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Differential Role of Cholecystokinin Receptor Subtypes in Opioid Modulation of Ongoing Maternal Behavior

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MIRANDA-PAIVA, C. M. AND L. F. FELICIO. *Differential role of cholecystokinin receptor subtypes in opioid modulation of ongoing maternal behavior.* PHARMACOL BIOCHEM BEHAV. **64**(1) 165–169, 1999.—Cholecystokinin (CCK) can have effects opposite those of opioids. The present study was undertaken to determine whether peripheral injections of antagonists of the CCK_1 receptor (lorglumide) and the CCK_2 receptor (L-365,260) can influence the effects of morphine on maternal behavior during lactation. A total of 110 female Wistar rats were tested on days 5 and 6 postpartum. Groups were randomly assigned to morphine vehicle (MV—SC) + saline (S—IP), MV + lorglumide (LOR: 1.0 or 10.0 mg/kg), MV + L-365,260 (10 mg/kg), morphine chlorhydrate (MC: 7.0 mg/kg) + S, MC + LOR (1.0 or 10.0 mg/kg), and MC + L-365,260 (1.0 or 10 mg/kg). Maternal behavior testing was started 30 min after the injections, at which time pups were placed in the home cage of their mother. Latencies for retrieval, grouping, and crouching responses were scored. The results show that both lorglumide and L-365,260 potentiated the MC-induced inhibition of maternal behavior. In addition L-365,260 treatment alone inhibited maternal behavior. Blockade of both the CCK_1 and CCK_2 receptors potentiated the morphine-induced disruption of maternal behavior, while CCK_2 antagonism alone also inhibited this behavior. The results suggest that CCK antagonism of opioid-induced disruption of maternal behavior occurs due to the action of CCK on both CCK_1 and CCK_2 receptor subtypes. © 1999 Elsevier Science Inc.

CCK_1 CCK_2 CCK_A CCK_B CCK-8 Lorglumide L-365,260 Morphine Opioids Parental care

THE gastrointestinal peptide hormone cholecystokinin (CCK) has been proposed to act as a neurotransmitter or neuromodulator in the central nervous system. CCK-like peptide and CCK mRNA have been found to be widely distributed through out the mammalian brain (2,37,47), with 80% of the compound corresponding to the terminal octapeptide CCK-8 (Asp-Tyr-SO_3H-Met-Gly-Trp-Met-Asp-Phe-NH_2). The fully sulfated form of CCK-8 has a high level of bioactivity. Under certain conditions CCK-8 has been reported to have opposite effects to those of opioids (23,38,50). There are two CCK receptor subtypes, CCK_1 and CCK_2, previously named CCK_A and CCK_B (1). Their distribution overlaps with that of opioid receptors (43). CCK-8 has about the same affinity for both CCK_1 and CCK_2 receptor types, while cholecystokinin tetrapeptide (CCK-4) shows very low affinity for CCK_1 receptor, 1000 times lower than CCK-8, and the same affinity as CCK-8 for the CCK_2 receptor (10,48). There are specific nonpeptide antagonists for these receptors (7). The availability of various selective nonpeptide CCK receptor antagonists, though varying in specificity and cleaningness, has led to correlative studies identifying the specific receptor subtypes that modulate various physiological and behavioral responses to opioids (32,51,52) and to other neurotransmitters (44,45). Lorglumide (±)-4-[(3,4-dichlorobenzoyl) amino]-5-(dipentylamino)-5-oxopentanoic acid sodium, and the benzodiazepine-based L-365,260 are compounds with high affinity for CCK_1 and CCK_2 receptors, respectively (8,12). L-365,260 has high affinity for the human for CCK_2 receptor and reasonable selectivity compared with CCK_1 receptor. Both lorglumide and L-365,260 have excellent central nervous system penetration, are orally bioavailable, and have low toxicity (15). Opioid effects such as increase in food consumption (2,25,30,33), thermoregulation (18), analgesia (13,17,24,54), and tolerance to morphine (36) are antagonized by CCK-8.

