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Intracisternal administration of interleukin-1β attenuates naloxone-precipitated withdrawal in morphine-dependent mice

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Abstract

The effect of central administration of interleukin-1β on naloxone-precipitated withdrawal in morphine-dependent mice was studied. The degree of physical dependence on morphine was estimated by counting the number of jumps precipitated by naloxone, one of the typical withdrawal signs. Intracisternal (i.c.) administration of interleukin-1β (0.01–1 ng/5 μl per mouse) to morphine-dependent mice 30 min prior to the injection of naloxone (10 mg/kg i.p.) decreased the number of jumps in a dose-dependent manner. The effect of interleukin-1β (1 ng) was significantly antagonized when it was co-administered with interleukin-1 receptor antagonist (1 μg/mouse). These results suggest that centrally administered interleukin-1β could attenuate naloxone-precipitated withdrawal in morphine-dependent mice via interleukin-1 receptors in the brain. Co-administration of α-melanocyte-stimulating hormone (300 ng/mouse) or α-helical corticotropin-releasing factor (CRF)-(9–41), a CRF receptor antagonist (300 ng/mouse), with interleukin-1β also antagonized the inhibitory effect of interleukin-1β (1 ng). Moreover, i.c. administration of CRF (200 ng/mouse) significantly decreased the number of jumps.

Keywords: Interleukin-1; Interleukin-1 receptor antagonist; α-MSH (α-melanocyte-stimulating hormone); α-Helical CRF-(9–41); CRF (corticotropin-releasing factor); Morphine withdrawal

1. Introduction

Interleukin-1 is a cytokine which plays important roles in immune and inflammatory responses. Furthermore, recently, this cytokine has been reported to have various effects on the central nervous system (CNS) including the induction of fever (Kluger, 1991), elicitation of slow-wave sleep (Opp and Krueger, 1991), loss of appetite (Plata-Salamán et al., 1988), activation of the hypothalamo-pituitary-adrenal axis (Sapolsky et al., 1987), modulation of pain transmission (Nakamura et al., 1988; Oka et al., 1993), inhibition of long-term potentiation in the mouse mossy fiber-CA3 system (Katsuki et al., 1990), depression of Ca^{2+} currents in hippocampal neurons (Plata-Salamán and ffrench-Mullen, 1994) and enhancement of $GABA_A$ receptor function (Miller et al., 1990). Interleukin-1 immunoreactivity was shown in the human hypothalamus (Breder et al., 1988) and rat forebrain (Lechan et al., 1990). It has been reported that interleukin-1β mRNA is detected in the normal rat brain (Bandtlow et al., 1990) and is markedly induced by the systemic injection of endotoxin (Ban et al., 1992), methamphetamine (Yamaguchi et al., 1991) or kainic acid (Minami et al., 1990). Moreover, in the brain, interleukin-1 receptor was identified by radioligand binding (Farrar et al., 1987) and its mRNA was detected by in situ hybridization histochemistry (Cunningham et al., 1992). These findings support the idea that interleukin-1 may play a role of neuromodulator in the CNS.

Several studies have shown that cytokines, such as interferon-α (Dafny, 1983), and immunomodulating agents, such as muramyl dipeptide (Dougherty et al., 1987), can modify morphine withdrawal phenomena. In addition, recently, it has been reported that peripheral administration of lipopolysaccharide derived from *Pantoea agglomerans* and tumor necrosis factor-α (TNF-α) inhibit morphine withdrawal jumping behavior in mice (Okutomi et al., 1992). These substances

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are shown to induce and/or enhance the synthesis of interleukin-1 (Dinarello and Krueger, 1986; Dinarello et al., 1986; Gerrard et al., 1987; Ban et al., 1992). Particularly, as described above, peripheral administration of endotoxin is shown to induce interleukin-1β mRNA in the brain. These findings suggest the possibility that peripherally administered lipopolysaccharide and TNF-α suppress morphine withdrawal jumping behavior in mice, at least in part, through the production of interleukin-1β in the brain. As the first step to examine this hypothesis, we studied the effect of centrally administered interleukin-1β on naloxone-precipitated withdrawal in morphine-dependent mice. The degree of morphine withdrawal syndrome was evaluated by counting the number of jumps, one of the typical withdrawal signs in mice. It has been shown that the frequency of jumps well reflects the degree of physical dependence on morphine (Bläsig et al., 1973). Since it is well known that the central effects of interleukin-1β are suppressed by co-administration of α-melanocyte-stimulating hormone (α-MSH) or α-helical corticotropin-releasing factor (CRF)-(9–41), a CRF antagonist, in many experimental preparations (Opp et al., 1988; Rothwell, 1989; Weiss et al., 1991; Nakamori et al., 1993), we further investigated whether the effect of interleukin-1β on morphine withdrawal jumping behavior could be antagonized by these neuroactive substances.

