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Effects of Caerulein and CCK Antagonists on Tolerance Induced to Morphine Antinociception in Mice

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ZARRINDAST, M. R., A. ZABIHI, M. REZAYAT, H. RAKHSHANDEH, M. GHAZI-KHANSARI AND R. HOSSEINI. *Effects of caerulein and CCK antagonists on tolerance induced to morphine antinociception in mice.* PHARMACOL BIOCHEM BEHAV **58**(1) 173–178, 1997.—Different groups of mice received one daily dose (50 mg/kg) of morphine subcutaneously (SC) for 3, 4 or 5 days to develop tolerance to the opioid. The antinociceptive response of morphine (9 mg/kg) was tested in the hot-plate test 24 h after the last dose of the drug. Tolerance to morphine was obtained in all groups. The group of mice that received morphine for 4 days was employed for the rest of the experiments. Pretreatment of animals with a single dose of caerulein (0.025, 0.05, and 0.1 mg/kg, SC) 30 min prior to receiving morphine (50 mg/kg; during the development of tolerance to the opioid) on day 1, 2, 3, 4 or 5 of morphine administration potentiate antinociception induced by morphine (test dose of 9 mg/kg). The dose of 0.05 mg/kg of caerulein, used 30 min before morphine administration on day 3, was also used to evaluate the effects of antagonists on caerulein-induced decrease in tolerance. The selective cholecystokinin (CCK) receptor antagonists, MK-329 [1-methyl-3-(2 indoloyl)amino-5-phenyl-3H-1,4-benzodiazepin-2-one; 0.25 and 0.5 mg/kg] or L-365,260 [3R(+)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N-(3-methyl-phenyl)urea; 0.25 and 0.5 mg/kg] decreased potentiation of morphine response induced by caerulein. MK-329 or L-365,260, when were injected 35 min before morphine injection during the development of tolerance and on day 3, decreased the tolerance to morphine. A single administration of MK-329 or L-365,260 (in the absence of caerulein) 35 min and 48 h before the test dose of morphine (9 mg/kg) potentiated the antinociception of morphine in nontolerant animals. In conclusion, CCK mechanism(s) may interact with morphine tolerance. © 1997 Elsevier Science Inc.

CCK agents Morphine Tolerance Mice

THE PEPTIDE cholecystokinin (CCK) occurs in many areas of the central nervous system, primarily as the sulphated octapeptide CCK-8 (20,25,29). The chemically related peptides caerulein (ceruletide: caerulein diethylammonium hydrate) and CCK-8 exert a wide variety of pharmacological effects, one of which is its influence on opiate-induced antinociception (2,10,14,23,34). There is considerable evidence that these peptides may play an important role in pain transmission by modulating central nervous system opioid mechanisms (10,11,15,18,22,23). CCK-related peptides may be opioid antagonists (9), and CCK antagonists may potentiate morphine-induced antinociception (6,7,16,19,27) and reverse or prevent morphine tolerance (5–7,17,24,30). Our previous studies have shown that CCK and related peptides can potentiate morphine antinociception (32) and decrease morphine tolerance (21) in the tail-flick test. The tail-flick response may be mostly a spinal reflex (13), and the hot-plate test may involve supraspinal and coordinate meter activity (28). CCK and the related peptide caerulein probably attenuate morphine dependence (33). Because the pathway for the tail-flick test may differ from that of the hot-plate test (1,11), we decided to examine the effect of CCK receptor mechanism(s) on the development of tolerance to the antinociceptive effect of morphine in the hot-plate test.

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MATERIALS AND METHODS

Subjects

The subjects were male albino mice weighing 25–30 g at the start of the experiment. The animals were allowed free access to food and water, except during the experimental sessions, as described in the following section. Pain sensitivity was measured by the hot-plate test accoridng to the method of Eddy and Leimbach (9), with a minor modification. Briefly, the animal was placed on a surface (23 × 23 cm) maintained at 55 ± 0.2°C surrounded by a plexiglass wall 20-cm high. The apparatus (Farad Co., Iran) was equipped with a timer and a thermocouple to maintain a constant temperature. Licking the forepaws or lifting a hindpaw from the surface was used as the end point for the determination of response latencies. Failure to respond by 45 s resulted in a termination of the test (cutoff). Each animal was used only once.