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CCK-8 has been implicated both in the induction (22) and maintenance of maternal behavior (26,34). In addition to the involvement of CCK in maternal behavior, studies have shown that CCK can act as an endogenous opioid antagonist in the regulation of ongoing maternal behavior (14). Both lateral ventricle and medial preoptic area infusions of CCK blocked the disruptive effects of beta-endorphin on the maintenance of maternal behavior in lactating rats (14,26). Previous studies have shown that maternal behavior is under the inhibitory influence of opiates (9,16,20–29,35,39,49,53). Infusing beta-endorphin, an endogenous opioid, into the ventricular system of lactating rats dose dependently blocks normal maternal behavior (27). Based upon these findings, we hypothesized that 1) maternal behavior may be differentially modulated by CCK receptors subtypes and 2) opioid modulation of ongoing maternal behavior may be differentially modulated by CCK receptor subtypes as well. To test these hypotheses, we evaluated the influence of peripheral injections of CCK_1 (lorglumide) and CCK_2 (L-365, 260) receptor blockers on the effects of morphine on maternal behavior during lactation.

METHOD

Subjects

Nulliparous female Wistar rats, derived from the same strain, weighing 200–300 g and about 90 days of age at the beginning of the experiments, were used. Animals were divided at random into experimental groups of at least eight rats each and individually housed in opaque polypropylene cages (41 × 34 × 16 cm) that contained approximately 1.0 liters of medium-grade pine flakes. Food and water were available ad lib to the animals in light (0600–1800 h)- and temperature- (20–25°C)-controlled rooms. The females were mated to males from our colony. After giving birth (day 0 of lactation) females were left with their litters (culled to 6 pups on day 1 of lactation) until testing for maternal behavior. The animals used in this study were maintained in accordance with the guidelines of the Committee on Animals of the Colégio Brasileiro de Experimentação Animal (COBEA) and the Committee on Care and Use of Laboratory Animal Resources, National Research Council, U.S.A.

Maternal Behavior Testing

A total of 110 female rats were tested for maternal behavior on days 5 and 6 postpartum in two experiments. In both experiments, pups were removed between 0900 and 1000 h on each test day. Then, 30 min later, mothers were injected subcutaneously with morphine vehicle (1 mg benzioc acid and 1 mg potassium metabisulphite in 1 ml of twice-distilled water, MV) and intraperitoneally with saline (S) on day 5 (group MV+S). On day 6, the animals were submitted to one of the following treatments:

Experiment 1: Morphine chlorhydrate plus saline (Casa Granado, SP, Brazil; 7.0 mg/kg; $n = 16$; group MC+S), morphine vehicle plus the CCK_1 receptor antagonist lorglumide (Research Biochemicals International, RBI; 1.0 mg/kg, $n = 5$ or 10.0 mg/kg; $n = 7$; groups MV+LOR:1 and MV+LOR:10, respectively); morphine chlorhydrate plus lorglumide (1.0 mg/kg, $n = 17$ or 10.0 mg/kg; $n = 15$; groups MC+LOR:1 and MC+LOR:10, respectively).

Experiment 2: Morphine chlorhydrate plus saline (7.0 mg/kg; $n = 16$; group MC+SAL), morphine vehicle plus the CCK_2 receptor antagonist L-365,260 (Merck Sharp & Dohme; 1.0 mg/kg, $n = 7$ or 10 mg/kg; $n = 10$; groups MV+L-365,261:1 and MV+L-365,261:10, respectively), and morphine chlorhydrate plus L-365,260 (1.0 mg/kg, $n = 7$ or 10 mg/kg, $n = 10$; groups MC+L-365,260:1 and MC+L-365,260:10, respectively).

Previous experiments from our laboratory have shown that even though 10.0 mg/kg MC inhibited maternal behavior, a 7.0-mg/kg dose of MC did not significantly delay the expression of full maternal behavior (unpublished results). Because the present study was designed to test the CCK blockage-induced potentiation of inhibition of maternal behavior, we decided to inject the dose of 7.0 mg/kg MC. The total volume injected into each animal never exceeded 2 ml/kg/day. The test for maternal responsiveness was started 30 min after the treatment with these drugs, at which time three pups were placed in the home cage of their mother. Animals were observed continuously for 15 min, then at 15-min intervals up to 1 h. Latencies for pup retrieval, grouping, and crouching were recorded during the test session. Animals were scored as fully maternal if they retrieved all three pups to the nest and crouched over them for 3 consecutive min. If animals were not maternal after 1 h, they were spot checked every hour until full maternal behavior was recorded. Events observed after the first 15 min of continuous observation were recorded at the time first observed, i.e., if the female was first seen to crouch over the young at 60 min, the crouching latency was scored as 60 min (or 3600 s). The same criterion was used for all other responses.

