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Biphasic effects of intracerebroventricular interleukin-1β on mechanical nociception in the rat

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Abstract

The effects of interleukin-1β on the mechanical nociceptive threshold in the rat were examined using the paw-pressure test. An intracerebroventricular (i.c.v.) injection of interleukin-1β at doses of 10 and 100 pg/rat caused hyperalgesia to mechanical stimuli. Higher doses of interleukin-1β (1 and 10 ng/rat) induced an analgesic effect. The coadministration of the interleukin-1 receptor antagonist completely antagonized the hyperalgesic and analgesic effects of interleukin-1β. An i.c.v. injection of α-helical-corticotropin-releasing factor [9–41] 15 min prior to interleukin-1β administration completely blocked the hyperalgesic and analgesic effects of interleukin-1β. An i.c.v. injection of sodium salicylate 15 min prior to interleukin-1β administration inhibited the hyperalgesic effect of interleukin-1β, but not the analgesic effect. These results suggest that interleukin-1β produces biphasic effects on the mechanical nociceptive threshold through the interleukin-1 receptor in the brain and that a corticotropin-releasing factor-mediated pathway is involved. Furthermore, the hyperalgesic effect of interleukin-1β may be mediated by prostaglandins.

Keywords: Interleukin-1β; Biphasic effect; Mechanical nociception; (Rat)

1. Introduction

Interleukin-1β is a cytokine which plays important roles in the immune and inflammatory systems (Dinarello, 1991). Interleukin-1 has various effects also on the central nervous system, such as increasing body temperature (Kluger, 1991), inducing slow-wave sleep (Krueger et al., 1984), anorexia (Mrosovsky et al., 1989), activating the hypothalamus-pituitary-adrenal axis (Berkenbosch et al., 1987) and attenuating neuronal activity in the hippocampus (Plata-Salaman and ffrench-Mullen, 1992) and amygdala (Yu and Shinnick-Gallagher, 1994). We reported the increased expression of interleukin-1β mRNA in the brain after the administration of a neurostimulant (methamphetamine, Yamaguchi et al., 1991), immobilization stress (Minami et al., 1991) and induced convulsions (Minami et al., 1990). In addition, the inhibition of hippocampal long-term potentiation by interleukin-1β was demonstrated by electrophysiological means (Katsuki et al., 1990). These findings suggest that interleukin-1 is produced and plays a role as neuromodulator in the brain. In this context, the effects of centrally administered interleukin-1 on nociception have been examined. Nakamura et al. (1988) have demonstrated that intracisternal administration of interleukin-1α produces an analgesic effect on phenylquinone-induced writhing behavior in mice. In contrast, Oka et al. (1993) discovered, using the hot-plate test, that an intracerebroventricular (i.c.v.) administration of interleukin-1β caused hyperalgesia in the rat and this effect was inhibited by the prior administration of sodium salicylate but not α-helical-corticotropin-releasing factor [9–41] (α-helical-CRF [9–41]), a corticotropin-releasing factor (CRF) receptor antagonist. Although these findings suggest that interleukin-1 has some modulatory effects on nociceptive transmission, the direction of the effects, that is, analgesia or hyperalgesia, is controversial. These conflicting results might be due to differences in experimental conditions, such as the methods used to test nociception, animal species or the doses of interleukin-1. In these studies, chemical and thermal stimuli were used as noxious

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stimuli in mice and rats, respectively. However, the effects of central administration of interleukin-1 on mechanical nociception remain to be examined. In this study, we investigated the effects of i.c.v. administration of interleukin-1β on mechanical nociception in the rat using the paw-pressure test. Furthermore, we examined the involvement of endogenous CRF and prostaglandins in the effects of interleukin-1β.

2. Materials and methods

2.1. Animals

All experiments using male Sprague-Dawley rats weighing 220–280 g (6–8 weeks old) followed the ethical guidelines for investigations of experimental pain in conscious animals (Zimmermann, 1983). Animals were kept at a constant ambient temperature (24 ± 1°C) under a 12-h light and dark cycle with free access to food and water. After arrival, rats were kept in plastic cages with chips for at least one day until a guide cannula was implanted.

2.2. Implantation of guide cannula

Under pentobarbital anesthesia (50 mg/kg i.p.), a stainless steel guide cannula (o.d. 0.7 mm) was stereotaxically (P 0.8, L 1.5, H 2.0) implanted according to the atlas of Paxinos and Watson (1986). After surgery, the animals were returned to the cages and housed individually.

