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Effects of Intraventricular Injection of Morphine and β-Endorphin on Serotonin Release from the Spinal Cord in Rats

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JUNG, J.-S., D.-K. SONG, H.-W. SUH AND Y.-H. KIM. *Effects of intraventricular injection of morphine and β-endorphin on serotonin release from the spinal cord in rats.* PHARMACOL BIOCHEM BEHAV **49**(4) 1037–1042, 1994.—Effects of intraventricular (third ventricle) injection of morphine and β-endorphin on the release of serotonin (5-HT; 5-hydroxytryptamine) and 5-HIAA (5-hydroxy indolacetic acid) from the spinal cord were studied using urethane anesthetized spinally perfused rats. Intraventricular injection of morphine (25 μg) increased the 5-HT level in the perfusate about threefold. The increase of 5-HT release reached at peak between 30 and 60 min after the first injection of morphine. However, the levels of 5-HIAA, a metabolite of 5-HT, was not significantly altered by intraventricular injection of morphine. Furthermore, second intraventricular injection of morphine at the same dose did not increase 5-HT level in the spinal perfusate. In contrast to the results with morphine, β-Endorphin (10 μg) administered intraventricularly did not alter the release of 5-HT and 5-HIAA from the spinal cord. In addition, acute antinociceptive tolerance to intraventricular morphine induced by a prior intraventricular injection of morphine was studied in pentobarbital anesthetized rats. Acute tolerance was induced by intraventricular pretreatment with morphine (20 μg) for 120 min and the same dose of morphine was injected intraventricularly. The tail-flick test was used as an antinociceptive test. Pretreatment of rats with morphine intraventricularly reduced inhibition of the tail-flick response to intraventricularly injected morphine. The results support our previous hypothesis that β-endorphin and morphine administered supraspinally activate separate descending systems. Spinopetal serotonergic descending pathway is selectively activated by intraventricularly injected morphine but not β-endorphin. The production of acute antinociceptive tolerance to morphine injected intraventricularly may be due to, at least, a reduction of the release of 5-HT from the spinal cord.

Morphine β-Endorphin 5-HT release Spinal cord Supraspinal
Pain control system (descending) Tolerance

OUR previous reports have demonstrated that morphine and β-endorphin administered supraspinally produce their antinociceptive effects by stimulation of different types of opioid receptors and subsequent activation of different descending pain inhibitory systems. The antinociception induced by morphine given intracerebroventricularly is mediated by the stimulation of μ-opioid receptors and the activation of spinopetal serotonergic system, while the antinociception induced by β-endorphin given intracerebroventricularly is mediated by the stimulation of ε-opioid receptors and the activation of spinal opioid systems (15,17,23,28).

In addition to pharmacological studies, biochemical studies have demonstrated that supraspinally microinjected morphine increased the release of serotonin (5-HT; 5-hydroxytryptamine) from the spinal cord (6). In contrast to the effect of morphine, intraventricular injection of β-endorphin increased the release of Met-enkephalin, an opioid peptide, from the spinal cord, while intraventricular injection of morphine did not alter the release of Met-enkephalin from the spinal cord (16,21,28–30). However, the effect of β-endorphin on 5-HT release from the spinal cord has not been characterized.

We have previously demonstrated that the acute antinociceptive tolerance was developed 2–3 h after intracerebroven-

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tricular administration of morphine (20). However, the biochemical mechanisms involved in acute antinociceptive tolerance development by morphine administered supraspinally have not been characterized.

The present experiments were then designed a) to determine whether intraventricular injection of β-endorphin and morphine may have differential effects on 5-HT release from the spinal cord, and b) to examine the effect of second intraventricular injection of morphine on the inhibition of the tail-flick response and the release of 5-HT from the spinal cord induced by morphine administered intraventricularly.

METHOD

Subjects

Male Sprague–Dawley rats, weighing 250–350 g, were used. Animals were housed two per group in a room maintained at 22 ± 0.5°C with an alternating 12 L : 12 D cycle. Food and water were available ad lib. Each animal was used only once.

