0022-3565/00/2921-0181$03.00/0
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
JPET 292:181–187, 2000

Vol. 292, No. 1
Printed in U.S.A.

Corticotropin-Releasing Hormone$_1$ Receptors Mediate Consensus Interferon-α YM643-Induced Depression-Like Behavior in Mice

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Accepted for publication September 8, 1999 This paper is available online at http://www.jpet.org

ABSTRACT

Depression-like behavior induced by YM643, a consensus interferon-α (IFN-α), was evaluated with the tail-suspension test in mice and compared with depression-like behavior induced by sumiferon, a natural IFN-α. To investigate the mechanism of IFN-α-induced depression-like behavior, the effects of the tricyclic antidepressant imipramine, the cyclooxygenase inhibitor indomethacin, the opioid receptor antagonist naloxone, and the selective corticotropin-releasing hormone receptor antagonist CP-154,526 on IFN-α-induced depression-like behavior were evaluated. Intravenously injected YM643 (2×10^8–2×10^9 U/kg) and sumiferon (2×10^6–2×10^7 I.U./kg) dose-dependently increased immobility time. Repeated s.c. injection of either YM643 (6×10^6–6×10^8 U/kg) or sumiferon (6×10^4–6×10^6 I.U./kg) for 7 days also dose-dependently increased immobility time. After i.c.v. injection of either YM643 (2×10^6 U/mouse) or sumiferon (6×10^4 I.U./mouse), significant prolongation of immobility time also was observed. Pretreatment with imipramine (30 mg/kg s.c.) significantly reduced the YM643- or sumiferon-induced increases in immobility time. CP-154,526 (0.3–3 mg/kg s.c.) dose-dependently reduced YM643- or sumiferon-induced increases in immobility time with ID_{50} values of 0.6 mg/kg against YM643 and 1.3 mg/kg against sumiferon. However, neither indomethacin (10 mg/kg s.c.) nor naloxone (3 mg/kg s.c.) had any effect on YM643- or sumiferon-induced increases in immobility time. These results suggest that IFN-α centrally induces depression-like behavior in mice that can be alleviated with imipramine. The results also suggest that activation of corticotropin-releasing hormone receptors is involved in IFN-α-induced depression-like behavior, but the prostaglandin and opioid systems do not participate in this process.

YM643, a consensus interferon-α (IFN-α), is a synthetic, recombinant type I IFN. Its primary structure was derived by assigning the most commonly observed amino acid found at each position in several IFN-α nonallelic subtypes to generate a consensus sequence. Consensus IFN-α is effective in treating chronic hepatitis C (Tong et al., 1997). However, psychiatric side effects are common and frequently cause discontinuation of therapy. Among a variety of psychiatric side effects, depression is the most serious because it sometimes leads to suicide (Malaguarnera et al., 1998). Unfortunately, the mechanism by which IFN-α induces depression is not clear.

Several groups reported that IFN-α-induced depression in patients with hepatitis C could be successfully treated with antidepressants such as imipramine, amitriptyline, fluoxetine, or mianserin (Levenson and Fallon, 1993; Otsubo et al., 1997). It also was reported that IFN-α increased prostaglandin (PG) release in mice (Ohdo et al. 1997). In cats, i.c.v.-injected PGs show central nervous system (CNS) depressant effects such as immobility (Holmes and Trim, 1985). Plasma PG concentrations are elevated in patients with depression (Calabrese et al., 1986). Moreover, IFN-α is known to bind to opioid receptors; IFN-α displaces [^{3}H]naloxone bound to rat cerebral cortical tissue (Menzies et al., 1992). Recently, it was reported that plasma corticotropin-releasing hormone (CRH) levels increase in patients with depression (Catalan et al., 1998; Mitchell, 1998), and that the selective CRH_1 receptor antagonist CP-154,526 showed antidepressant-like effects in rats with stress-induced depression-like behavior (Mansbach et al. 1997). Interestingly, IFN-α was reported to stimulate the hypothalamic-pituitary-adrenal axis of rats and CRH release in isolated rat brain (Gisslinger et al., 1993; Raber et al., 1997).

The mouse tail-suspension test is a good model for human depression and has been frequently used to evaluate the efficacy of drugs designed to treat depression (Steru et al.,

Received for publication July 1, 1999.

ABBREVIATIONS: IFN-α, interferon-α; PG, prostaglandin; CNS, central nervous system; CRH, corticotropin-releasing hormone; IL-1β, interleukin-1β.

1985; Perrault et al., 1992). To examine the potency of YM643 in causing depression-like behavior and to elucidate the mechanism by which IFN-α induces depression-like behavior, the effect of YM643 was evaluated with the tail-suspension test in mice. The results were compared with those for sumiferon, a natural IFN-α. Additionally, imipramine, indomethacin, naloxone, and CP-154,526 were used to clarify the mechanism of IFN-α-induced depression-like behavior.