2.3. Materials

Human recombinant interleukin-1β and the interleukin-1 receptor antagonist were gifts from Otsuka Pharmaceutical Co. (Tokushima, Japan). Sodium salicylate and α-helical-CRF were purchased from Sigma Chemical Co. (St. Louis, MO, USA). All other chemicals were purchased from Nacalai tesque (Kyoto, Japan).

2.4. Drug administration

Interleukin-1β and the interleukin-1 receptor antagonist were dissolved in phosphate-buffered saline (PBS, pH 7.6) containing 0.1% bovine serum albumin. Sodium salicylate and α-helical-CRF [9–41] were dissolved in saline. The doses of drugs used in this study are those referred to by Oka et al. (1993) except for the dose of α-helical-CRF [9–41], which was 10-fold higher, because it was not effective at the doses they used. All drugs were administered via the injection cannula which reached the lateral ventricle (P 0.8, L 1.5, H 4.0) when attached to the guide cannula. The drugs were administered i.c.v. in a volume of 5 μl at a constant rate of 10 μl/min. The interleukin-1 receptor antagonist was coadministered with interleukin-1β, while α-helical-CRF [9–41] and sodium salicylate were given 15 min prior to interleukin-1β. The doses of interleukin-1β injected were not revealed until the nociceptive threshold was measured.

2.5. Measuring the nociceptive threshold

The nociceptive threshold of the hind paw to mechanical stimulation was measured using an analgesimeter (Ugo Basile, Milan, Italy) with a cone-shape piston at a loading rate of 32 g/s, and the pressure eliciting paw withdrawal was determined. After 5–7 days of recovery after implantation of the guide cannula, the rats were habituated to the procedure for measuring the nociceptive threshold three times per day. After two days of habituation, the nociceptive threshold of each animal was measured following two additional habituation procedures, and the value of the threshold was taken as a control. Within 10 min after measuring the control value of the threshold, the drugs were administered as described above and the threshold was measured at 15, 30, 60, 90, 120, 150 and 180 min after the administration of interleukin-1β. In some experiments, rectal temperature was measured at 0, 60, 120 and 180 min after the administration of interleukin-1β. The nociceptive thresholds were measured between 12:00 and 16:00.

2.6. Statistical analysis

The nociceptive threshold at each time point is presented as the mean of the percentage of the control ± S.E.M. Differences were compared using the Mann-Whitney's U-test. $P < 0.05$ was considered significant.

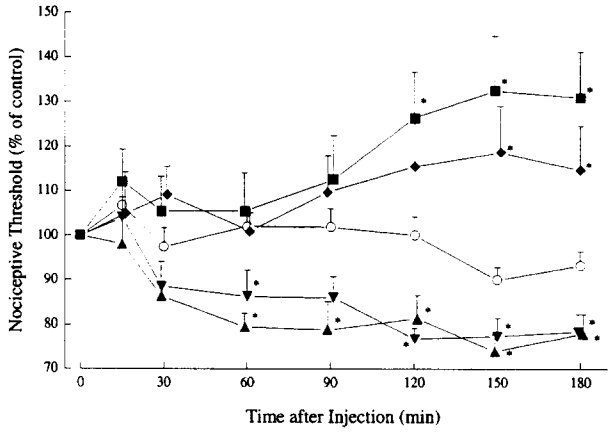

Fig. 1. Time courses of the effects of i.c.v. injection of interleukin-1β on the mechanical nociceptive threshold. The nociceptive threshold at each time point is presented as the mean percentage of the control ± S.E.M. ○, vehicle ($n = 26$); ▼, interleukin-1β 10 pg ($n = 10$); ▲, interleukin-1β 100 pg ($n = 9$); ◆, interleukin-1β 1 ng ($n = 10$) and ■, interleukin-1β 10 ng ($n = 9$). * $P < 0.05$ compared with the vehicle-injected group (Mann-Whitney's U-test).

3. Results

3.1. Effects of an i.c.v. injection of interleukin-1β on the mechanical nociceptive threshold

We examined the effects of i.c.v. injection of interleukin-1β on the nociceptive threshold of paw-pressure stimulation (Fig. 1a). At doses of 10 and 100 pg/rat, the threshold tended to decrease at 30 min and it was significantly lowered at 60 min after the injection when compared with that of the group injected with the vehicle (PBS + 0.1% bovine serum albumin). The nociceptive thresholds were decreased to about 80% of the control level and remained at these levels 180 min after drug administration.

However, 1 and 10 ng/rat of interleukin-1β tended to increase the nociceptive threshold at 90 min after administration. The i.c.v. administration of interleukin-1β at a dose of 1 ng/rat significantly elevated the nociceptive threshold to 118.60 ± 10.51% and 114.74 ± 9.94% of the control level at 150 and 180 min, respectively ($n = 10$). Interleukin-1β at a dose of 10 ng/rat significantly raised the nociceptive threshold to 126.54 ± 10.18%, 132.41 ± 12.37% and 130.97 ± 10.27% of the control level at 120, 150 and 180 min after administration, respectively ($n = 9$).