Spinal Cord Perfusion Procedures

The experiments were designed to study the release of 5-HT and 5-HIAA from the spinal cord by morphine and β-endorphin injected intraventricularly in rats according to the procedure described previously (16). Rats were injected with urethane (800 mg/kg, IP) and methylatropine bromide (2 mg/kg, IP) and were mounted in a stereotaxic apparatus. An inflow catheter made of PE-10 tubing (approximately 0.75 mm in diameter) was inserted down the subarachnoid space so that the tip lay in the vicinity of the lumbar segments (7.5 cm) and an outflow cannula made of PE-50 tubing was placed in the open cisternal space. The inflow and outflow tubings were placed in separate channels of a Gilson peristaltic pump and perfused with an artificial CSF at a rate of 50 μl/min. The outflow tubing stored the spinal perfusate between air gaps into test tubes on a fraction collector. Each test tube contained 100 μl of perchloric acid (0.1 M) solution. A 25-μl Hamilton microsyringe connected with a segment of PE-50 tubing to an injection cannula made of 27 g stainless steel tubing was prefilled with either saline, morphine, or β-endorphin solution. The injection cannula was stereotaxically inserted into the third ventricle (coordinate: AP, +3.4 mm; L, 0.0 mm and D, 4.1 mm from the skull surface using the bregma as zero). Morphine, at a dose of 25 μg in an injection volume of 5 μl, was injected immediately after sample number 1 and 5, while β-endorphin, at a dose of 10 μg in an injection volume of 5 μl, was injected immediately after sample number 1. Each spinal perfusate sample was collected for 30 min before the opioid injection and every 30 min for 120 min after the opioid injection.

HPLC Analysis

The perfusates were collected on ice. After the samples were centrifuged using a refrigerating microcentrifuge for 10 min, the supernatant were filtered through a 0.45 Millipore HV-4 filter unit. Twenty-five microliters of the filterate was injected onto C18 μ-Bondapak column (Waters, Milford, MA). As a mobile phase, 25 mM KH_2PO_4 (adjusted to pH 3.8) containing sodium octanesulfonic acid (0.2 mM), disodium EDTA (0.25 mM) and acetonitrile (11% v/v) was used. The flow rate was 0.8 ml/min and the oxidation potential was 0.55 V.

Antinociception Test

The experiments were carried out in pentobarbital-anesthetized rats. Rats were anesthetized with pentobarbital sodium (40 mg/kg, IP) and were mounted in a stereotaxic apparatus (David Korf Instruments, Tujunga, CA). Pentobarbital but not urethane was used as an anesthetic agent in the tail-flick test because urethane, at an anesthetic dose, inhibits the tail-flick response. The anesthetic state was maintained by injecting 6 to 10 mg/kg of pentobarbital sodium every 45 min or as needed. An injection cannula made of 30-gauge stainless steel tubing connected to a 10 μl Hamilton microsyringe with a segment of PE-10 tubing was prefilled with morphine solution and were inserted stereotaxically into the third ventricle. Morphine (20 μg) was injected intraventricularly in a volume of 5 μl for each injection. The antinociceptive response induced by morphine was assessed by the tail-flick test (1,2). The intensity of the radiant heat for the tail-flick response was adjusted so that the animal flicked the tail in 4–6 s before intraventricular injection of morphine. The tail-flick response was measured 15, 30, 45, 60, 90, and 120 min after intraventricular injection. Two hours after the first intraventricular injection of morphine, the same dose of morphine was injected intraventricularly. Changes of latency of the tail-flick responses were expressed as percent maximal possible effect

