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CCK_A, But Not CCK_B, Agonists Suppress the Hyperlocomotion Induced by Endogenous Enkephalins, Protected From Enzymatic Degradation by Systemic RB 101

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DAUGE, V., P.-J. CORRINGER AND B. P. ROQUES. *CCK_A, but not CCK_B, agonists suppress the hyperlocomotion induced by endogenous enkephalins, protected from enzymatic degradation by systemic RB 101.* PHARMACOL BIOCHEM BEHAV **50**(2) 133-139, 1995.—Interactions between CCKergic and enkephalinergic systems were studied in mice using behavioral responses measured in Animex. The hyperlocomotion induced by 5 mg/kg of RB 101, a mixed inhibitor of enkephalin-degrading enzymes able to cross the blood-brain barrier, was previously shown to be mediated by δ-opioid receptor stimulation. The IP administration of a CCK_A agonist, Boc-Tyr-Lys-(CONH-*o*-tolyl)-Asp-Phe-NH_2 (0.1, 1, 10 μg/kg), suppressed the hyperlocomotion produced by IV injection of 5 mg/kg of RB 101. The effect of the CCK_A agonist was suppressed by a selective CCK_A antagonist, devazepide, injected IP at doses of 20 and 200 μg/kg and was potentiated by the selective δ-opioid antagonist naltrindole at the doses of 0.03 mg/kg. IP injection of the selective CCK_B agonist BC 264 (0.1-1 mg/kg) did not modify the RB 101-induced hyperlocomotor effect. These results reinforce the observed physiological antagonism between the endogenous CCK and opioid systems but are at variance with the responses measured in stressful conditions. It is concluded that CCK_A, but not CCK_B, receptor activation counteracts the opioid-related hyperlocomotion.

CCK_A and CCK_B agonists Inhibitor of enkephalin degradation Locomotor activity
Interactions between CCK and enkephalins Mice

THE OVERLAPPING distributions of opioid and cholecystokinin (CCK) peptides and of their receptors (19,40) in the central nervous system have led to a large number of studies aimed at clarifying the functional relationships between these two neuropeptides. Biochemical experiments have shown that if the stimulation of CCK receptors resulted in modulating the functioning of the opioidergic system, this system could in turn regulate the release of CCK peptides (3,31,37,41,51,52). Most of the pharmacological studies devoted to the role of CCK and enkephalins have been focused on the control of pain. Thus, a functional antagonism between CCKergic and opioidergic systems has been evidenced by using several behavioral responses evoked by painful thermal, chemical, or mechanical stimuli (16,28). Because these two endogenous peptides bind to several receptor subtypes (i.e., μ- and δ-opioid binding sites for enkephalins, CCK_A and CCK_B receptors for CCK_8), recent studies investigated the relative contributions of these receptor subtypes (14,15,32). The most interesting results involved the demonstration of a tonic or phasic release of endogenous CCK modulating, through CCK_B receptors, the nociceptive threshold by a negative control on μ-opioid receptors at both spinal and supraspinal levels [(28) and ref. therein, (42)]. Thus, the role of CCK could be to reestablish the nociceptive threshold increased by endogenous opioids when the stimuli is no longer present or when a safety stimuli occurs (46). In contrast to these numerous experiments devoted to analgesia, few studies have been done to investigate the functional relationships between CCK and opioid peptides

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in behavioral responses. Nevertheless, adverse interactions between CCK_8 and morphine or β-endorphin have been observed to occur in feeding (47), catalepsy (23), body-shaking behavior (24), and in locomotor activity in hamsters (38) in conditioned suppression of motility test (13) and within a drug discrimination procedure (30). On the other hand, a potentiation by CCK_8 of morphine-mediated reduction of distress vocalization (45) and on schedule-controlled behavior in rats has been reported (48). In addition, the CCK_A antagonist devazepide was shown to counteract the effects of morphine in the conditioned place preference test (20).

It is well known that exogenous and endogenous opioids play a critical role in the control of mood. In rodents, they produce self-stimulation, autoadministration, and an increase of locomotor activity [reviews in (35,36,49)]. On the other hand, peripheral and central administration of CCK_8 suppress locomotor activity in rodents (4,21,50). This effect has been proposed to originate in part from the periphery (8) and to occur by CCK_A receptor stimulation (1,25). In both cases, the mesolimbic dopaminergic system was proposed to have a crucial role [reviews in (7,9,26)].