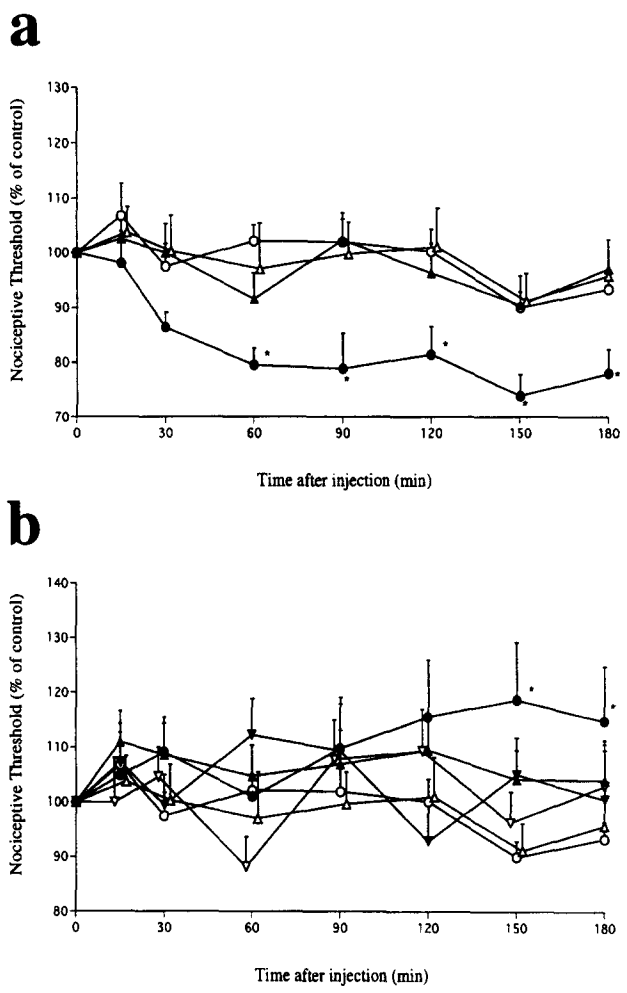

Fig. 2. (a) Time course of the effect of simultaneous injection of the interleukin-1 receptor antagonist and interleukin-1β (100 pg) on the hyperalgesic effect. ○, vehicle ($n = 26$); ●, interleukin-1β 100 pg ($n = 9$); △, interleukin-1 receptor antagonist 100 ng ($n = 12$) and ▲, interleukin-1 receptor antagonist 100 ng + interleukin-1β 100 pg ($n = 14$). * $P < 0.05$ compared with the group given vehicle (Mann-Whitney's U-test). (b) Time course of the effect of the simultaneous injection of interleukin-1 receptor antagonist and interleukin-1β (1 ng) on the analgesic effect. ○, vehicle ($n = 26$); ●, interleukin-1β 1 ng ($n = 10$); △, interleukin-1 receptor antagonist 100 ng ($n = 12$); ▽, interleukin-1 receptor antagonist 1 μg ($n = 7$); ▲, interleukin-1 receptor antagonist 100 ng + interleukin-1β 1 ng ($n = 16$) and ▼, interleukin-1 receptor antagonist 1 μg + interleukin-1β 1 ng ($n = 10$). * $P < 0.05$ compared with the group injected with the vehicle (Mann-Whitney's U-test).