Procedure of Development of Tolerance to Morphine

For tolerance induction, groups of 9 mice were chosen randomly. Mice were treated subcutaneously (SC) with morphine (50 mg/kg) once a day for 3, 4 or 5 days. To evaluate the degree of tolerance, the antinociceptive effect of a test dose of the morphine (9 mg/kg) was measured on the 4th, 5th or 6th day (24 h after a last dose of morphine; 50 mg/kg, during the development of tolerance to morphine). Maximum tolerance was obtained when morphine (50 mg/kg) was administered for 3–5 days. Therefore, chronic injection of morphine (50 mg/kg) for 4 days was used for the rest of experiments, and the tolerance was tested 24 h after the last dose of morphine (day 5).

Antinociception Testing

To measure antinociception, different doses of morphine (3, 6 and 9 mg/kg, SC) were injected. Antinociception was determined every 15 min for 60 min by using the hot-plate test (baseline: 2.5–3.5 s, cutoff: 45 s) with a hot-plate apparatus. Antinociception was determined according to the method of Yaksh et al. (31) and expressed as a percentage of the maximum possible effect (%MPE).

Drug Treatment

Animals in Experiment 1 received a daily dose of 50 mg/kg morphine for 3, 4 or 5 days. Antinociception of the test dose of morphine (9 mg/kg) was determined on days 4, 5 or 6, respectively.

Animals in Experiment 2 received a daily dose of 50 mg/kg morphine for 4 days. The development of tolerance was measured on day 5 of the experiment by using different test doses of morphine (3, 6 and 9 mg/kg).

Animals in Experiment 3 received either saline (10 ml/kg) or different doses of caerulein (0.025, 0.05 and 0.1 mg/kg) on day 1, 2, 3 or 4, 30 min before morphine (50 mg/kg) injection. Tolerance was assessed on the day 5 (24 h after last dose of morphine) by using the test dose of morphine (9 mg/kg). The same doses of caerulein also were injected 30 min before the test dose of morphine on day 5.

Animals in Experiment 4 received either saline or different doses of caerulein (0.025, 0.05 and 0.1 mg/kg) on day 3 30 min before morphine administration (50 mg/kg; while developing tolerance), and test doses of morphine (3 and 6 mg/kg) were tested on day 5.

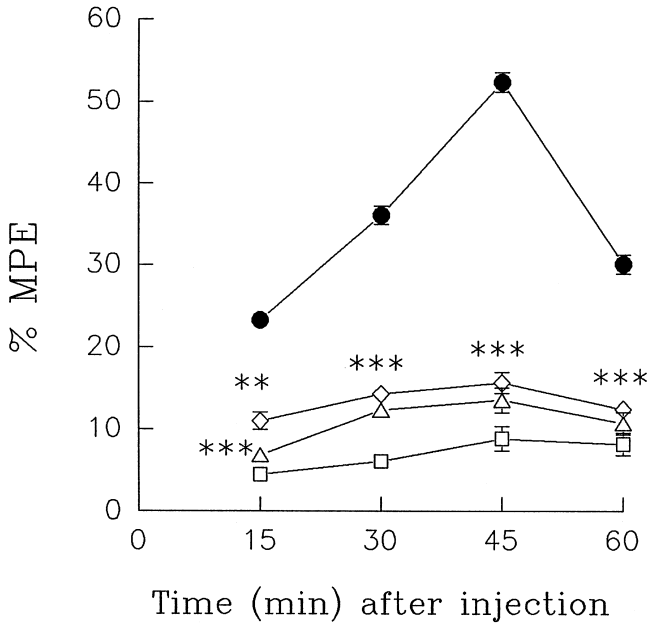

FIG. 1. Effects of morphine in tolerant and nontolerant mice. Animals were injected with morphine (50 mg/kg, SC) for 3 (square), 4 (triangle) or 5 (diamond) days to develop tolerance. Antinociception of the test dose of morphine (9 mg/kg) was tested either in nontolerant mice (circle) or 24 h after the last dose of morphine (50 mg/kg) in tolerant animals. Each point is the mean ± SEM of %MPE for 9 mice. $^{**}p < 0.01$; $^{***}p < 0.001$, significantly different from the respective nontolerant control group.