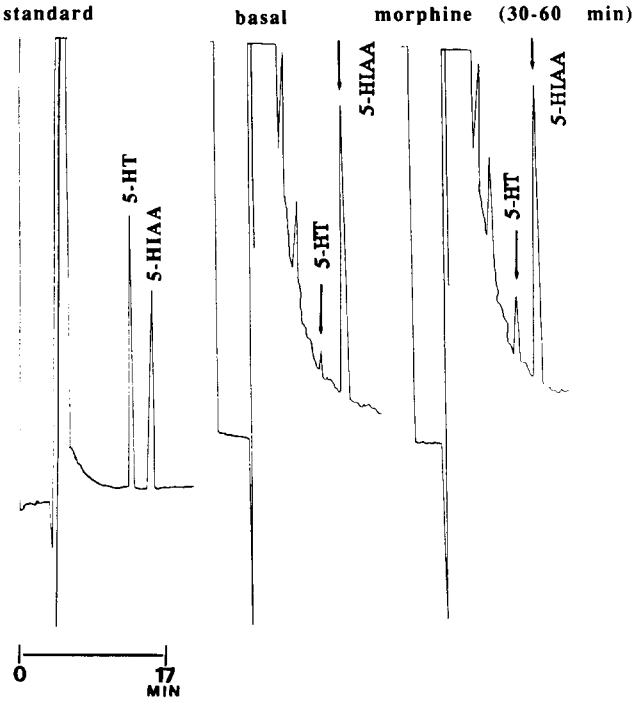

FIG. 1. Representative chromatograms of the basal efflux and release of 5-HT (serotonin, 5-hydroxytryptamine) and 5-HIAA (5-hydroxy indole acetic acid) determined in the sample of the spinal perfusate and their comparison with standards after intraventricular (third ventricle) injection of morphine (25 μg). Abscissa: time in min after injection onto Bondapak column. Because 5-HT and 5-HIAA were separated by column chromatography prior to quantification, the small two peaks that precede the 5-HT peak are, as yet, unidentified. Release of 5-HT was evoked by intraventricular administration of morphine (25 μg) during collection of the second sample (30–60 min).