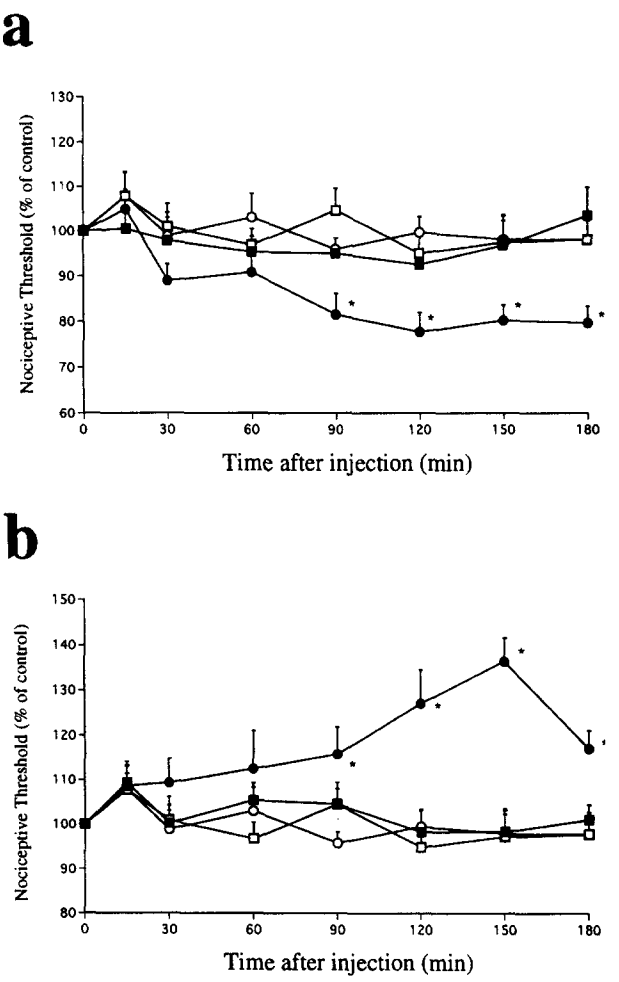

Fig. 3. (a) Time course of the effect of α-helical-CRF [9–41] (1 μg, i.c.v.) on the hyperalgesic effect of interleukin-1β (100 pg, i.c.v.). α-helical-CRF [9–41] was administered 15 min before interleukin-1β. ○, saline + PBS ($n = 15$); □, α-helical-CRF [9–41] 1 μg + PBS ($n = 14$); ●, saline + interleukin-1β 100 pg ($n = 11$) and ■, α-helical-CRF [9–41] 1 μg + interleukin-1β 100 pg ($n = 7$). * $P < 0.05$ compared with the saline + PBS-injected group (Mann-Whitney's U-test). (b) Time course of the effect of α-helical-CRF [9–41] (1 μg, i.c.v.) on the analgesic effect of interleukin-1β (1 ng, i.c.v.). ○, saline + PBS ($n = 15$); □, α-helical-CRF [9–41] 1 μg + PBS ($n = 14$); ●, saline + interleukin-1β 1 ng ($n = 12$) and ■, α-helical-CRF [9–41] 1 μg + interleukin-1β 1 ng ($n = 6$). * $P < 0.05$ compared with the group given saline + PBS (Mann-Whitney's U-test).

3.2. Effects of the interleukin-1 receptor antagonist on the hyperalgesic and analgesic effects of interleukin-1β

An i.c.v. injection of the interleukin-1 receptor antagonist alone (100 ng or 1 μg/rat) did not alter the mechanical nociceptive threshold (Fig. 2b). The hyperalgesic effect of interleukin-1β (100 pg/rat) was completely blocked by the simultaneous administration of the interleukin-1 receptor antagonist at a dose of 100 ng which was 1000 times higher than that of interleukin-1β (Fig. 2a). A simultaneous injection of the interleukin-1 receptor antagonist at a dose of 1 μg/rat completely antagonized the analgesic effect of 1 ng/rat of interleukin-1β (Fig. 2b). Furthermore, the interleukin-1 receptor antagonist even at a lower dose (100 ng/rat) suppressed the analgesic effects of interleukin-1β (Fig. 2b).