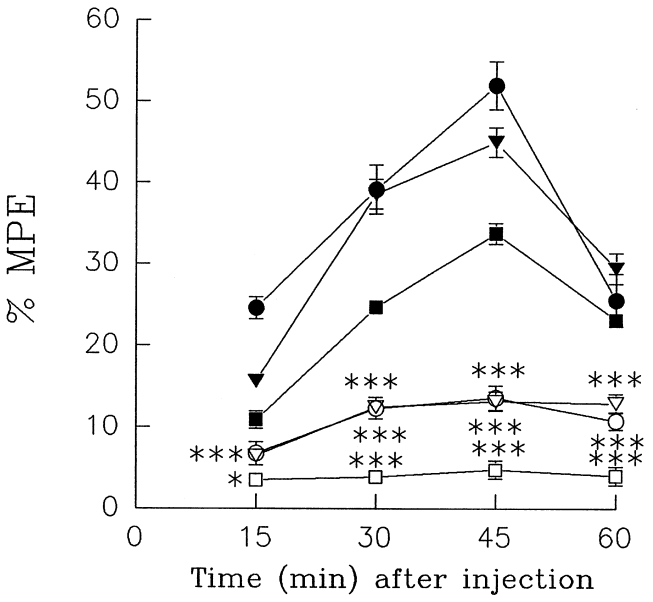

FIG. 2. Effects of different test doses of morphine in nontolerant and tolerant mice. Animals received either saline (10 ml/kg, SC) or morphine (50 mg/kg, SC) for 4 days to develop tolerance. Antinociception of 3 (solid square), 6 (solid triangle) and 9 (solid circle) mg/kg of morphine were tested in nontolerant mice. The same doses of morphine [3 (open square), 6 (open triangle) and 9 (open circle) mg/kg] were also tested in tolerant animals. Each point is the mean ± SEM of %MPE for 9 animals. $^{*}p < 0.05$; $^{***}p < 0.001$ vs. the respective control in nontolerant animals.

TABLE 1

EFFECT OF CAERULEIN INJECTED DIFFERENT DAYS ON MORPHINE TOLERANCE

	Latencies (s) After Test Dose of Morphine			
Treatment (mg/kg)	15 min	30 min	45 min	60 min
Saline	6.8 ± 1.1	12.4 ± 0.8	13.5 ± 1.3	10.7 ± 0.9
CLN 0.1 (1st day)	9.9 ± 1.2	22.3 ± 2.0**	32.9 ± 2.3***	29.2 ± 2.5***
CLN 0.1 (2nd day)	10.7 ± 1.6	28.3 ± 2.6***	32.8 ± 2.4***	32.2 ± 2.6***
CLN 0.1 (3rd day)	17.9 ± 1.4***	27.0 ± 2.1***	34.6 ± 4.4***	32.4 ± 2.4***
CLN 0.1 (4th day)	20.2 ± 2.8***	23.8 ± 3.0**	31.6 ± 1.9***	29.4 ± 2.7***
CLN 0.1 (5th day)	18.2 ± 2.1***	30.5 ± 2.1***	31.4 ± 3.3***	23.1 ± 2.8***
CLN 0.05 (1st day)	14.3 ± 1.3**	18.4 ± 2.0	27.2 ± 2.5***	23.4 ± 3.1***
CLN 0.05 (2nd day)	12.8 ± 0.8*	16.8 ± 1.3	28.9 ± 2.0***	23.8 ± 1.8***
CLN 0.05 (3rd day)	17.8 ± 1.7***	32.3 ± 1.8***	32.6 ± 1.7***	25.1 ± 2.6***
CLN 0.05 (4th day)	10.7 ± 1.6	25.5 ± 2.4***	29.8 ± 2.6***	25.1 ± 2.3***
CLN 0.05 (5th day)	15.2 ± 1.0**	25.5 ± 2.3***	28.9 ± 2.7***	26.7 ± 1.7***
CLN 0.025 (2nd day)	1.3 ± 0.9*	7.7 ± 1.8	11.1 ± 2.4	6.3 ± 1.9
CLN 0.025 (3rd day)	0.8 ± 0.9*	11.1 ± 2.2	10.6 ± 1.8	5 .9 ± 1.2
CLN 0.025 (4th day)	3.6 ± 1.6	7.8 ± 1.9	11.9 ± 1.7	10.4 ± 2.2

Morphine (50 mg/kg, SC) was injected daily for 4 days to develop tolerance to morphine antinociception. The animals received a single injection of saline (10 ml/kg, SC) or different doses of caerulein (0.025, 0.05 and 0.1 mg/kg, SC) 30 min before morphine on days 1st–4th or 30 min before the test dose of morphine (9 mg/kg, SC) on day 5. Data are stated as the mean ± SEM of %MPE for 9 mice.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. saline-treated control animals.