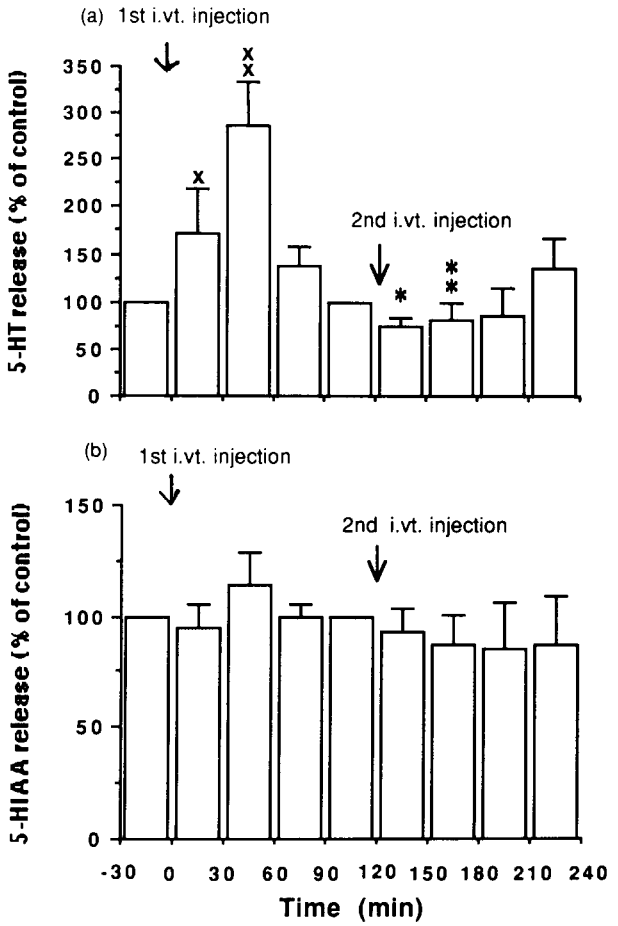

FIG. 2. The effect of intraventricular injection of morphine on the release of 5-HT (a) and 5-HIAA (b) from the spinal cord in rats. Rats were injected with the first intraventricular morphine (25 μg) at time zero. The second injection with the same dose of morphine was performed 120 min after the first injection. The amount of 5-HT and 5-HIAA released after the first and second morphine injection was obtained every 30 min for 120 min. The amount of 5-HT or 5-HIAA collected for 30 min (−30 to 0 min) before intraventricular injection of morphine was defined to be 100%. The basal release levels of 5-HT and 5-HIAA in the spinal perfusate were 1.215 ± 0.256 and 32.13 ± 3.08 ng/ml, respectively. Data for 5-HT and 5-HIAA after morphine injection are expressed as percent of basal release of 5-HT and 5-HIAA, respectively. The vertical bars indicate the standard error of the mean. The number of animal used for each group was 5. ($^{x}p < 0.05$, $^{xx}p < 0.01$ compared to the basal release of 5-HT; $*p < 0.01$, $**p < 0.05$ compared to 5-HT level increased by the first intraventricular morphine administration.)

(% MPE), which was calculated $[(T_1 - T_0)/(T_2 - T_0)] \times 100$, where T_0 and T_1 were the tail-flick latencies before and after the injection of opioid agonist and T_2 was the cutoff time that was set at 10 s for the tail-flick test.

Statistical Analysis

Statistical analysis was carried out by ANOVA test. *p*-Values less than 0.05 were considered to indicate statistical significance. The amount of 5-HT or 5-HIAA collected for 30 min before intraventricular injection was defined to be 100%. All subsequent measurements were normalized to and expressed as a percentage of this control measurement. Tests of statistical significance were performed on these normalized amounts of 5-HT release using analysis of variance with Scheffe's post hoc test.

Drugs Used

The drugs used were β-endorphin (Peninnsula Laboratories, Ind., Belmont, CA) and morphine HCl (Je-il Pharmaceutical Comp., Taegu, Korea). All drugs used were dissolved in a sterile saline (0.9% NaCl).

RESULTS

Effect of Intraventricular Injection of Morphine on 5-HT and 5-HIAA Release from the Spinal Cord

The basal levels 5-HT and 5-HIAA in the spinal perfusate perfused for 30 min were 1.215 ± 0.256 and 32.13 ± 3.08 ng/ml, respectively. Intraventricular injection of saline (5 μl) did not alter the 5-HT and 5-HIAA levels in the spinal perfusate (data not shown). Intraventricular injection of morphine at a dose of 25 μg increased the release of 5-HT from the spinal cord into the spinal perfusate as shown in Fig. 1. The time course of the release of 5-HT after the intraventricular injection of morphine is shown in Fig. 2. 5-HT in the spinal perfusate increased and reached its peak in 30 to 60 min after injection and declined gradually and returned to the preinjection level in 120 min. However, the second intraventricular injection of morphine at the same dose was unable to increase the release of 5-HT from the spinal cord (Fig. 2a).

We also examined the effect of intraventricular injection of morphine on 5-HIAA release from the spinal cord and found that the level of 5-HIAA was not altered by intraventricular injection of morphine at the same dose (Figs. 1 and 2b).