The present study was therefore performed to examine the effects of a CCK_A agonist, Boc-Trp-Lys-(CONH-*o*-tolyl)-Asp-Phe-NH_2 (39), and a selective CCK_B agonist, BC 264 (6), on the hyperlocomotion induced in mice by the endogenous opioid peptides (2). An increase in the extracellular level of endogenous enkephalins was obtained by administration of the mixed inhibitor of enkephalin-degrading enzymes, RB 101 {*N*-[(*R*,*S*)-2-benzyl-3[(*S*)(2-amino-4-methylthio)butyl dithio]-1-oxopropyl]-L-phenylalanine benzyl ester} (18), which crosses the blood-brain barrier. The type of CCK receptors (CCK_A or CCK_B) involved in the effects of RB 101 was confirmed by the use of the selective CCK_A antagonist, devazepide (5).

METHOD

Animals

Male CD_1 albino mice (Charles River, France), weighing 20–24 g, were housed in groups of 20 in conditions of constant temperature (22 ± 1°C) and humidity (50 ± 5%). Food and water were available ad lib.

Apparatus

The apparatus consisted of a rodent housing cage placed on the floor of an Animex Activity Meter type S (LKB Farad, Sweden), in which an electromagnetic field is disturbed, resulting in an impulse when the activity of the animals exceeds a preset level. The experiments were performed in a quiet and dimly illuminated room (50 lx).

Procedure

The mice were placed in the experimental room 1 day before testing. The experiments were performed between 1200 and 1900 h. Counts for motor activity were registered each 5 min during a 15-min period, except for Experiment 1 in which counts were registered during a 10-min period. The animals were used only once.

Experiment 1. Thirty-seven mice were used in the experiment with the CCK_A agonist. Four groups of 9–10 mice were injected IP with saline or the CCK_A agonist (0.001, 0.01, 0.1 mg/kg) 30 min before the 10-min Animex test. Each dose of the CCK_A agonist and saline was tested each day. Seventy mice were studied in the experiment with BC 264. Seven groups of 10 mice were injected IP with saline or BC 264 (0.25, 0.5, 1, 2.5, 5.0, 10.0 mg/kg) 30 min before the 10-min Animex test. Each dose of BC 264 and saline was tested each day.

Experiment 2. Eighty-four mice were used in the study with the CCK_A agonist and RB 101. Twelve groups of seven mice were first injected IP with saline or the CCK_A agonist (0.001, 0.01, 0.1, 1, 10 μg/kg) 25 min before injection IV of vehicle or RB 101 (5 mg/kg) and then placed on the Animex 5 min later. Each dose of CCK_A agonist, RB 101 and controls was tested each day.

Experiment 3. One hundred and eight mice were used in the experiment with devazepide (200 μg/kg). Eight groups of 12–14 mice were first injected IP with 0.5% of carboxymethylcellulose CMC (0.5%) or devazepide (200 μg/kg) 10 min before saline or the CCK_A agonist injected IP at a dose of 1 μg/kg. RB 101 (5 mg/kg, IV) or vehicle was administered 25 min after the CCK_A agonist. Mice were placed on the Animex 5 min later. Each compound and vehicle was tested each day. Sixty mice were used in the experiment with devazepide (20 μg/kg). Eight groups of 7–9 mice were IP injected with CMC (0.5%) or devazepide (20 μg/kg) 10 min before saline or the CCK_A agonist injected IP at a dose of 1 μg/kg. RB 101 (5 mg/kg, IV) or vehicle was administered 25 min after the CCK_A agonist. Mice were placed on the Animex 5 min later. Each compound and vehicle was tested each day.

Experiment 4. Ninety-five mice were used in the experiment with naltrindole and the CCK_A agonist. Ten groups of 8–12 mice were first injected IP with saline or the CCK_A agonist (1, 10, 100 μg/kg) 10 min before saline or naltrindole administered SC at a dose of 0.1 or 1 mg/kg. Mice were placed on the Animex 20 min later. Each compound and vehicle was tested each day.