Animals in Experiment 5 received the CCK receptor antagonists, MK-329 and L-365,260 (0.25 and 0.5 mg/kg, respectively) 5 min before the injection of caerulein (0.05 mg/kg; 35 min before 50 mg/kg morphine) on day 3. The effect of drugs on the development of tolerance to morphine was evaluated by measuring the antinociceptive property of the test dose of morphine (9 mg/kg) on day 5.

Animals in Experiment 6 were injected with the CCK receptor antagonists MK-329 and L-365,260 (0.25 and 0.5 mg/kg, respectively) 35 min prior to morphine (50 mg/kg) injection on day 3, and tolerance was assessed on day 5.

Animals in Experiment 7 (nontolerant mice) received different doses of CCK antagonists alone, and antinociceptive response of morphine (9 mg/kg) was measured in the hot-plate test.

Drugs

The following drugs were used: ceruletide (caerulein diethylamonium hydrate; Farmitalia, Italy), morphine sulphate (MacFarlan Smith Ltd., England), and MK-329 [1-methyl-3-(2 indoloyl) amino-5-phenyl-3H-1,4-benzodiazepin-2-one] and L-365,260 [3R(+)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1, 4-benzodiazepin-3-yl)-N-(3-methyl-phenyl)urea; Merck Sharp & Dohme, England]. Morphine and caerulein were dissolved in saline. MK-329 and L-365,260 were dissolved in di-

TABLE 2

EFFECT OF 3 DOSES OF CEARULEIN IN PREVENTION OF TOLERANCE OF MORPHINE

	Latencies (s) After Test Dose of Morphine			
Treatment (mg/kg)	15 min	30 min		45 min
Saline ± Mor 3	3.5 ± 0.8	3.9 ± 0.9	4.8 ± 1.1	4.0 ± 1.2
CLN 0.1 ± Mor3	3.7 ± 0.9	7.9 ± 1.4	14.9 ± 1.8**	11.1 ± 1.7*
CLN 0.05 ± Mor 3	2.9 ± 1.0	7.5 ± 1.7	14.7 ± 2.3**	9.5 ± 2.1
CLN 0.025 ± Mor 3	0.2 ± 0.6	4.1 ± 0.7	5.6 ± 1.2	4.8 ± 1.0
Saline ± Mor 6	6.5 ± 1.4	12.5 ± 1.3	13.2 ± 1.5	12.9 ± 1.1
CLN 0.1 ± Mor 6	7.7 ± 1.8	14.9 ± 2.0	29.5 ± 2.2***	18.2 ± 1.6*
CLN 0.05 ± Mor 6	10.8 ± 0.8*	18.8 ± 2.0**	29.2 ± 1.9***	18.9 ± 2.7*
CLN 0.025 ± Mor 6	3.7 ± 1.5	6.7 ± 1.2*	13.7 ± 1.8	11.3 ± 1.4

Morphine (50 mg/kg, SC) was injected daily for 4 days to develop tolerance to morphine antinociception. The tolerant animals received a single injection of saline (10 ml/kg, SC) or different doses of caerulein (0.025, 0.05 and 0.1 mg/kg, SC) 30 min before morphine on day 3, and tolerance to morphine (3 and 6 mg/kg) was tested on day 5. Data are stated as the mean ± SEM of %MPE for 9 mice.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. saline-treated control animals.