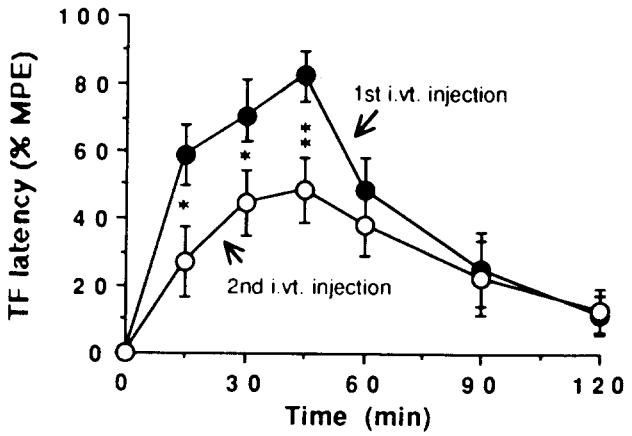

FIG. 3. Second injection of morphine administered intraventricularly (IVT) develops an acute antinociceptive tolerance. Rats were injected with morphine (20 μg) intraventricularly (third ventricle). The second injection with the same dose of morphine was performed 120 min after the first injection. The inhibition of the tail-flick response was measured 15, 30, 45, 60, 90, and 120 min after the first and second IVT injection of morphine. % MPE denotes the maximal possible effect. The vertical bars indicate the standard error of the mean. The number of animal used was 10. ($*p < 0.01$; $**p < 0.05$ compared to %MPE produced by the first intraventricular morphine administration.)

Acute Antinociceptive Tolerance Study

To determine if the first intraventricular injection of morphine develops an acute antinociceptive tolerance, 20 μg of morphine was injected intraventricularly in pentobarbital-anesthetized rats. The inhibition of the tail-flick response reached at peak 45 min and returned to the control level 120 min after the first intraventricular injection of morphine. After an intraventricular morphine injection, animals developed an acute antinociceptive tolerance. The inhibition of the tail-flick response induced by the first injection of morphine was markedly attenuated after the second injection of the same dose of morphine, as shown in Fig. 3.

Effect of Intraventricular Injection of β-Endorphin on 5-HT and 5-HIAA Release From the Spinal Cord

In contrast to the results with morphine, intraventricular injection of β-endorphin at a dose of 10 μg did not alter the release of 5-HT from the spinal cord (Figs. 4 and 5a). In addition, 5-HIAA level was not altered by intraventricular injection of β-endorphin (Figs. 4 and 5b).

DISCUSSION

The results of the present studies demonstrate that morphine administered intraventricularly increases the release of

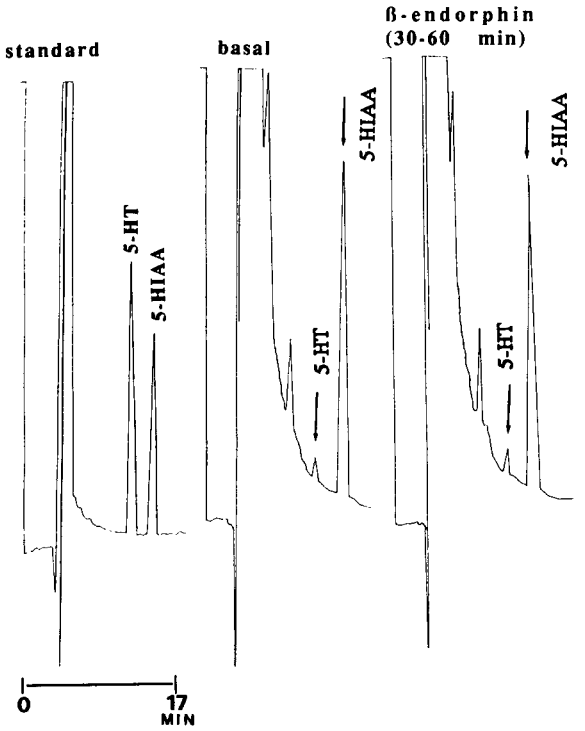

FIG. 4. Representative chromatograms of the basal efflux and release of 5-HT (serotonin, 5-hydroxytryptamine) and 5-HIAA (5-hydroxy indole acetic acid) determined in the sample of the spinal perfusate and their comparison with standards after intraventricular (third ventricle) injection of β-endorphin (10 μg). Abscissa: time in min after injection onto Bondapak column. Because 5-HT and 5-HIAA were separated by column chromatography prior to quantification, the small two peaks that precede the 5-HT peak are, as yet, unidentified.