Statistical Analysis

The data were subjected to one-way analysis of variance (ANOVA) followed by multiple comparisons by the Tukey–Kramer test. A probability of $p < 0.05$ was considered significant for all comparisons made.

RESULTS

The results show that both lorglumide (Table 1, Fig. 1) and L-365, 260 (Table 2 and Fig. 2) potentiated the inhibitory effects of MC on maternal behavior. In addition, 10 mg/kg L-365, 260 treatment alone inhibited maternal behavior. In Experiment 1, rats treated with MC plus 10 mg/kg lorglumide (group: MC + LOR: 10) showed significantly longer latencies for first $F = (114, 15)\ 2.92$, $p < 0.016$), second and third pup retrieval, grouping, crouching, ($F = 55.06, 93.03, 80.62, 102.35$, respectively; $p < 0.0001$ Table 1) and full maternal behavior ($F = 138.12$, $p < 0.0001$; Fig. 1) than all other experimental groups. In Experiment 2, rats treated with MC plus L,365,260 (groups: MC + L,365,260, 10.0 mg/kg) showed longer latencies for the first, second, and third pup retrieval, grouping, crouching, $F = (94, 5)\ 115.26, 153.24, 147.98, 283.51, 54.86$, respectively, $p < 0.0001$; Table 2) and full maternal behavior ($F = 30.06$; $p < 0.0001$; Fig. 2) than all other experimental groups. In addition, group MV + L,365,260 (10.0 mg/kg) showed significantly longer latencies for grouping, crouching, and full maternal behavior than all other groups but MC + L,365,260 (10.0 mg/kg).

DISCUSSION

Previous reports have shown the CCK interacts with opioids controlling maternal behavior, playing a role mainly in the maintenance of this behavior (14,26). The present experiments were designed to study the role of the CCK receptor subtypes in ongoing maternal behavior and their possible interactions with opioids in this context as well. The results show that both the CCK_1 and CCK_2 receptor blockers lorglumide and L-365,260, respectively, potentiated the inhibitory effects of MC on maternal behavior. In addition, treatment

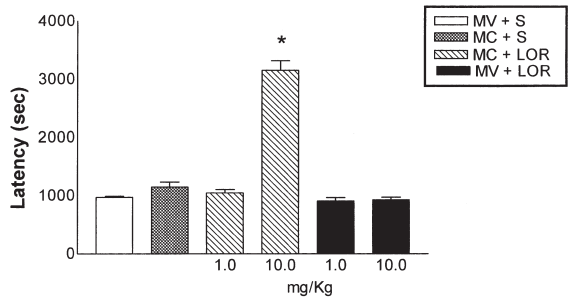

FIG. 1. Effects of the blockade of CCK_1 receptor by 1.0 or 10.0 mg/kg lorglumide on latencies for full maternal behavior. Groups were randomly assigned to morphine vehicle plus saline (MV+S; $n = 60$), morphine chlorhydrate plus lorglumide (MC+LOR; $n = 17$ and 15 for 1.0 and 10.0 mg/kg, respectively), morphine chlorhydrate plus saline (MC+S; $n = 16$), and morphine vehicle plus lorglumide (MV+LOR; $n = 5$ and 7 for 1.0 and 10 mg/kg, respectively). *$p < 0.0001$ compared to all other groups. Data are reported as means ± standard error.