Experiment 5. Seventy mice were used in the experiment with RB 101, naltrindole, and the CCK_A agonist. Eight groups of 8–10 mice were first injected IP with saline or the CCK_A agonist (0.1 μg/kg) 10 min before saline or naltrindole administered SC at a dose of 0.03 mg/kg. Twenty-five minutes after CCK_A agonist, mice received RB 101 at the dose of 5 mg/kg or vehicle IV and were placed on the Animex 5 min later. Each compound and controls were tested each day.

Experiment 6. Thirty-six mice were used for the BC 264 experiment. Six groups of six mice were first injected IP with saline or BC 264 (0.1, 1 mg/kg) 25 min before IV injection of vehicle or 5 mg/kg of RB 101 and were placed on the Animex 5 min later. Each dose of BC 264, RB 101, and controls was tested each day.

Chemicals and Drug Treatment

All compounds used in this study were synthesized in the laboratory using previously described methods. The CCK_A agonist, Boc-Trp-Lys-(CONH-*o*-tolyl)-Asp-Phe-NH_2 (39), and the selective CCK_B agonist BC 264 [Boc-Tyr(SO_3H)-gNle-mGly-Trp-(NMe)Nle-Asp-Phe-NH_2] (6) were dissolved in 0.9% saline and IP injected at 0.1 ml/10 g, except for Experiments 3 and 5 in which the volume of the injections was 0.05 ml/10 g. The CCK_A agonist exhibits the following affinities: for CCK_A receptors (guinea pig pancreas) IC_{50} is 16 ± 3 nM; for CCK_B receptors (guinea pig cortex) IC_{50} is 1900 ± 240 nM (39). BC 264 exhibits the following affinities: for CCK_A receptors (guinea pig pancreas) K_i is 355 ± 120 nM; for CCK_B receptors (guinea pig cortex) K_i is 0.39 ± 0.15 nM (6).

The mixed inhibitor of enkephalin-degrading enzymes RB 101 {*N*-[*R*,*S*)-2-benzyl-3[(*S*)(2-amino-4-methylthio)-butyldithio]-1-oxopropyl]-L-phenylalanine benzyl ester} (18) was used at 5 mg/kg. It was dissolved in a mixture of EtOH/cremophore El/H_2O (1/1/8) and slowly injected IV (30 s) in the dorsal tail vein of mice. The injection volume was 0.1 ml/10 g.

Naltrindole, a selective δ-opioid antagonist (34), was dissolved in 0.9% saline. Devazepide, a selective CCK_A antagonist (5), was suspended in 0.5% carboxymethylcellulose.

Data Analysis

The results of the experiments were analyzed by one-way analysis of variance (ANOVA) after verification that there was not a day effect. The significant differences between individual means were then identified using Duncan's test (pairwise comparison) or Dunnett's *t*-tests for comparison with control. To verify the dose-effect response, a simple linear regression analysis was performed. The level of significance was set at $p < 0.05$.

RESULTS

Experiment 1

One-way ANOVA of cumulative 10-min data showed a significant effect in the CCK_A agonist experiment for dose, $F(3, 33) = 4.341$, $p < 0.01$ (Table 1). The CCK_A agonist injected IP at a dose of 0.1 mg/kg, 30 min before the test, significantly decreased the locomotor activity of mice. One-way ANOVA of cumulative 10-min data showed a significant effect in the BC 264 experiment for dose, $F(6, 63) = 7.257$, $p < 0.01$ (Table 1). BC 264 increased the locomotor activity of mice after IP injection of 2.5 and 10 mg/kg 30 min before the test. The dose of 5 mg/kg of BC 264 induced a nonsignificant increase of motor activity. Nevertheless, a dose-effect response was shown by the regression analysis [the standard value of the slope (0.563) is significant, $t = 5.493$, $p < 0.01$].

TABLE 1

EFFECT OF CCK-$_A$ AND CCK_B AGONISTS ON THE LOCOMOTOR ACTIVITY IN MICE MEASURED IN ANIMEX

Compounds	Dose (mg/kg)	Number of Counts
Vehicle		151.5 ± 26.6
CCK-A agonist	0.001	150.0 ± 24.3
	0.01	137.4 ± 28.5
	0.1	53.2 ± 10.5†
Vehicle		176.7 ± 17.2
BC 264	0.25	174.7 ± 35.4
	0.5	150.5 ± 26.1
	1.0	169.4 ± 16.3
	2.5	263.2 ± 29.9*
	5.0	229.6 ± 22.0
	10.0	365.5 ± 40.6†

Compounds were injected 30 min before the 10-min test period. Results are expressed as mean ± SEM of 9-10 mice per group.