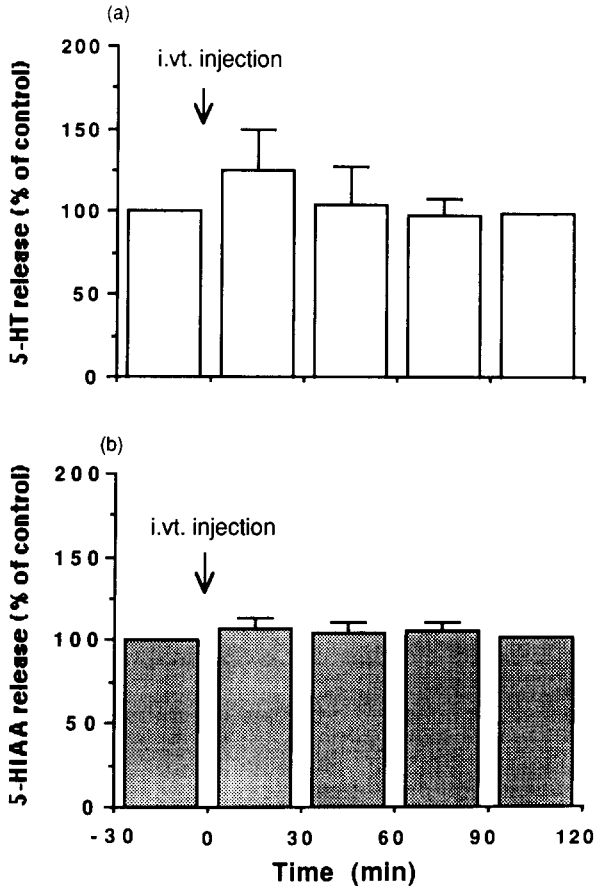

FIG. 5. Intraventricular injection of β-endorphin does not affect the release of 5-HT (a) and 5-HIAA (b) from the spinal cord in rats. Rats were injected with β-endorphin (10 μg) intraventricularly (third ventricle) at time zero. The amount of 5-HT and 5-HIAA released after β-endorphin injection was obtained every 30 min for 120 min. The amount of 5-HT or 5-HIAA collected for 30 min (−30 to 0 min) before intraventricular injection of morphine was defined to be 100%. The basal release levels of 5-HT and 5-HIAA in the spinal perfusate were 1.215 ± 0.256 and 32.13 ± 3.08 ng/ml, respectively. Data for 5-HT and 5-HIAA are expressed as percent of basal release of 5-HT and 5-HIAA, respectively. The vertical bars indicate the standard error of the mean. The number of animal used for each group was 5.

5-HT without altering the level of 5-HIAA in the spinal perfusates. The changes in 5-HIAA levels could be difficult to observe, possibly due to the following reason. The 1-2 ng of 5-HT formed gives rise to not more than 1-2 ng of 5-HIAA (10), the relatively high basal concentration of 5-HIAA (as compared to 5-HT) will obscure small changes in 5-HIAA levels. In addition, higher doses of β-endorphin (up to 25 μg) administered intraventricularly failed to increase the release of 5-HT and 5-HIAA from the spinal cord (data not shown). Our results are supported by the findings that microinjection of morphine into nucleus reticularis paragigantocelullularis causes the release of 5-HT from the spinal cord (6), suggesting that descending system activated by morphine administered supraspinally involves spinopetal serotonergic system while descending system activated by β-endorphin administered intraventricularly does not.

The findings of the present biochemical studies are further

supported by several previous pharmacological studies. a) Blockade of the spinal serotonergic receptors by methysergide effectively antagonized the inhibition of the tail-flick response induced by morphine but not that induced by β-endorphin administered into periaqueductal gray, rostroventral medulla, or intracerebroventricularly (5,7,8,23,31). b) The inhibition of serotonin reuptake by fluoxetine selectively potentiated inhibition of the tail-flick response induced by morphine but not that induced by β-endorphin administered intracerebroventricularly (16,19). c) Intrathecal injection of serotonin produce antinociception (4,12,34). d) Depletion of serotonin in the spinal cord by intrathecal injection of a neurotoxic drug, 5,7-dihydroxytryptamine, antagonizes the antinociceptive effects of morphine administered intracerebroventricularly or systemically (9,13,22). However, degeneration of serotonergic neurons produced by 5,7-dihydroxytryptamine was ineffective in altering the inhibition of the tail-flick response induced by intracerebroventricularly administered β-endorphin (22). The findings indicate that descending serotonergic pain inhibitory systems are involved in supraspinally administered morphine-induced antinociception.