2. Materials and methods

2.1. Materials

Molecular sieve 4A 1/8 was purchased from Nacalai Tesque (Kyoto, Japan). Morphine hydrochloride was from Takeda Co. (Osaka, Japan). The morphine pellets containing 11.5 ± 0.3 mg of morphine hydrochloride each were prepared according to the method of Hui and Roberts (1975) except for the use of morphine hydrochloride instead of morphine sulphate. α-MSH and CRF were from Peptide Institute (Osaka, Japan). α-Helical CRF-(9–41) and naloxone hydrochloride were from Sigma Chemical Co. (St. Louis, MO). Human recombinant interleukin-1β (molecular weight 17376) and interleukin-1 receptor antagonist (molecular weight 17256.5) were gifts from Otsuka Pharmaceutical Co. (Tokushima, Japan). Interleukin-1β, interleukin-1 receptor antagonist, α-MSH, α-helical CRF-(9–41), and CRF were dissolved in phosphate-buffered saline (PBS) containing 0.1% bovine serum albumin. Naloxone hydrochloride was dissolved in saline. The doses of these drugs in the present study were as follows: interleukin-1β (0.01, 0.1, 0.3 or 1 ng), interleukin-1 receptor antagonist (0.5 or 1 μg), α-MSH (100 ng, 300 ng or 1 μg), α-helical CRF-(9–41) (100 or 300 ng), CRF (1, 10, 100 or 200 ng/5 μg per mouse) and naloxone (10 mg/kg). In the case of the inactivation of interleukin-1β, it was boiled for 30 min.

2.2. Animals

Male ddY mice weighing 20–24 g were used. They were kept at a constant ambient temperature of 23 ± 1° C under a 12-h light/dark cycle and were provided food and water ad libitum. All of the mice were used only once.

2.3. Development of morphine dependence

First, the mice used in this study were selected by using the tail-pinch assay (Takagi et al., 1966). The base of the tail including the anal mucosa was pinched by an artery clip with 500 g pressure. We used the mice which bit the clip within 2 s. Then, the mouse was rendered morphine-dependent by s.c. implantation of a morphine pellet containing 11.5 ± 0.3 mg of morphine hydrochloride at the back of the neck for 48 h. The mice that served as control were implanted with placebo pellets. Pellet implantation was carried out between 13:00 p.m. and 15:00 p.m. according to the method of Hui and Roberts (1975). 30 min after implantation of the morphine pellet, none of the mice bit the clip in the tail-pinch assay, while all the mice implanted with placebo pellets bit the clip within 2 s.

48 h after implantation of the morphine pellet, nociceptive threshold was measured by tail-pinch assay again in the mouse still implanted with the pellet. For further studies, we used the mice which bit the clip within 2 s. The pellets which were removed from the mice 30 min after the tail-pinch assay contained 4.77 ± 0.2 mg of morphine hydrochloride and could produce the antinociceptive effect in other naive mice when implanted s.c. Then the mice were placed into a plexiglass cylinder 25 cm in diameter and 30 cm in height for 30 min in order to habituate to the experimental environment. The mice which showed jumping behavior during this procedure were discarded.

2.4. Method and timing of the central administration

After the 30-min habituation period, the implanted pellet was removed without anesthesia (Hui and Roberts, 1975). After removal of the pellet, vehicle (0.1% bovine serum albumin in PBS) was administered intracisternally (i.c.) or intracerebroventricularly (i.c.v.) to morphine-dependent mice in a volume of 5 μl according to the method of Ueda et al. (1979) or the method of Haley and McCormick (1957), respectively, 30 min before the i.p. administration of naloxone (10 mg/kg). To determine the optimal timing of administration of interleukin-1β, 1 ng of interleukin-1β was i.c. administered 0.5, 5, 15, 30, 60 or 90 min before i.p. administration of naloxone (10 mg/kg). After adminis-

tration of vehicle or interleukin-1β, the mice were returned back into a plexiglass cylinder. After the administration of naloxone, the mice were immediately returned back into a plexiglass cylinder and the number of jumps was counted every 5 min for 40 min. The effects of interleukin-1β or vehicle on morphine withdrawal jumping behavior were examined between 13:00 p.m. and 17:00 p.m.