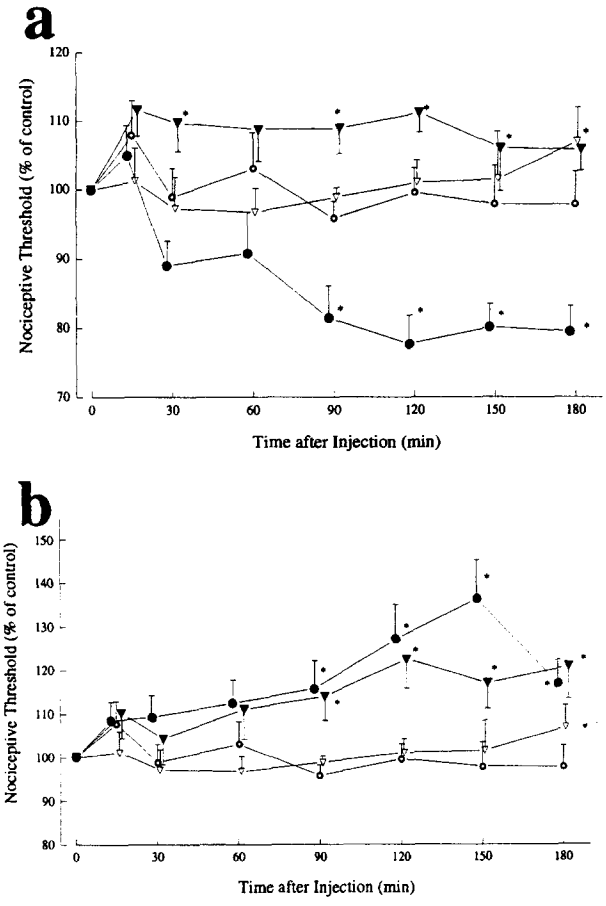

Fig. 4. (a) Time course of the effect of sodium salicylate (100 ng, i.c.v.) on the hyperalgesic effect of interleukin-1β (100 pg, i.c.v.). Sodium salicylate was administered 15 min prior to interleukin-1β. ○, saline + PBS ($n = 15$); ▽, sodium salicylate 100 ng + PBS ($n = 8$); ●, saline + interleukin-1β 100 pg ($n = 11$); ▼, sodium salicylate 100 ng + interleukin-1β 100 pg ($n = 8$). * $P < 0.05$ compared with the group given saline + PBS (Mann-Whitney's U-test). (b) Time course of the effect of sodium salicylate (100 ng, i.c.v.) on the analgesic effect of interleukin-1β (1 ng, i.c.v.). ○, saline + PBS ($n = 15$); ▽, sodium salicylate 100 ng + PBS ($n = 8$); ●, saline + interleukin-1β 1 ng ($n = 12$); ▼, sodium salicylate 100 ng + interleukin-1β 1 ng ($n = 10$). * $P < 0.05$ compared with group given saline + PBS (Mann-Whitney's U-test).

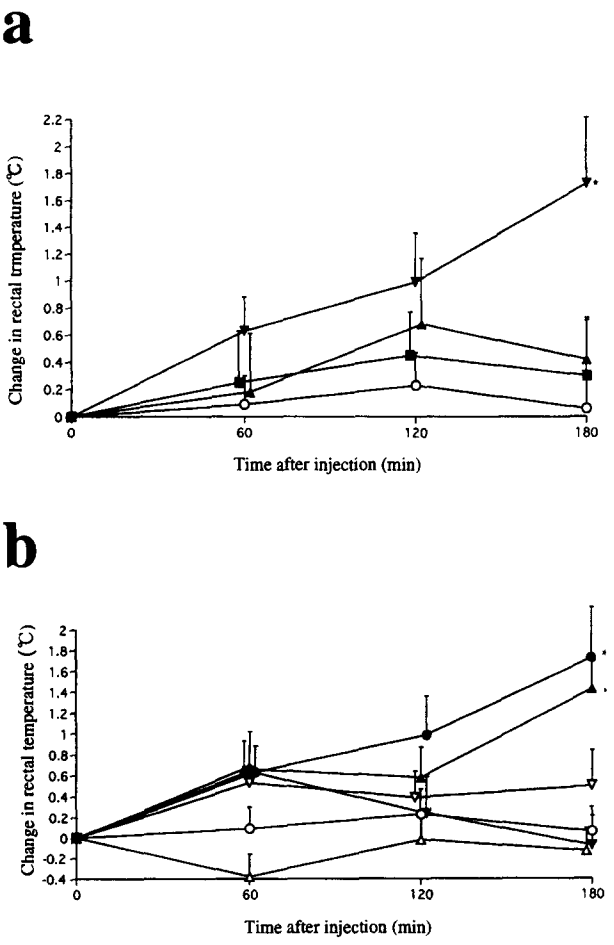

Fig. 5. (a) Time courses of the effects of i.c.v. administration of interleukin-1β on rectal temperature. The change in rectal temperature is presented as the mean percentage of the control ± S.E.M. ○, vehicle ($n = 14$); ■, interleukin-1β 10 pg ($n = 10$); ▲, interleukin-1β 100 pg ($n = 9$); ▼, interleukin-1β 1 ng ($n = 7$). * $P < 0.05$ compared with group given the vehicle (Mann-Whitney's U-test). (b) Time course of the effect of the simultaneous injection of interleukin-1 receptor antagonist on the pyrogenic effect of interleukin-1β (1 ng). ○ vehicle ($n = 14$); ● interleukin-1β 1 ng ($n = 7$); △, interleukin-1 receptor antagonist 100 ng ($n = 12$), ▽, interleukin-1 receptor antagonist 1 μg ($n = 7$); ▲, interleukin-1 receptor antagonist 100 ng + interleukin-1β 1 ng ($n = 16$); ▼, interleukin-1 receptor antagonist 1 μg + interleukin-1β 1 ng ($n = 10$). * $P < 0.05$ compared with the group given the vehicle (Mann-Whitney's U-test).