Evidence have been accumulated that β-endorphin and morphine stimulate different types of opioid receptors for antinociception at supraspinal sites. β-Funaltrexamine and naloxone, selective mu-opioid receptor antagonists, given intracerebroventricularly effectively antagonize the antinociception induced by morphine administered intracerebroventricularly but are not effective or less effective in antagonizing the antinociception induced by β-endorphin administered intracerebroventricularly (15,23).

β-Endorphin-(1-27) injected intracerebroventricularly antagonizes the antinociception induced by β-endorphin administered intracerebroventricularly but does not affect the antinociceptive effects of morphine (3,11,24), suggesting that the differential effects of morphine and β-endorphin administered intraventricularly on the release of 5-HT from the spinal cord may be attributed to the stimulation of different opioid receptors at supraspinal sites; μ-opioid receptors for morphine and ε-receptors for β-endorphin.

In the present study, we found that the acute tolerance in the production of antinociception was observed 2 h after intraventricular administration of morphine. This result in rats is consistent with our previous report in mice (20). The finding, in the present biochemical study, that the second intraventricular injection of morphine could not elicit the release of 5-HT from the spinal cord suggests that this acute tolerance in 5-HT release from the spinal cord may, at least, be responsible for the development of acute antinociceptive tolerance.

Other studies have further demonstrated that β-endorphin and morphine produce their antinociception by activating separate descending systems. We have previously demonstrated that β-endorphin administered supraspinally causes a release of immunoreactive Met-enkephalin from the spinal cord in urethane anesthetized rats (16,21). In addition, we found that pretreatment of mice intrathecally with thiorphan and bestatin effectively potentiated inhibition of the tail-flick response induced by β-endorphin administered intracerebroventricularly (16,19). Furthermore, we have recently found that thiorphan and bestatin added into the perfusate for intrathecal perfusion increased markedly the Met-enkephalin content in the spinal perfusate released by β-endorphin injected supraspinally (16). The involvement of Met-enkephalin in β-endorphin-induced antinociception is also supported by other studies. a) Blockade of opioid receptors by intrathecal injection of naloxone or other opioid antagonists effectively antagonizes inhibition of the tail-flick response induced by β-endorphin given supraspinally (15,23,25,27). b) A single intracerebroventricular injection of β-endorphin produces an acute tolerance to delta-opioid receptor activity for antinociception in the spinal cord (18). c) Intrathecal injection of antibody to Met-enkephalin but not antibodies to Leu-enkephalin, dynorphins, and β-endorphin antagonizes inhibition of the tail-flick response induced by β-endorphin given intracerebroventricularly in mice (27). d) Intrathecal injection of Met-enkephalin and other opioids produce antinociception (14,32). The evidences described above give support to the contention that Met-enkephalin is the mediator for β-endorphin-induced antinociception.

Previous studies have demonstrated that a) morphine given intracerebroventricularly does not release Met-enkephalin from the spinal cord (28). b) Intrathecal injection of naloxone or other opioid receptor blockers does not antagonize inhibition of the tail-flick response induced by morphine given intracerebroventricularly (23-25). c) Intrathecal injection of antibody to Met-enkephalin does not antagonize inhibition of the tail-flick response induced by morphine given intracerebroventricularly (27). d) Inhibition of the degradation of Met-enkephalin by intrathecal injection of thiorphan or bestatin did not potentiate inhibition of the tail-flick response induced by morphine given intracerebroventricularly (16). These studies indicate that Met-enkephalin and its associated opioid receptors in the spinal cord are not involved in supraspinally administered morphine-induced inhibition of the tail-flick response.

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