2.5. Effects of interleukin-1β and other drugs on naloxone-precipitated withdrawal

After the 30-min habituation period, the implanted pellet was removed without anesthesia. Soon after removal of the pellet, interleukin-1β (0.01, 0.1, 0.3 or 1 ng/5 μl per mouse), heat-inactivated interleukin-1β (1 ng) or CRF (1, 10, 100 or 200 ng/5 μl per mouse) was administered i.c. to morphine-dependent mice. Interleukin-1 receptor antagonist (0.5 or 1 μg), α-MSH (100, 300 ng or 1 μg) or α-helical CRF-(9–41) (100 or 300 ng) was i.c. administered by itself or co-administered with interleukin-1β (1 ng). 30 min after the i.c. administration of the drugs, naloxone (10 mg/kg) was administered i.p. Then the mice were returned back into a plexiglass cylinder and the number of jumps was counted every 5 min for 40 min. The effects of various drugs on morphine withdrawal jumping behavior were examined between 13:00 p.m. and 17:00 p.m. Doses of α-MSH and α-helical CRF-(9–41) were determined on the basis of previous reports which have shown that the central effects of interleukin-1β are antagonized by α-MSH or α-helical CRF-(9–41) in several experimental preparations. (Opp et al., 1988; Rothwell, 1989; Weiss et al., 1991; Nakamori et al., 1993; Oka et al., 1993).

2.6. Data analysis

Data are presented as means ± S.E.M. of the total number of jumps during 40 min. In the experiment which examined the timing of central administration of interleukin-1β and dose-dependent effects of interleukin-1β and CRF on morphine withdrawal, data were analyzed using a one-way analysis of variance followed by Bonferroni's test. Other experimental data were analyzed by Mann-Whitney U-test. Differences with a $P < 0.05$ were considered significant.

3. Results

3.1. Effects of i.c. and i.c.v. administrations of vehicle on morphine withdrawal jumping behavior

In the case of morphine-dependent mice which were given neither i.c. nor i.c.v. injection, the number of jumps elicited by the i.p. injection of naloxone was 59.8 ± 13.8. The number of jumps elicited by naloxone in the morphine-dependent mice which were i.c. injected with vehicle was 61.3 ± 11.5. There was no statistical difference between these two groups. However, i.c.v. administration of vehicle decreased the number of jumps to 5.9 ± 2.4. These results let us adopt i.c., but not i.c.v., injection as a method to administer the drugs in the following experiments. In the mice implanted with a placebo pellet, i.p. injection of naloxone failed to precipitate jumping behavior both with and without i.c. injection of vehicle 30 min before naloxone.

3.2. Determination of the optimal timing to administer interleukin-1β

Fig. 1A shows the time course of jumping behavior elicited by the i.p. administration of naloxone. In the mice i.c. administered vehicle 30 min before naloxone, jumping behavior was frequently observed within 20 min following the i.p. administration of naloxone and was almost eliminated 40 min after naloxone. To determine the optimal time to administer interleukin-1β, 1 ng of interleukin-1β was administered to morphine-dependent mice at 0.5, 5, 15, 30, 60 or 90 min before i.p. administration of naloxone. The mean number of jumps and S.E.M. was 54.5 ± 11.8, 30.2 ± 11.1, 19.2 ± 5.64, 13.0 ± 4.21, 14.1 ± 6.95 or 23.0 ± 7.21, respectively (Fig. 1B). The i.c. administration of interleukin-1β 15, 30 and 60 min before naloxone significantly decreased morphine withdrawal jumping behavior. This result is thought to reflect the inhibitory effect of interleukin-1β on morphine withdrawal jumping behavior, but not the apparent decrease in jumping behavior due to the alteration in time course of it, because the jumping behavior of all groups examined was elicited soon after i.p. administration of naloxone, and then almost disappeared within 40 min after naloxone. Since the i.c. administration of interleukin-1β 30 min before naloxone was the most effective means to attenuate morphine withdrawal jumping behavior, i.c. administration of interleukin-1β and/or other substances, such as interleukin-1 receptor antagonist, α-MSH, α-helical CRF-(9–41) and CRF, was carried out 30 min before naloxone in the following experiments.