*$p < 0.05$ and †$p < 0.01$ vs. vehicle-treated controls (ANOVA followed by Dunnett's *t*-test).

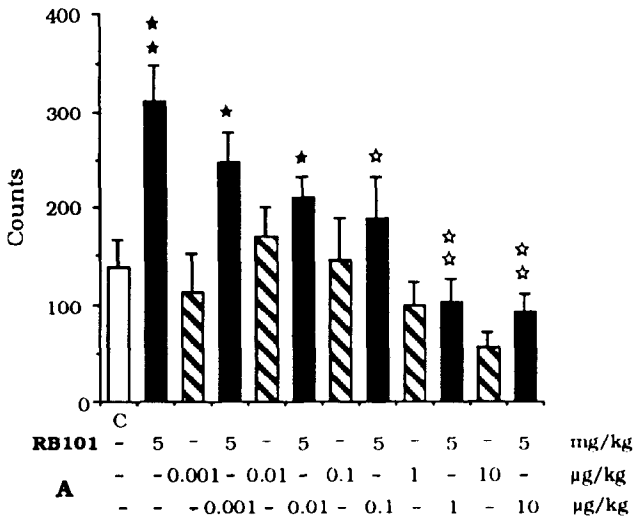

FIG. 1. Effects of the CCK_A agonist on the hyperlocomotion induced by RB 101 IV injected at 5 mg/kg. The CCK_A agonist was injected IP 25 min before RB 101. Mice were tested in the Animex 5 min after RB 101 injection. A = CCK_A agonist. C = control. Fifteen-minute cumulative data are presented. ★$p < 0.05$, ★★$p < 0.01$ vs. control group, ☆$p < 0.05$, ☆☆$p < 0.01$ vs. RB101-treated group, Duncan's test.

Experiment 2: CCK_A Agonist + RB 101

One-way ANOVA of cumulative 15-min data showed a significant treatment effect for the CCK_A agonist + RB 101 for dose, $F(11, 72) = 7.863$, $p < 0.001$ (Fig. 1). RB 101 (5 mg/kg, IV) induced a significant increase in motor activity that is comparable to previous results (2). The CCK_A agonist did not modify activity significantly at any dose. However, a clear tendency to decrease locomotor activity was shown at 10 µg/kg. Twenty-five minutes after IP injection of the CCK_A agonist, a decrease of the hyperactivity produced by IV injection of 5 mg/kg of RB 101 was observed. A significant decrease, compared to the RB 101 group, was obtained with 0.1 ($p < 0.05$), and 1 and 10 µg/kg ($p < 0.01$) of the CCK_A agonist. In the CCK_A agonist 0.001 µg/kg + RB 101 group, there was a significant increase in motor activity. A dose-effect response was shown by the regression analysis [the standard value of the slope (0.4514) is significant, $t = 12.379$, $p < 0.003$].

Experiment 3: Devazepide + CCK_A Agonist + RB 101

One-way ANOVA of cumulative 15-min data showed a significant treatment effect in the devazepide experiment [devazepide 200 µg/kg, $F(7, 100) = 4.813$, $p = 0.0001$; devazepide 20 µg/kg, $F(7, 52) = 8.422$, $p = 0.0001$] (Fig. 2A,B). RB 101 (5 mg/kg, IV) induced a significant increase in motor activity. The previous IP administration of the CCK_A agonist (1 µg/kg) significantly decreased the hyperlocomotion induced by RB 101 ($p < 0.01$). The administration of 20 µg/kg of devazepide + saline did not modify the RB 101-induced hyperlocomotion, whereas the administration of 200 µg/kg of devazepide decreased (not statistically significant) the effect of RB 101. Devazepide (20 or 200 µg/kg) suppressed the antagonistic effect of the CCK_A agonist on the hyperlocomotion induced by RB 101 ($p < 0.05$). Furthermore, devazepide (20