Materials and Methods

Animals. Male ddY mice weighing 23 to 36 g (SLC, Hamamatsu, Japan) were used. The animals were given ordinary laboratory food and tap water ad libitum and housed under artificial light for 13 h/day (from 7:30 AM to 8:30 PM). All experiments were performed in compliance with the regulations of the Animal Ethical Committee of Yamanouchi Pharmaceutical.

Tail-Suspension Test. The tail-suspension test was based on the method of Steru et al. (1985). Mice were suspended by the tail for 6 min, and the immobility time was measured.

Simple Technique for i.c.v. Injection of Drug. A cannula for i.c.v. injection of drugs was inserted according to the method of Nakajima et al. (1993) with minor modifications. Mice were anesthetized with sodium pentobarbital (80 mg/kg i.p.) and placed in a stereotaxic frame (Type 900; David Kopf Instruments, Tujunga, CA). A hole was made through the skull with a needle aimed 0.9 mm lateral to the central suture and 0.4 mm posterior to the bregma. A 24-gauge cannula beveled at one end over a distance of 3.2 mm (Safelet-Cas; Nipro, Osaka, Japan) was implanted into the third cerebral ventricle for i.c.v. injection. The cannula was fixed to the skull with dental cement and capped with silicon. Animals were used experimentally 5 to 7 days after implantation.

Experimental Protocols. To obtain a dose-response curve for YM643- and sumiferon-induced depression as measured by the tail-suspension test, a bolus dose of each drug was i.v. injected into mice. The tail-suspension test was performed 15 min after drug administration. Mice also were s.c. injected with YM643 and sumiferon once a day for 7 days, and a dose-response curve also was obtained at the end of repeated treatment; the tail-suspension test was performed 30 min after the last drug administration. To investigate the site where IFN-α acts to induce depression, the effects of i.c.v.-injected YM643 and sumiferon on depression were examined with the tail-suspension test. For i.c.v. injection, a 24-gauge injection insert was attached to a microsyringe with PE-20 tubing. YM643 and sumiferon were i.c.v. injected over 30 s, and the tail-suspension test was performed 15 min after i.c.v. administration.

In another series of experiments, the inhibitory effects of imipramine (30 mg/kg s.c.), naloxone (3 mg/kg s.c.), indomethacin (10 mg/kg s.c.), and CP-154,526 (0.3–3 mg/kg s.c.) on YM643- or sumiferon-induced depression were examined. Imipramine at a dose of 30 mg/kg s.c. was reported to have a sufficient antidepressant effect in mice (Galeotti et al., 1999). Indomethacin, naloxone, and CP-154,526 at s.c. doses of 10, 3, and 3 mg/kg, respectively, also were reported to sufficiently block cyclooxygenase, opioid receptors, and CRH_1 receptors, respectively, in rats (Little et al., 1995; Lundkvist et al., 1996; Serrano et al., 1998). Imipramine, indomethacin, naloxone, or CP-154,526 were injected 30 min before YM643 (2×10^9 U/kg i.v.) or sumiferon (2×10^7 I.U./kg i.v.) administration. The tail-suspension test was performed 15 min after YM643 or sumiferon administration.

Locomotor Activity. Twelve mice were assigned to each treatment group. To measure the amount of locomotor activity for 5 min with a locomotor activity measuring apparatus (SCANET MV-10; Toyo Sangyo Co., Ltd, Toyama, Japan), three animals at a time were placed in the box on a measuring apparatus before and 0.25, 0.5, 1, and 2 h after YM643 (2×10^9 U/kg i.v.) or sumiferon (2×10^7 I.U./kg i.v.) administration. The locomotor activity was calculated from four determinations.

Statistics. All values are expressed as means ± S.E., or as means with 95% CL. Linear regression analysis was used to obtain ID_{50} values. The differences between treatment groups were compared by Dunnett's test and Tukey's test. Probabilities of <5% ($P < .05$) were considered significant.

Drugs. YM643 (IFN alphacon-1), a consensus IFN-α, was prepared by Amgen Inc. (Thousand Oaks, CA). CP-154,526, butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-amine hydrochloride, was synthesized by the Yamanouchi Pharmaceutical Co., Ltd. (Ibaraki, Japan). Sumiferon was purchased from Sumitomo Pharmaceuticals Co., Ltd. (Osaka, Japan). Imipramine hydrochloride and naloxone hydrochloride were purchased from Sigma Chemical Co. (St. Louis, MO). Indomethacin was purchased from Wako Pure Chemical (Osaka, Japan). Imipramine and naloxone were dissolved in physiological saline. Indomethacin was dissolved in a minimum amount of 1 N NaOH and diluted with a 200 mM $NaHCO_3$ solution. CP-154,526 was dissolved in a minimum amount of 0.1 N HCl and diluted with physiological saline. YM643 was diluted with phosphate-buffered saline containing 0.01% polyoxyethylenesorbitan mono-oleate. Sumiferon was diluted with distilled water containing 0.15% human albumin (Sigma Chemical Co.), 0.076% glycine (Wako Pure Chemical), and 0.122% tris(hydroxymethyl)aminomethane (Sigma Chemical Co.). Drugs were administered to mice at a volume of 1 ml/kg i.v., 1 ml/kg s.c., or 10 μl/mouse i.c.v. All drug doses are given as the free base. Activities of YM643 and sumiferon are expressed as U and I.U., respectively, and both 1 U and 1 I.U. show 50% protection against vesicular stomatitis virus infection in human HeLa cells.