3.3. Dose-dependent attenuation of morphine withdrawal jumping behavior by interleukin-1β

The cumulative number of jumps during the 40-min observation period is shown in Fig. 2. That of the vehicle-administered group was 61.3 ± 11.5. I.c. administration of interleukin-1β dose dependently (0.01–1 ng) suppressed morphine withdrawal jumping behavior. Significant effects were observed at the doses of 300 pg (mean ± S.E.M. = 17.1 ± 3.9, $P < 0.05$) and 1 ng (mean

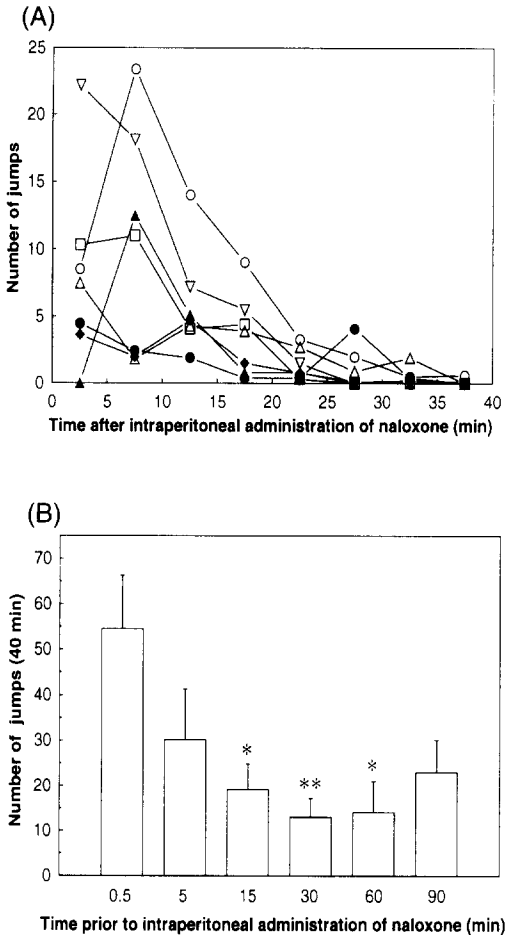

Fig. 1. (A) Time course of naloxone-precipitated jumping behavior in morphine-dependent mice. The mice were rendered morphine-dependent by s.c. implantation of a morphine pellet for 48 h. After pellet removal, vehicle was intracisternally administered 30 min (○) or interleukin-1β (1 ng) was intracisternally administered 0.5 (▽), 5 (□), 15 (▲), 30 (♦), 60 (●), 90 min (△) before naloxone (10 mg/kg, i.p.). The number of jumps was counted every 5 min for 40 min. Each point represents the mean number of jumps ($n = 10$). (B) Timing for the intracisternal administration of interleukin-1β. Interleukin-1β (1 ng) was intracisternally administered at 0.5, 5, 15, 30, 60 or 90 min prior to naloxone (i.p.) in morphine-dependent mice. Each bar represents the mean number of jumps ± S.E.M. for 40 min ($n = 10$). The significant effects were observed at 15 min, 30 min and 60 min. * $P < 0.05$, ** $P < 0.01$ compared with vehicle-treated mice (ANOVA followed by Bonferroni's test).

± S.E.M. = 13.0 ± 4.2, $P < 0.01$). None of the doses tested was found to alter the time course of jumping behavior. Heat-inactivated interleukin-1β (1 ng) had no effect on morphine withdrawal jumping behavior.

3.4. Effects of interleukin-1 receptor antagonist on attenuation of morphine withdrawal jumping behavior by interleukin-1β

As shown in Fig. 3, co-administration of interleukin-1 receptor antagonist (0.5 or 1 μg) with interleukin-1β (1 ng) antagonized the inhibitory effect of interleukin-1β