3.3. Effects of α-helical-CRF [9–41] on the hyperalgesic and analgesic effects of interleukin-1β

An i.c.v. injection of saline 15 min before interleukin-1β administration did not affect the hyperalgesic and analgesic effects of 100 pg/rat and 1 ng/rat of interleukin-1β, respectively (Fig. 3a,b). An i.c.v. injection of α-helical-CRF [9–41] (1 μg/rat) followed by PBS did not change the nociceptive threshold compared with the group given saline + PBS (Fig. 3a,b). The prior administration of α-helical-CRF [9–41] (1 μg/rat, i.c.v.) blocked the hyperalgesic (Fig. 3a) and analgesic (Fig. 3b) effects of interleukin-1β.

3.4. Effects of sodium salicylate on the hyperalgesic and analgesic effects of interleukin-1β

An i.c.v. injection of sodium salicylate (100 ng/rat) followed by PBS did not change the nociceptive threshold compared with that of the group given saline + PBS (Fig. 4a,b). An i.c.v. injection of sodium salicylate followed by interleukin-1β (100 pg/rat) not only blocked the hyperalgesic effect of interleukin-1β, but also significantly increased the nociceptive threshold compared with that of the group given saline + PBS (Fig. 4a). The prior administration of sodium salicylate did not significantly alter the analgesic effect of the higher dose (1 ng/rat) of interleukin-1β (Fig. 4b).

3.5. Effects of interleukin-1β and the interleukin-1 receptor antagonist on the rectal temperature

As shown in Fig. 5a, an i.c.v. injection of 1 ng/rat of interleukin-1β significantly increased the rectal temperature by 1.73 ± 0.49 C° ($n = 7$) at 180 min after the injection. However, the lower doses of interleukin-1β (10 pg and 100 pg/rat, i.c.v.) did not significantly change the rectal temperature. The increase in rectal temperature caused by interleukin-1β (1 ng/rat) was suppressed by simultaneous injection of 1 μg/rat of the interleukin-1 receptor antagonist, but not by the lower dose (100 ng/rat) at which it suppressed the analgesic effect of interleukin-1β. The interleukin-1 receptor antagonist alone (100 ng and 1 μg/rat) did not alter the rectal temperature.

4. Discussion

In this study, we demonstrated that interleukin-1β has biphasic effects on mechanical nociception depending upon the dose. Lower doses (10 pg and 100 pg/rat, i.c.v.) of interleukin-1β caused hyperalgesia, whereas higher doses (1 ng and 10 ng/rat, i.c.v.) were analgesic.

Nakamura et al. have demonstrated that the site of the analgesic effect of interleukin-1α is in the brain (Nakamura et al., 1988). However, Ferreira et al. showed that interleukin-1β given systemically is a potent hyperalgesic agent with a peripheral site of action (Ferreira et al., 1988). Although we observed the hyperalgesic effect of interleukin-1β at doses of 10 pg/rat or 100 pg/rat, the effect observed might derive from a peripheral effect of interleukin-1β. However, we could not observe any hyperalgesic effect after intraperitoneal administration of interleukin-1β (100 pg/rat, $n = 4$, data not shown). Thus, the sites of biphasic effects of i.c.v. interleukin-1β are in the brain.

Oka et al. (1993) have reported that an i.c.v. injection of interleukin-1β caused a hyperalgesic effect on thermal nociception in the rat hot plate test. In their report, there was a significant reduction of paw-lick latency after i.c.v. injection of interleukin-1β at doses of 100 pg/kg and 1 ng/kg, but not at higher doses (10 ng/kg to 1 μg/kg). Our findings that the lower doses of interleukin-1β elicited hyperalgesia in the paw pressure test are in agreement with those of Oka et al. (1993). However, in contrast with our results, they did not demonstrate any changes in thermal nociception at higher doses (10 ng/kg to 1 μg/kg) of the cytokine. This may be because their observation period (90 min) was shorter than ours. In this study, the mechanical nociceptive threshold increased between 120 and 180 min after the administration of interleukin-1β. Alternatively, it might be due to the difference in the modalities of nociceptive stimuli.

Nakamura et al. (1988) have reported that intracisternal injection of interleukin-1α to the mouse caused analgesia in the phenylquinone writhing test. In their study, interleukin-1α was administered at doses of 20–500 ng/kg. Their findings are not contradictory to our results obtained with the higher doses of interleukin-1β, as we found that interleukin-1β had analgesic effects at doses of 1 and 10 ng/rat, which roughly correspond to 5 and 50 ng/kg, respectively. However, they observed analgesic effects of interleukin-1α between 5 and 20 min after injection, whereas we demonstrated those of interleukin-1β between 120 and 180 min after administration. They examined the effect of interleukin-1α on chemical nociception in the mouse, whereas we examined the effect of interleukin-1β on mechanical nociception in the rat. It remains to be examined whether this discrepancy in the time course is due to differences in the species of animals, modalities of nociceptive stimuli or the cytokines.

