difficult to conclude that such potentiation is a function of its κ antagonist activity. Thus, it remains unknown whether antagonists of the κ-opioid receptor subtype can potentiate CCK's stimulus effects, or if this subtype is involved in any manner with other instances of CCK–opioid interactions.

The ability of naloxone to potentiate the effects of CCK is consistent with the reported findings that CCK may have endogenous opioid antagonist activity. While consistent, the specific mechanism(s) underlying naloxone's ability to potentiate CCK's stimulus effects is not known. Identification of such mechanisms may be provided by the determination of the specific mechanism(s) underlying the antagonistic interactions of CCK and the opioid agonists. Many possible mechanisms have been presented to account for such antagonism. For example, CCK has been suggested to block allosterically opioid binding, consequently antagonizing opioid effects (23). Others have argued that CCK and morphine act oppositionally on common cellular processes [e.g., G proteins (44), CA^{2+} flux (2,11), epinephrine activity (17)]. Accordingly, CCK when administered before morphine either produces opposite biochemical effects or prevents morphine from exerting its biochemical actions. Although there is no consensus as to the basis for CCK's antagonism of the opioids, there seems to be little support for the possibility that such antagonism is a result of the action of CCK at opiate receptors—that is, CCK does not bind to or directly act at any of the opioid-receptor subtypes [(23,44,49,52,70); see, however, (18) for binding profiles for CCK antagonists]. Although many mechanisms have been proposed to account for CCK's antagonism of opioid activity in specific preparations, it remains unknown to what extent these mechanisms can be applied to naloxone's potentiation of CCK activity or other instances of CCK–opioid interactions (e.g., antagonism of CCK by the opioids or potentiation of opioid activity by CCK antagonists). What is clear is that the interactions between CCK and the opioids are multifaceted and based on a variety of biochemical, physiologic, and behavioral mechanisms.

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