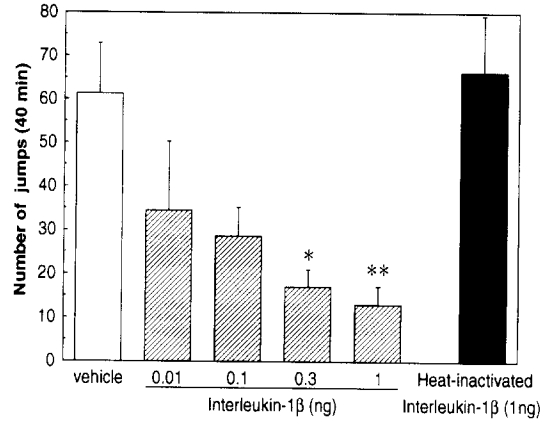

Fig. 2. Dose-dependent inhibitory effect of interleukin-1β on naloxone-precipitated jumping behavior in morphine-dependent mice. Vehicle, interleukin-1β (0.01–1 ng) or heat-inactivated interleukin-1β (1 ng) was administered intracisternally 30 min before naloxone (10 mg/kg, i.p.). Each bar represents the mean number of jumps ± S.E.M. for 40 min ($n = 10$). * $P < 0.05$, ** $P < 0.01$ compared with vehicle-treated mice (ANOVA followed by Bonferroni's test).

on morphine withdrawal jumping behavior. The mean number of jumps and S.E.M. was 21.7 ± 8.22 or 31.3 ± 8.01, respectively. A significant effect was observed in the case of the co-administration of interleukin-1 receptor antagonist at the dose of 1 μg ($P < 0.05$ compared with the group i.c. injected with 1 ng of interleukin-1β alone), but this treatment could not fully antagonize the effect of interleukin-1β ($P < 0.01$ compared with the group i.c. injected with vehicle). I.c. administration of interleukin-1 receptor antagonist (0.5 or 1 μg/mouse) alone had no significant effect on morphine withdrawal jumping behavior, and the mean

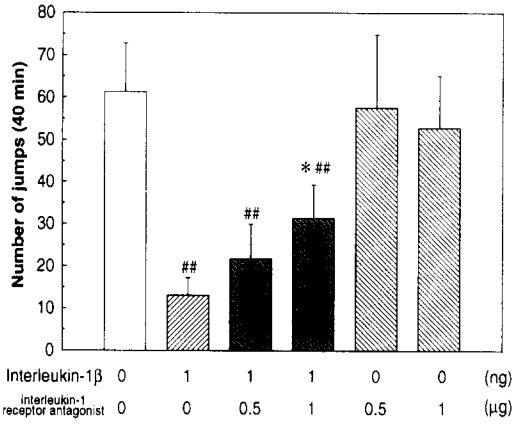

Fig. 3. Effect of co-administration of interleukin-1 receptor antagonist with interleukin-1β on naloxone-precipitated jumping behavior in morphine-dependent mice. Vehicle, interleukin-1β, interleukin-1 receptor antagonist, or interleukin-1β plus interleukin-1 receptor antagonist was intracisternally administered 30 min before naloxone (10 mg/kg, i.p.). Each bar represents the mean number of jumps ± S.E.M. for 40 min ($n = 10$). * $P < 0.05$ compared with interleukin-1β (1 ng)-treated mice (Mann-Whitney U-test). ## $P < 0.01$ compared with vehicle-treated mice (Mann-Whitney U-test).

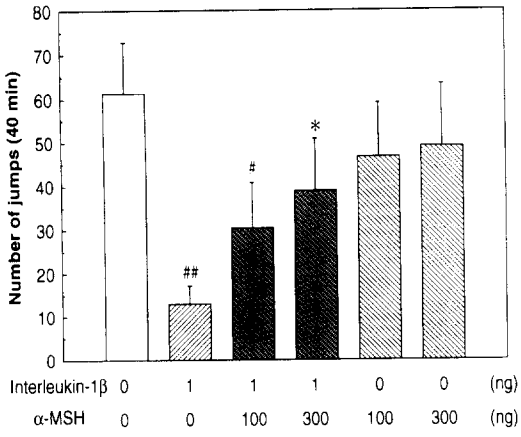

Fig. 4. Effect of co-administration of α-MSH with interleukin-1β on naloxone-precipitated jumping behavior in morphine-dependent mice. Vehicle, interleukin-1β, α-MSH or interleukin-1β plus α-MSH was intracisternally administered 30 min before naloxone (10 mg/kg, i.p.). Each bar represents the mean number of jumps ± S.E.M. for 40 min ($n = 10$). * $P < 0.05$ compared with interleukin-1β (1 ng)-treated mice (Mann-Whitney U-test). # $P < 0.05$, ## $P < 0.01$ compared with vehicle-treated mice (Mann-Whitney U-test).

number of jumps and S.E.M. was 57.5 ± 17.3 or 52.8 ± 12.29, respectively.