We demonstrated that the co-administration of the interleukin-1 receptor antagonist blocked both the hyperalgesic and analgesic effects of interleukin-1β, suggesting that the biphasic effects of interleukin-1β on the mechanical nociceptive threshold are mediated by the interleukin-1 receptor. Types 1 and 2 of interleukin-1 receptors have been identified (Dinarello, 1991). However, the interleukin-1 receptor antagonist does not bind to the type 2 interleukin-1 receptor with high affinity (McMahan et al., 1991). Furthermore, type 1 (Yabuuchi et al., 1994), but not type 2 (unpublished observations), interleukin-1 receptor mRNA is expressed in the normal rat brain. These findings suggest that the biphasic effects of interleukin-1β on mechanical nociception are mediated by type 1 interleukin-1 receptor.

Interleukin-1β is known to be an endogenous pyrogen (Kluger, 1991). There is a possibility that the biphasic effects on mechanical nociceptive thresholds are secondary effects to fever induced by interleukin-1β. However, the hyperalgesic effect of interleukin-1β was produced at non-pyrogenic doses (10 pg and 100 pg/rat). Moreover, although the analgesic dose (1 ng/rat) of interleukin-1β significantly increased the body temperature, this effect was antagonized by co-administering the interleukin-1 receptor antagonist at a dose of 100 ng/rat, at which dose

the pyrogenic effect of interleukin-1β was not suppressed. These observations suggest that the hyperalgesic and analgesic effects of interleukin-1β are not secondary to its pyrogenic property.

It has been reported that i.c.v. injections of interleukin-1 activate CRF neurons in the hypothalamus (Ju et al., 1991). In this study, we demonstrated that the hyperalgesic and analgesic effects of interleukin-1β were inhibited by the prior administration of α-helical-CRF [9–41] at the same dose, suggesting that these effects of interleukin-1β on the nociceptive thresholds are mediated by endogenous CRF. Kita et al. (1993) have reported that the analgesic effects of interleukin-1α are inhibited by the administration of α-helical-CRF [9–41] in the mice writhing test. However, Oka et al. (1993) have reported that the hyperalgesia induced by interleukin-1β is not attenuated by α-helical-CRF [9–41] in the rat hot plate test. They used α-helical-CRF [9–41] at a dose of 100 ng/kg, which is about 40 times lower than that in our present study, which may explain the lack of effects on the inhibition of the thermal nociceptive threshold caused by interleukin-1β in their study.

It has been postulated that some of the effects of interleukin-1β on the CNS, including the increased body temperature (Kluger, 1991), are mediated by prostaglandins which are reportedly released by interleukin-1β in the brain (Dinarello and Bernheim, 1981). In this context, we demonstrated that the hyperalgesic but not the analgesic effect of interleukin-1β was mediated via a cyclooxygenase-dependent pathway. Moreover, an i.c.v. injection of prostaglandin E_2 elicits hyperalgesia in the rat hot plate test (Oka et al., 1994). These findings suggest that prostaglandin E_2 is synthesized in the brain following i.c.v. administration of interleukin-1β and that it probably mediates the hyperalgesic effect of the cytokine.

The hyperalgesic effect of the lower doses of interleukin-1β in the paw-pressure test was blocked by prior treatment with α-helical-CRF [9–41] and sodium salicylate. This suggests that the endogenous CRF and prostanoids function in parallel or in sequence to induce hyperalgesia. The fact that the analgesic effect of higher doses of interleukin-1β was blocked by α-helical-CRF [9–41], but not by sodium salicylate demonstrates that the analgesic effect of interleukin-1β is mediated by endogenous CRF and not by prostanoids.

Sodium salicylate caused the lower doses of interleukin-1β to induce the analgesic rather than the hyperalgesic effect. The reason for this inversion remains unclear. Further examination is necessary to elucidate this.

The i.c.v. administration of interleukin-1 modulates mechanical (this study), thermal (Oka et al., 1993) and chemical (Kita et al., 1993) nociception. Furthermore, neuronal stimulants (Minami et al., 1990; Yamaguchi et al., 1991) and immobilization stress (Minami et al., 1991) induce interleukin-1β mRNA expression in the rat brain. These findings suggest that interleukin-1 is produced in the brain and functions as a neuromodulator to regulate the transmission of nociceptive information.

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References

Berkenbosch, F., J.V. Oers, A.D. Rey, F. Tilders and H. Besedovsky, 1987, Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1, Science 238, 524.