TABLE 3

EFFECT OF CAERULEIN IN THE PRESENCE OR THE ABSENCE OF CCK ANTAGONISTS IN TOLERANT MICE

Treatment (mg/kg)	Latencies (s) After the Test Dose of Morphine			
	15 min	30 min	45 min	60 min
Saline 10 ml/kg + CLN	17.8 ± 1.7	32.2 ± 1.8	32.6 ± 1.7	25.1 ± 2.6
L-365, 260 0.25 + CLN	4.7 ± 1.4***	14.5 ± 1.5**	19.3 ± 2.7**	19.5 ± 3.3
L-365, 260 0.5 + CLN	6.7 ± 1.5**	17.2 ± 2.6*	17.8 ± 2.2**	14.1 ± 3.2*
MK-320 0.25 + CLN	9.5 ± 2.4*	17.7 ± 3.3*	20.6 ± 1.9**	13.9 ± 1.7*
MK-320 0.5 + CLN	17.4 ± 3.2	23.7 ± 4.9	30.2 ± 2.4	14.4 ± 2.2*
MK-329 1.0 + CLN	15.2 ± 2.0	22.6 ± 3.6	23.1 ± 3.6*	15.1 ± 2.3*

Morphine (50 mg/kg, SC) was injected daily for 4 days to develop tolerance to morphine antinociception. On day 3, the tolerant animals received a single injection of saline (10 ml/kg) or caerulein (0.05 mg/kg) 30 min before morphine administration or CCK antagonists 35 min before morphine administration, and tolerance to morphine (9 mg/kg) was tested on day 5. Data are stated as the mean ± SEM of %MPE for 9 mice.

*$p < 0.05$, **$p < 0.01$, ***p < 0.001 different from CLN-treated control animals.

methylsulfoxide (40%) and water (60%), respectively. All the drugs were administered subcutaneously. The doses of caerulein and CCK antagonists were based on published studies (6,33).

Data Analysis

Analysis of variance and the Newman-Keul test were used to evaluate the significance of the results. A value of $p < 0.05$ was considered significant.

RESULTS

Development of Tolerance to Morphine Antinociception

Animals received morphine (50 mg/kg, SC) on day 3, 4 or 5, and the antinociceptive response of a test dose of morphine (9 mg/kg) was tested on days 4, 5 and 6 (24 h after the last dose of 50 mg/kg morphine). Animals that become tolerant exhibited only a small antinociceptive effect (Fig. 1).

Animals treated for 4 days with morphine (50 mg/kg) also developed a tolerance to antinociception induced by different doses of morphine (3, 6 and 9 mg/kg; Fig. 2).

Effect of Caerulein on Morphine-tolerant Animals

Different doses of caerulein (0.025, 0.05 and 0.1 mg/kg) were given once daily 30 min before morphine injection on day 1, 2, 3, 4 or 5 during the development of tolerance to the opioid, and the test dose of morphine (9 mg/kg) was administered 24 h after last dose of morphine (50 mg/kg). Tolerance to morphine was reduced by caerulein (0.05 and 0.1 mg/kg; Table 1).

Different doses of caerulein (0.025, 0.05 and 0.1 mg/kg) were also administered to mice 30 min prior to morphine injection on day 3, and different doses of morphine (3 and 6 mg/kg) were tested on day 5. When doses of 3 or 6 mg/kg of morphine were used, caerulein reduced tolerance (Table 2).

Effects of CCK Receptor Antagonists on Morphine Tolerance in the Presence or Absence of Caerulein

When CCK-A receptor antagonist MK-329 (0.25 and 0.5 mg/kg) or CCK-B receptor antagonist L-365,260 (0.25 and 0.5 mg/kg) was injected 5 min before caerulein (35 min prior to morphine on day 3, during the development of tolerance to morphine), caerulein induced inhibition of morphine tolerance (Table 3).

When the antagonists were used without caerulein 35 min prior to morphine administration, morphine tolerance was reduced (Table 4).

Effects of CCK Receptor Antagonists on Morphine-induced Antinociception in the Hot-plate Test

Because CCK receptor antagonists decreased the response of caerulein on morphine tolerance, MK-329 or L-365,260

TABLE 4

EFFECT OF CCK ANTAGONISTS ON MORPHINE TOLERANCE

Treatment (mg/kg)	Latencies (s) After the Test Dose of Morphine			
	15 min	30 min	45 min	60 min
Saline	6.8 ± 1.1	12.3 ± 0.8	13.5 ± 1.3	10.7 ± 0.9
MK-329 0.25	20.3 ± 2.3**	29.3 ± 2.3**	29.2 ± 3.2*	19.3 ± 2.5
MK-329 0.5	16.9 ± 2.1*	24.1 ± 4.1*	29.2 ± 5.6*	17.2 ± 3.7*
L-365,260 0.25	19.1 ± 2.8**	27.8 ± 4.7**	30.0 ± 3.8*	22.9 ± 2.5*
L-362,260 0.5	16.7 ± 3.0*	22.7 ± 2.6*	24.9 ± 3.2*	23.4 ± 3.6