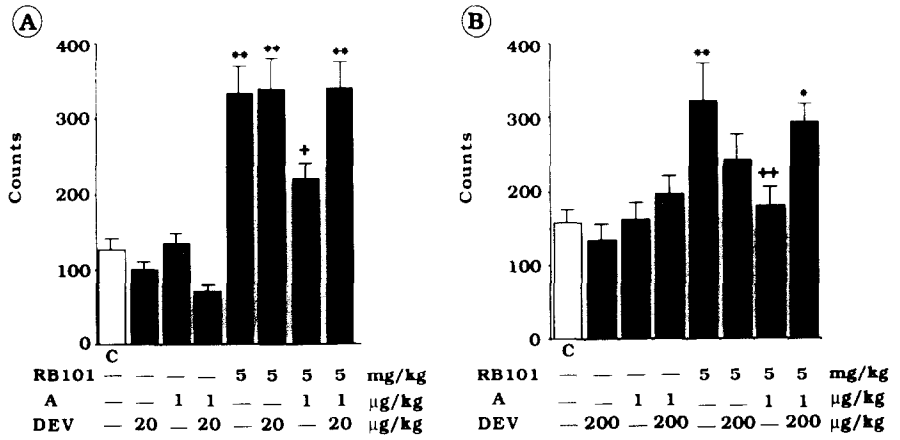

FIG. 2. Antagonistic effect by IP injected devazepide (A) 20 µg/kg and (B) 200 µg/kg, 40 min before test of the suppression by the CCK_A agonist of the hyperlocomotion induced by RB 101. The CCK_A agonist (1 µg/kg) was injected IP 25 min before RB 101 IV injected at 5 mg/kg. Mice were tested in the Animex 5 min after RB 101 injection. A = CCK_A agonist, DEV = devazepide, C = control. Fifteen-minute cumulative data are presented. $*p < 0.05$, $**p < 0.01$ vs. control group, $+p < 0.05$, $++p < 0.01$ vs. RB 101-treated group, Duncan's test.

or 200 µg/kg) + CCK_A agonist + RB 101 did not significantly differ compared with RB 101 + devazepide.

Experiment 4: CCK_A Agonist + Naltrindole

One-way ANOVA of cumulative locomotor 15-min activity showed a significant treatment effect in the CCK_A agonist + naltrindole experiment, $F(9, 85) = 6.998$, $p = 0.0001$ (Fig. 3). The SC administration of naltrindole at a dose of 0.1 or 1 mg/kg 20 min before the test did not itself induce changes in locomotor activity of mice, even after pretreatment with the CCK_A agonist (1, 10, 100 µg/kg, IP).

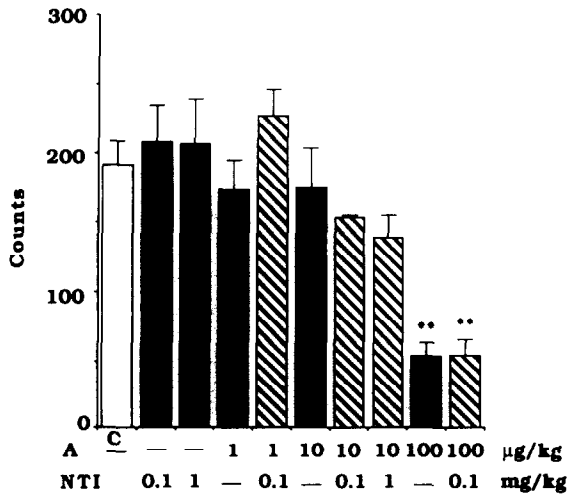

FIG. 3. Lack of effect of naltrindole (NTI) injected SC at 0.1 or 1 mg/kg 20 min before test, alone, or in combination with the CCK_A agonist (A) injected IP 30 min before test at doses of 1, 10, or 100 µg/kg). C = control. Fifteen-minute cumulative data are presented. $**p < 0.01$ vs. control group, Duncan's test.