3.5. Effects of α-MSH on attenuation of morphine withdrawal jumping behavior by interleukin-1β

Co-administration of α-MSH (100 or 300 ng) with interleukin-1β (1 ng) antagonized the inhibitory effect of interleukin-1β on morphine withdrawal jumping behavior. The mean number of jumps and S.E.M. was 30.4 ± 10.5 or 38.9 ± 12.0, respectively (Fig. 4). Significant antagonism was observed in the case of the co-administration of α-MSH at the dose of 300 ng ($P < 0.05$ compared with the group i.c. injected with 1 ng of interleukin-1β alone, and no significant difference from the group i.c. injected with vehicle). I.c. administration of α-MSH (100 or 300 ng) alone had no significant effect on morphine withdrawal jumping behavior, and the mean number of jumps and S.E.M. was 46.7 ± 12.4 or 49.1 ± 14.3, respectively. However, administration of α-MSH at the dose of 1 μg elicited frequent stretching and yawning, and decreased the number of morphine withdrawal jumps (the mean number of jumps and S.E.M. was 36.3 ± 6.61). Co-administration of α-MSH at the dose of 100 or 300 ng with interleukin-1β (1 ng) did not elicit stretching and yawning.

3.6. Effects of α-helical CRF-(9–41) on attenuation of morphine withdrawal jumping behavior by interleukin-1β

Co-administration of α-helical CRF-(9–41), a CRF receptor antagonist, (100 or 300 ng) with interleukin-1β (1 ng) antagonized the inhibitory effect of interleukin-1β on morphine withdrawal jumping behavior. The mean number of jumps and S.E.M. was 24.1 ± 4.47 or 41.5 ± 8.19, respectively (Fig. 5). A significant effect was observed in the case of the co-administration of α-helical CRF-(9–41) at the dose of 300 ng ($P < 0.05$ compared with the group i.c. injected with 1 ng of interleukin-1β alone, and no significant difference from the group i.c. injected with vehicle). I.c. administration of α-helical CRF-(9–41) (100 or 300 ng/mouse) alone had no significant effect on morphine withdrawal jumping behavior, and the mean number of jumps and S.E.M. was 53.8 ± 16.8 or 55.5 ± 15.8, respectively.

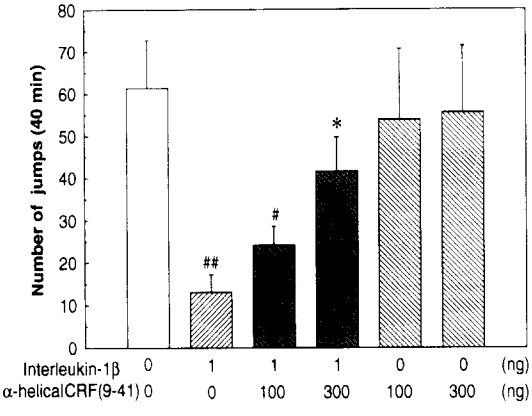

Fig. 5. Effect of co-administration of α-helical CRF-(9–41) with interleukin-1β on naloxone-precipitated jumping behavior in morphine-dependent mice. Vehicle, interleukin-1β, α-helical CRF(9–41), or interleukin-1β plus α-helical CRF-(9–41) was intracisternally administered 30 min before naloxone (10 mg/kg, i.p.). Each bar represents the mean number of jumps ± S.E.M. for 40 min ($n = 10$). * $P < 0.05$ compared with interleukin-1β (1 ng)-treated mice (Mann-Whitney U-test). # $P < 0.05$, ## $P < 0.01$ compared with vehicle-treated mice (Mann-Whitney U-test).

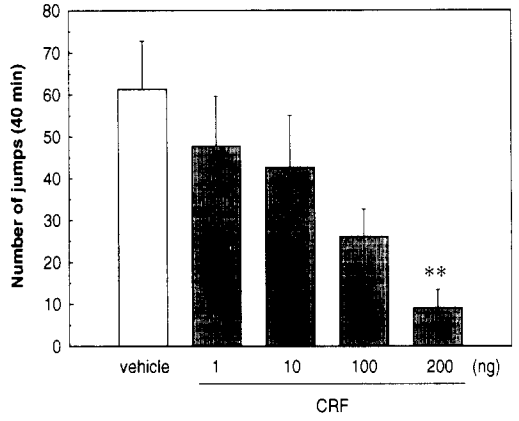

Fig. 6. Inhibitory effect of CRF on naloxone-precipitated jumping behavior in morphine-dependent mice. CRF was intracisternally administered 30 min before naloxone (10 mg/kg, i.p.). Each bar represents the mean number of jumps ± S.E.M. for 40 min ($n = 10$). ** $P < 0.01$ compared with vehicle-treated mice (ANOVA followed by Bonferroni's test).