Morphine (50 mg/kg, SC) was injected daily for 4 days to develop tolerance to morphine antinociception. The tolerant animals received a single injection of saline (10 ml/kg), MK-329 (0.25 and 0.5 mg/kg) or L-365,260 (0.25 and 0.5 mg/kg) on day 3, and tolerance to morphine (9 mg/kg) was tested on day 5. Data are stated as the mean ± SEM of %MPE for 9 mice.

*$p < 0.05$, **$p < 0.01$ vs. saline-treated animals.

(0.25 and 0.5 mg/kg, respectively) was injected 35 min or 48 h before the test dose of morphine (9 mg/kg) to evaluate the response of the antagonist alone, and antinociception was determined. Both MK-329 and L-365,260 decreased the morphine-induced antinociception in the hot-plate test (Fig. 3).

DISCUSSION

In the present study, morphine (50 mg/kg) administered daily for 3, 4 or 5 days induced tolerance to morphine antinociception in the hot-plate test. Pretreatment of the animals with a CCK-related peptide, caerulein, reduced tolerance to morphine antinociception. Similar results have been obtained in previous work with the tail-flick test (21), even though the doses used in the tail-flick test were lower than those used in the present study. The reason for these discrepancy is unknown, but a difference in neural system or species may be involved. The different effects of caerulein in the tail-flick and hot-plate tests underscore that the method of testing may influence the results, although the data are not strictly comparable. CCK-8 and caerulein have not consistently produced antinociception in the tail-flick test (33,34), but the systemic administration of caerulein and CCK-8 did show antinociception (2,11) in the hot-plate test. The measurement of antinociception by the tail-flick test may be predominantly spinally controlled, which differs from that by the hot-plate test, which may involve a higher center in pain assessment (1,11). The present results have shown that the effect of caerulein on the reduction of tolerance to opioid antinociception is active in a tests of thermal stimuli, even though caerulein was antinociceptive in the formalin test (unpublished data).

Some reports have indicated that morphine increases CCK release in the spinal cord (24) and that CCK receptor antagonist or CCK antiserum can attenuate morphine tolerance (5–7,17,30). Thus, the blockade of CCK receptors may reverse or prevent the development of tolerance to the opiate antinociception. However, our previous studies have shown that CCK receptor activation may prevent tolerance to morphine in mice (21).

Caerulein has high affinity for CCK-A and CCK-B receptors (4,8,12,22,29). Based on our results with the tail-flick test (21), both CCK-A and CCK-B receptor sites may be involved in the inhibition of morphine tolerance. The tail-flick test is largely a spinal reflex (13), although there is an additional supraspinal component (28), whereas the hot-plate test involves supraspinal and coordinate motor activity.

The present data are in agreement with our previous studies and suggest that CCK receptors are involved in morphine tolerance.

The selective CCK-A and CCK-B receptor antagonists MK-329 and L-365,260, respectively, decreased the influence of caerulein on morphine tolerance, thus supporting the involvement of CCK-A and CCK-B receptors in the tolerance to morphine antinociception. Dose-dependent and biphasic effects for CCK have been proposed. Large doses of CCK have induced pharmacological antinociception, whereas small doses of the peptide have produced physiological antagonism of opioid antinociception (1). Caerulein can change morphine-induced antinociception, depending on the pretreatment times (32). Considering these results, one can speculate that the CCK-ergic mechanism(s) has a modulatory role in opioid antinociception. Endogenous CCK may be a factor for determining the magnitude of the opioid antinociceptive response (1) and may have a biphasic action on opioid-induced effects such as tolerance to morphine antinociception. The roles of CCK receptors and probably their subtypes are likely important and need to be studied more. The present results are also consistent with previous results on the inhibitory effect of CCK-related peptides on morphine dependence in mice (33). The effect of the CCK receptor antagonists alone decreasing tolerance to morphine tolerance is similar to that reported elsewhere (6). The present data also indicate that a single administration of the CCK receptor antagonists can reduce morphine antinociception, depending on the time of administration. MK-329 or L-365,260 administered 48 h before morphine administration reduced the effect of the opioid in nontolerant animals. However, when the antagonists were in-