Experiment 5: CCK_A Agonist + Naltrindole + RB 101

One-way ANOVA of cumulative 15-min data showed a significant treatment effect, $F(7, 62) = 4.113$, $p = 0.0009$ (Fig. 4). Prior injection of naltrindole (0.03 mg/kg) did not suppress the hyperlocomotion induced by injection of RB 101 (5 mg/kg). The CCK_A agonist (0.1 µg/kg) slightly decreased the RB 101 effect. However, prior administration of CCK_A

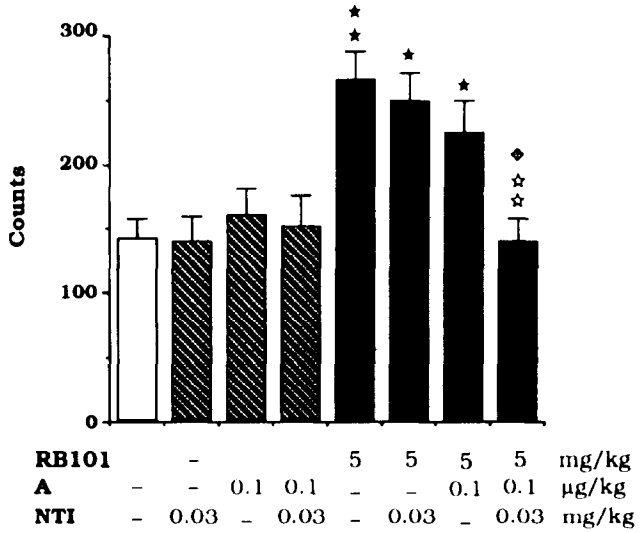

FIG. 4. Suppression of the hyperlocomotion induced by RB 101 (5 mg/kg, IV) by the association of CCK_A agonist (A) (0.1 µg/kg, IP) and naltrindole (NTI) (0.03 mg/kg, SC). The CCK_A agonist was injected 10 min before naltrindole and 25 min before RB 101. Mice were tested in Animex 5 min after RB 101 injection. C = control. Fifteen-minute cumulative data are presented. $\star p < 0.05$, $\star\star p < 0.01$ vs. control group, $\star\star p < 0.01$ vs. RB 101 group, $\diamond p < 0.05$ vs. naltrindole + RB 101 group and CCK-A agonist + RB 101 group, Duncan's test.

agonist and naltrindole antagonized the effect of RB 101 ($p < 0.01$), of naltrindole + RB 101 ($p < 0.05$), and of CCK_A agonist + RB 101 ($p < 0.05$).

Experiment 6: BC 264 + RB 101

One-way ANOVA of cumulative 15-min locomotor activity showed a significant treatment effect, $F(5, 30) = 5.585$ $p < 0.001$ (Fig. 5). BC 264 alone did not induce an effect nor did it modify the hyperactivity when in combination with RB 101.

DISCUSSION

The aim of this study was to investigate the possible relationships between CCK and enkephalin systems on the behavior of mice placed in a familiar environment. Previous experiments performed in our laboratory have shown that under nonstressful conditions, IV injection in mice of the systemically active mixed inhibitor of enkephalin-degrading enzymes, RB 101, induces a large dose-dependent increase in locomotor activity measured in the Animex meter (2). These effects are suppressed by the selective δ antagonist naltrindole, supporting the preferential involvement of δ-opioid receptors, which are stimulated by the protected endogenous enkephalins, in this behavioral response (2). An intermediate dose (5 mg/kg, IV) was therefore used in the present study to reveal a possible suppression or potentiation of RB 101-induced effects by CCK agonists. Under these conditions, the CCK_A agonist, Boc-Trp-Lys-(CONH-*o*-tolyl)-Asp-Phe-NH_2, IP injected in mice, dose-dependently suppressed the effect of RB 101. This inhibition was complete for doses of 1 and 10 μg/kg of the CCK_A agonist that alone did not significantly modify the motor activity of mice. However, at a higher dose (100 μg/kg), the CCK_A agonist produced a decrease in locomotor activity, as previously reported (1,21). The involvement of CCK_A receptors in the suppression of RB 101-induced hyperlocomotion was confirmed, as this effect was inhibited by the CCK_A antagonist devazepide, used at 20 and 200 μg/kg. A slight but not significant decrease of RB 101-induced hyperlocomotion was observed after 200 μg/kg of devazepide, possibly due to the loss of CCK_A selectivity of this antagonist at this concentration (28). The blockade of δ receptor by 0.1 or 1 mg/kg of naltrindole was unable to potentiate the hypolocomotion induced by 100 μg/kg of the CCK_A agonist. Nevertheless, in the presence of increased endogenous enkephalin levels, induced by the enkephalin-degrading enzyme inhibitor RB 101, an otherwise inactive dose of naltrindole (0.03 mg/kg) produced, in combination with the CCK_A agonist, a significant hypolocomotion. This indicates that the interaction between the effect of RB 101 and CCK_A agonist could occur by an action of endogenous enkephalins on δ-opioid receptors.