Dinarello, C.A., 1991, Interleukin-1 and interleukin-1 antagonism, Blood 77, 1627.

Dinarello, C.A. and H.A. Bernheim, 1981, Ability of human leukocytic pyrogen to stimulate brain prostaglandin synthesis in vitro, J. Neurochem. 37, 702.

Ferreira, S.H., Lorenzetti, B.B., Bristow, A.F. and Poole, S., 1988, Interleukin-1β as a potent hyperalgesic agent antagonized by a tripeptide analogue, Nature 334, 698.

Ju, G., J. Bo-Quan and H. Chuan-Shu, 1991, Activation of corticotropin-releasing factor-containing neurons in the paraventricular nucleus of the hypothalamus by interleukin-1 in the rat, Neurosci. Lett. 132, 151.

Katsuki, H., S. Nakai, Y. Hirai, K. Akaji, Y. Kiso and M. Satoh, 1990, Interleukin-1β inhibits long-term potentiation in the CA3 region of mouse hippocampal slices, Eur. J. Pharmacol. 181, 323.

Kita, A., K. Imano and H. Nakamura, 1993, Involvement of corticotropin-releasing factor in the antinociception produced by interleukin-1 in mice, Eur. J. Pharmacol. 237, 317.

Kluger, M.J., 1991, Fever: role of pyrogens and cryogens, Physiol. Rev. 71, 93.

Krueger, J.M., J. Walter, C.A. Dinarello, S.M. Wolff and L. Chedid, 1984, Sleeping – promoting effects of endogenous pyrogen (interleukin-1), Am. J. Physiol. 246, R994.

McMahan, C.J., J.L. Slack, B. Mosley, D. Cosman, S.D. Lupton, L.L. Brunton, C.E. Grubin, J.M. Wignall, N.A. Jenkins, C.I. Brannan, N.G. Copeland, K. Huebner, C.M. Croce, L.A. Cannizzarro, D. Benjamin, S.K. Dower, M.K. Spriggs and J.E. Sims, 1991, A novel IL-1 receptor, cloned from B cells by mammalian expression, is expressed in many cell types, EMBO J. 10, 2821.

Minami, M., Y. Kuraishi, T. Yamaguchi, S. Nakai, Y. Hirai and M. Satoh, 1990, Convulsants induce interleukin-1β messenger RNA in rat brain, Biochem. Biophys. Res. Commun. 171, 832.

Minami, M., Y. Kuraishi, T. Yamaguchi, S. Nakai, Y. Hirai and M. Satoh, 1991, Immobilization stress induces interleukin-1β mRNA in the rat hypothalamus, Neurosci. Lett. 123, 254.

Mrosovsky, N., L.A. Molony, C.A. Conn and M.J. Kluger, 1989, Anorexic effects of interleukin 1 in the rat, Am. J. Physiol. 257, R1315.

Nakamura, H., K. Nakanishi, A. Kita and T. Kadokawa, 1988, Interleukin-1 induces analgesia in mice by a central action, Eur. J. Pharmacol. 149, 49.

Oka, T., S. Aou and T. Hori, 1993, Intracerebroventricular injection of interleukin-1β induces hyperalgesia in rats, Brain Res. 624, 61.

Oka, T., S. Aou and T. Hori, 1994, Intracerebroventricular injection of

prostaglandin E_2 induces thermal hyperalgesia in rats: the possible involvement of EP_3 receptors, Brain Res. 663, 287.

Paxinos, G. and C. Watson, 1986, The Rat Brain in Stereotaxic Coordinates (Academic Press, Australia).

Plata-Salaman, C.R. and J.M.H. Ffrench-Mullen, 1992, Interleukin-1β depresses calcium currents in CA1 hippocampal neurons at pathophysiological concentrations, Brain Res. Bull. 29, 221.

Yabuuchi, K., M. Minami, S. Katsumata and M. Satoh, 1994, Localization of type I interleukin-1 receptor mRNA in the rat brain, Mol. Brain Res. 27, 27.

Yamaguchi, T., Y. Kuraishi, M. Minami, K. Yabuuchi and M. Satoh, 1991, Involvement of central β-adrenoceptors in the induction of hypothalamic interleukin-1β mRNA by methamphetamine, Neurosci. Res. 12, 432.

Yu, B. and P. Shinnick-Gallagher, 1994, Interleukin-1β inhibits synaptic transmission and induces membrane hyperpolarization in amygdala neurons, J. Pharmacol. Exp. Ther. 271, 590.

Zimmermann, M., 1983, Ethical guidelines for investigations of experimental pain in conscious animals, Pain 16, 109.