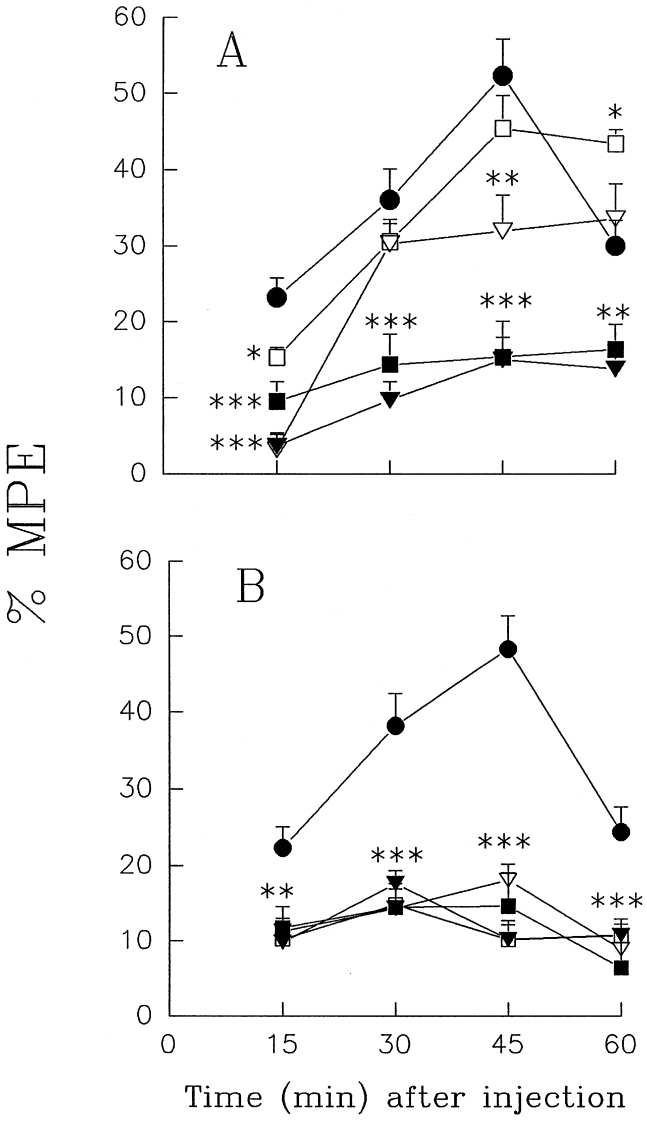

FIG. 3. Effects of CCK receptor antagonists on morphine-induced antinociception. Saline (solid circle, 10 ml/kg), MK-329 (solid triangle, 0.25 mg/kg; solid square, 0.5 mg/kg) or L-365,260 (open triangle, 0.25 mg/kg; open square, 0.5 mg/kg) was administered either (A) 35 min or (B) 48 h prior to morphine injection (9 mg/kg). Antinociception was measured 15, 30, 45 and 60 min after morphine injection and expressed as %MPE for 9 animals. $*p < 0.05$; $**p < 0.01$; ***$p < 0.001$ vs. vehicle-treated animals.

jected 35 min before morphine administration, only MK-329 decreased the response to morphine. The preventive effects of CCK receptor agonist and antagonist on the development of tolerance to morphine antinociception may be due to modulatory roles of the CCK receptors. Considering the similar effects of the CCK receptor agonist and antagonist, the drug may have a different affinity for various subtypes of CCK receptors. The direct effect of CCK on opiate receptors has been suggested (22), although the effect of the CCK peptide through induction of endogenous opioid peptide release has been proposed (25). Our results show that at a large part of the effect of caerulein is done by the receptors CCK-A and CCK-B, but another mechanism cannot be excluded. Furthermore, given the number and routes of administration, the doses of the peptide employed and the data from human studies, caerulein may have therapeutic utility (3). Moreover, caerulein and the CCK-related peptide may exert a potent and prolonged inhibitory effect on the development of morphine tolerance and dependence. This effect may reduce the toxic effect of opioid in pain relief.

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