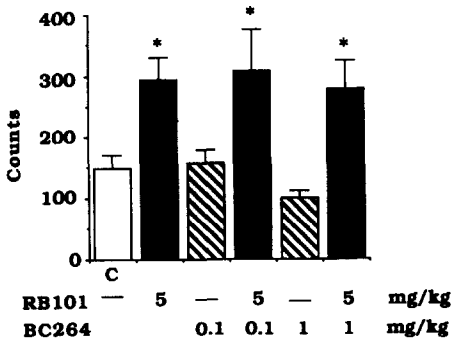

FIG. 5. Effect of BC 264 (selective CCK_B agonist) on the hyperlocomotion induced by RB 101 IV injected at 5 mg/kg. BC 264 was injected IP 25 min before RB 101. Mice were tested in the Animex 5 min after RB 101 injection. C = control. Fifteen-minute cumulative data are presented. *$p < 0.05$ vs. control group, Duncan's test.

The suppression of the hyperactivity produced by RB 101 by the CCK_A agonist could occur at the mesolimbic level in which CCK_8, enkephalins, and their receptors are present (43). Thus, the nucleus accumbens, which receives CCK fibers issuing from the nucleus tractus solitarius (44) and CCK-DA colocalized neuronal pathways from the ventral tegmental area (22), also contains enkephalinergic neurones and opioid receptors. D_2 receptors are present on the enkephalinergic neurons and CCK receptors on neurons and terminal fibers in which the neurotransmitters are actually unknown (GABA, enkephalins, SP, etc.). Furthermore, kelatorphan (17) or RB 101 injected in the nucleus accumbens or intravenously administered produced a hyperlocomotion in rodents that is suppressed by δ-opioid antagonists, suggesting that the effects of RB 101 are related to opioid activation by endogenous enkephalins. Furthermore, the inhibition of RB 101 responses by D_1 antagonist very likely results from an interaction between enkephalin and DAergic systems (2,10). Moreover, when injected in the nucleus accumbens, CCK_8 dose-dependently decreased the hyperlocomotion produced by local administration of kelatorphan in this structure (12). This could be due to a direct action of CCK_8 on the enkephalinergic neurons by decreasing enkephalin release or to an indirect action via an increase of DA release in the accumbens (26,29). However, the participation of other structures of the brain could also occur.

In contrast to compound A, the selective CCK_B agonist BC 264 (0.1–1 mg/kg, IP) did not modify the hyperlocomotion produced by RB 101 in mice. These doses of BC 264 did not change mice locomotion, whereas at higher doses (i.e., 2.5–10 mg/kg, IP) the CCK_B agonist increased global motor activity.

Interestingly, BC 264 produced anxiogenic-like effects in animals placed in stressful conditions (11,13), which could be in line with the participation of the CCKergic system in responses to anticipatory stress (33). Interestingly, CCK_B receptor blockade was shown to attenuate the suppression of motility in mice (stressful conditions), and this effect was blocked by the selective δ-opioid antagonist naltrindole, indicating that behavioral responses related to anxiety are under the tonic control of endogenous CCK and enkephalins (13). Taken together, these results show that the effect of opioids could be reduced either by CCK_A or CCK_B receptor stimulation, depending on the specific characteristics of the stimulus (familiar vs. stressful situation) and probably on the brain structures recruited, as also shown for pain control (27,46,51). Motivational systems are often organized in such a way that they are regulated by counteracting forces. One of the opposing processes could occur through CCK_A receptor stimulation. Therefore, CCK_8, acting on CCK_A and CCK_B receptors, and the endogenous opioids, acting on μ- and δ-opioid binding sites, may well constitute a physiological system critically involved in the coordinated control of several kinds of adaptative behaviors.

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