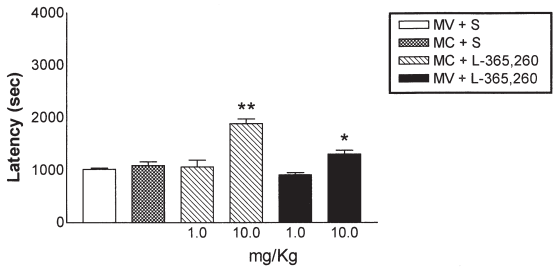

FIG. 2. Effects of the blockade of CCK_2 receptor by 1.0 or 10.0 mg/kg L-365,260 on latencies for full maternal behavior. Groups were randomly assigned to morphine vehicle plus saline (MV+S; $n = 50$), morphine chlorhydrate plus L-365,260; $n = 7$ and 10 for 1.0 and 10 mg/kg, respectively), morphine chlorhydrate plus saline (MC+S; $n = 16$), and morphine vehicle plus L-365,260 (MV+L-365,260; $n = 7$ and 10 for 1.0 and 10.0 mg/kg, respectively). *$p < 0.0001$ compared to morphine vehicle plus saline (MV+S) group. **$p < 0.0001$ compared to all other groups. Data are reported as means ± standard error.

with 10 mg/kg L-365,260 alone inhibited maternal behavior. These results suggest that both CCK_1 and CCK_2 receptors are involved in the modulatory effects of cholecystokinin on this behavior. In addition, the results suggest that the blockade of both CCK receptor subtypes potentiates the opioid-induced inhibition of maternal behavior.

Previous results have shown that CCK reverses the effects of opioids on various behaviors (4–6,31,40,41) and maternal behavior in particular (26). CCK has been shown to reverse the inhibitory effects of beta-endorphin on maternal behavior when injected both intracerebroventricularly and into the medial preoptic area (14,26). The present data are consistent with the antagonistic effects of CCK and opioids in the control of maternal behavior. It is well established that morphine has inhibitory effects on maternal behavior in lactating rats (9,39). Other authors have reported that 5.0 mg/kg morphine sulfate can inhibit ongoing maternal behavior of Sprague–Dawley rats (19). Under the conditions used in our laboratory, the inhibitory effect of morphine chlorhydrate on this behavior was not detected with the 7.0-mg/kg dose, but was observed only with doses of 10.0 mg/kg and higher (unpublished results). Because those doses are problematic, as they induce sedation, they were not considered in this study. These differences may be due to differences in animal strains and in the pharmaceutical formulation of the drug.

The lower dose (1.0 mg/kg) of lorglumide and L-365,260, alone or in combination with morphine chlorhydrate, did not significantly influence any maternal behavior parameter. This suggests that 1.0 mg/kg lorglumide or L-365,260 is not enough to induce a behaviorally meaningful CCK receptor blockade.

CCK-8 has almost the same affinity for both receptor subtypes, wheras CCK-4 shows very low affinity for the CCK_1 receptor, 1000 times lower than for CCK-8, and the same affinity as CCK-8 for the CCK_2 receptor (7,48). We have previously reported different behavioral responses to both stimulation and blockade of CCK_1 and CCK_2 receptors (44–46). The blockade of CCK_2 receptors by L-365,260 alone (group MV+L-365,260:10) was sufficient to significantly increase the latency of the various maternal behavior parameters measured. This effect was even more impressive because 7.0 mg/kg morphine chlorhydrate (group MC+S) had no significant effect on this behavior. This may be due to the blockade of a possible facilitatory effect on maternal behavior of endogenous CCK via CCK_2 receptors. Alternatively, the blockade of this cholecystokinin receptor subtype may have potentiated the inhibitory effects of endogenous opioids on this behavior (3,11,42). The same dose of lorglumide per se (group MV+LOR:10) did not induce changes in maternal behavior. Although possible drug nonspecific actions may not be completely discharged in this scenario, these data suggest that CCK_1 and CCK_2 receptors may play different roles in this behavior.

These results suggest that both CCK receptor subtypes play a role in the control of this important behavior. The development of drugs with improved pharmacological and pharmaceutical properties will certainly facilitate future studies on CCK role in this behavior. Future site-specific studies are necessary to elucidate this differential role of CCK receptor subtypes in the modulation of maternal behavior. For example, does CCK release during lactation in areas such as the medial preoptic area activate CCK_1 and CCK_2 receptors and block endogenous opioid activity in this neural region when females exhibit maternal care? The multiple physiological peptidergic modulation of ongoing maternal behavior deserves further investigation.

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