3.7. Effect of i.c. administration of CRF on morphine withdrawal jumping behavior

I.c. administration of CRF (1–200 ng) attenuated morphine withdrawal jumping behavior (Fig. 6). A significant effect was observed at the dose of 200 ng (mean number of jumps and S.E.M. was 9.1 ± 4.32, $P < 0.01$) compared with the group i.c. injected with vehicle.

4. Discussion

In this study, we investigated the effect of i.c. administration of interleukin-1β on naloxone-precipitated withdrawal jumping behavior in morphine-dependent mice. Since the development of physical dependence on morphine is well correlated with the development of tolerance (Way, 1993), we used morphine-tolerant mice selected with the tail-pinch assay. We adopted i.c. injection for central administration of interleukin-1β in the present experiments because of the inhibitory effect of i.c.v. injection of vehicle on morphine withdrawal jumping behavior. This inhibitory effect is consistent with that described in a previous report in which i.c.v. administration of saline inhibited naloxone-precipitated jumping in morphine-dependent mice (Miyamoto and Takemori, 1993).

In the present study, we found that i.c. administration of interleukin-1β attenuated naloxone-precipitated withdrawal jumping behavior in morphine-dependent mice in a dose-dependent manner. As heat-inactivated interleukin-1β (1 ng) had no effect on withdrawal jumping behavior, this inhibitory effect is due to interleukin-1β itself, but not due to heat-stable components like endotoxin which might contaminate the interleukin-1β solution. In addition, co-administration of interleukin-1 receptor antagonist, an endogenous antagonist peptide against interleukin-1, significantly antagonized the inhibitory effect of interleukin-1β on morphine withdrawal jumping behavior. These results suggest that interleukin-1β causes the inhibitory effect on morphine withdrawal jumping behavior through interleukin-1 receptors in the brain. In this study, the dose of interleukin-1 receptor antagonist needed to significantly antagonize the effect of interleukin-1β was 1000 times higher than that of interleukin-1β. It is reported that 100–10 000-fold excess interleukin-1 receptor antagonist is required to block several effects of interleukin-1 in vivo, such as induction of fever, hypotention, neutrophilia (Dinarello and Thompson, 1991) and sleep (Opp and Krueger, 1991).

A high density of ^{125}I-labeled interleukin-1 binding sites has been shown in the ventromedial hypothalamus and dorsal tegmental nucleus, a moderate density in the anterior preoptic area, amygdaloid nuclei, substantia nigra and raphe nuclei, and a low density in the nucleus accumbens (Farrar et al., 1987). In addition, in situ hybridization studies demonstrated that type I interleukin-1 receptor mRNA is expressed in the dorsal raphe nucleus (Cunningham et al., 1992). These regions are known to be involved in the development of morphine dependence and in the expression of withdrawal syndrome. Namely, naloxone-precipitated jumping behavior is blocked by lesioning of the ventromedial hypothalamus (Kerr and Pozuelo, 1971) or raphe nuclei (Bläsig et al., 1976). Injection of naloxone into the amygdala elicits jumping behavior in morphine-dependent rats (Calvino et al., 1979). Furthermore, injection of naloxone into the substantia nigra or ventral tegmental area precipitates withdrawal in morphine-dependent rats (Baumeister et al., 1989) and injection of metylnaloxonium into the nucleus accumbens of morphine-dependent rats produces place aversion (Stinus et al., 1990). These findings suggest a possibility of some interaction between interleukin-1 and opioid systems in the brain.

α-MSH is a proopiomelanocortin-derived pituitary hormone. It has been reported that i.c.v. administration of α-MSH antagonizes morphine-induced analgesia and the development of morphine dependence, but not the expression of naloxone-precipitated withdrawal in acute morphine-dependent mice (Contreras and Takemori, 1983). In this study, i.c. administration of α-MSH at the dose of 100 or 300 ng alone did not affect the number of jumps, indicating that α-MSH does not prevent naloxone-precipitated withdrawal in chronic morphine-dependent mice. At the dose of 1 μg, α-MSH decreased the number of jumps. However, it also elicited frequent stretching and yawning behaviors not only in morphine-dependent mice but also in naive mice. Co-administration of α-MSH (100 or 300 ng/mouse) with interleukin-1β antagonized the inhibitory effect of interleukin-1β on morphine withdrawal jumping behavior. It has been shown that α-MSH inhibits a variety of in vivo effects of interleukin-1 like fever, sleep, hyperalgesia, hepatic synthesis of acute phase protein, neutrophilia, enhancement of plasma corticosterone (Dinarello, 1991; Kluger, 1991). The mechanism for these antagonistic effects of α-MSH is not clear. It has no competitive activity for interleukin-1 binding to rat brain (Farrar et al., 1987).

The effect of interleukin-1β on jumping behavior was antagonized also by co-administration with α-helical CRF-(9–41), a CRF receptor antagonist. Moreover, i.c. administration of CRF could attenuate naloxone-precipitated withdrawal jumping behavior. These results suggest that endogenous CRF is involved in the inhibitory effect of interleukin-1β. Opioids have various effects on neuroendocrine functions. In particular, the effects on the hypothalamo-pituitary-adrenal axis have been well studied (Pechnick, 1993). It has been

reported that acute administration of opioid agonists activates the hypothalamo-pituitary-adrenal axis and elicits the release of CRF. Subsequently CRF stimulates the release of adrenocorticotropic hormone (ACTH) and β-endorphin from pituitary. Chronic administration of opioid agonists is known to result in development of tolerance to their effects on the hypothalamo-pituitary-adrenal axis in rat (Ignar and Kuhn, 1990) and to reduce the release of CRF from the hypothalamus in rat (Buckingham and Cooper, 1984). In addition, a significant reduction of β-endorphin-like immunoreactivity in plasma was observed in chronically morphine-treated rats (Martínez et al., 1990). Interleukin-1 stimulates the expression of CRF gene in the hypothalamus and the release of CRF, and then elicits the release of ACTH and β-endorphin (Suda et al., 1990; Sapolsky et al., 1987; Berkenbosch et al., 1987). Administration of β-endorphin has been shown to suppress withdrawal jumping behavior in morphine-dependent mice (Tseng et al., 1976). Moreover, it has been reported that interleukin-1 enhances ^{125}I-β-endorphin binding to rat brain slice (Wiedermann, 1989). The inhibitory effect of interleukin-1β on morphine withdrawal jumping behavior might be partly attributed to an enhancement of the release of β-endorphin and of its binding to opioid receptors. These findings, including the results of our present study, suggest the possibility that interleukin-1β attenuates morphine withdrawal jumping behavior through the activation of the hypothalamo-pituitary-adrenal axis, which is suppressed in chronically morphine-treated mice.

As the inhibitory effect of interleukin-1β on morphine withdrawal jumping behavior was not completely antagonized by the co-administration with α-helical CRF, it is conceivable that there are other mechanisms for interleukin-1β to produce its inhibitory effect on morphine withdrawal jumping behavior, besides the mechanism through endogenous CRF. Prostaglandins, which mediate several effects of interleukin-1 including fever (Dinarello, 1991) and hyperalgesia (Oka et al., 1993), might partly mediate this inhibitory effect. Indeed, it has been shown that the cyclooxygenase inhibitor indomethacin facilitates acute dependence on morphine (Nielsen and Sparber, 1985). Another possible mechanism is the direct inhibitory action of interleukin-1β on neuronal cells. It has been demonstrated that interleukin-1β depresses voltage-dependent calcium currents in CA1 hippocampal neurons (Plata-Salamán and ffrench-Mullen, 1994) and augments $GABA_A$ receptor function in cortical synaptosomes (Miller et al., 1990). Because both calcium channel blockers (Ramkumar and El-Fakahany, 1988) and benzodiazepine receptor agonists (Valverde et al., 1992) have been shown to suppress naloxone-precipitated morphine withdrawal syndrome, depression of calcium channels and enhancement of GABAergic activity by interleukin-1β may contribute to the attenuation of morphine withdrawal jumping behavior.

Further investigations are needed to clarify the mechanisms for the inhibitory effect of interleukin-1β on morphine withdrawal jumping behavior.

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