Results

YM643 and Sumiferon-Induced Depression-Like Behavior. The immobility time during a 6-min tail-suspension test was 70.7 ± 7.2 s in vehicle-treated mice ($n = 40$). Both i.v. injected YM643 (2×10^8–2×10^9 U/kg) and sumiferon (2×10^6–2×10^7 I.U./kg) dose-dependently increased immobility time in mice (Fig. 1). Repeated s.c. injection of either YM643 (6×10^6–6×10^8 U/kg) or sumiferon (6×10^4–6×10^6 I.U./kg) once a day for 7 days also dose-dependently increased immobility time (Fig. 2). YM643 (2×10^6 U/mouse) and sumiferon (6×10^4 I.U./mouse) injected directly into cerebral ventricles significantly increased immobility time (Fig. 3). The depression-inducing effect of sumiferon was ~10 to 100 times more potent than that of YM643 in single i.v., repeated s.c., and single i.c.v. dosing.

Mechanisms of IFN-α-Induced Depression-Like Behavior. Imipramine (30 mg/kg s.c.) decreased tail-suspension-induced immobility in mice (Fig. 4). Pretreatment with imipramine significantly reduced the increased immobility time induced by YM643 at 2×10^9 U/kg i.v. or sumiferon at 2×10^7 I.U./kg i.v. (Fig. 4). A single s.c. injection of indomethacin (10 mg/kg) did not affect immobility time (Fig. 5). Pretreatment with indomethacin had no effect on increase in immobility time induced by YM643 or sumiferon (Fig. 5). A single s.c. injection of naloxone (3 mg/kg) slightly increased immobility time (Fig. 6). Pretreatment with naloxone had no effect on the increased immobility time induced by YM643 or sumiferon (Fig. 6). However, CP-154,526 (3 mg/kg s.c.), a selective CRH_1 receptor antagonist, significantly reversed the increased immobility induced by YM643 or sumiferon without affecting immobility time in vehicle-treated mice (Fig. 7). This effect of CP-154,526 (0.3–3 mg/kg s.c.) was dose dependent, and the ID_{50} values of CP-154,526 in alleviating YM643- or sumiferon-induced depression were 0.6 (0.001–1.3) or 1.3 (0.5–4.7) mg/kg s.c., respectively (Fig. 8).

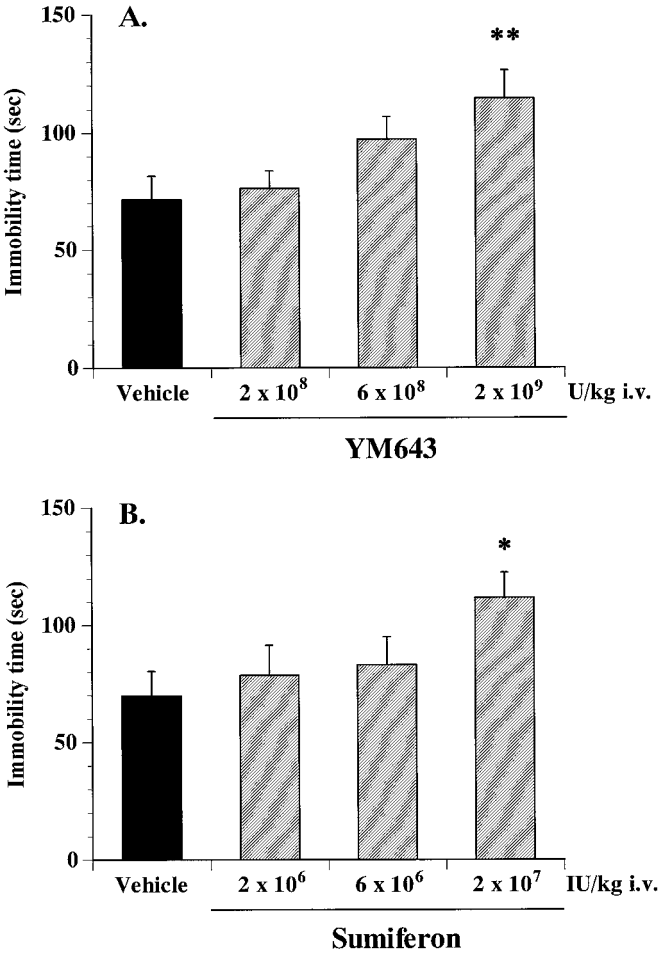

Fig. 1. Effect of i.v. injected YM643 (A) and sumiferon (B) on immobility time in the mouse tail-suspension test. Drugs were i.v. injected into mice 15 min before the test. Each column represents the mean ± S.E. of total immobility time during 6 min calculated from 20 animals. $^{*}P < .05$, $^{**}P < .01$ versus vehicle-treated group (Dunnett's test).

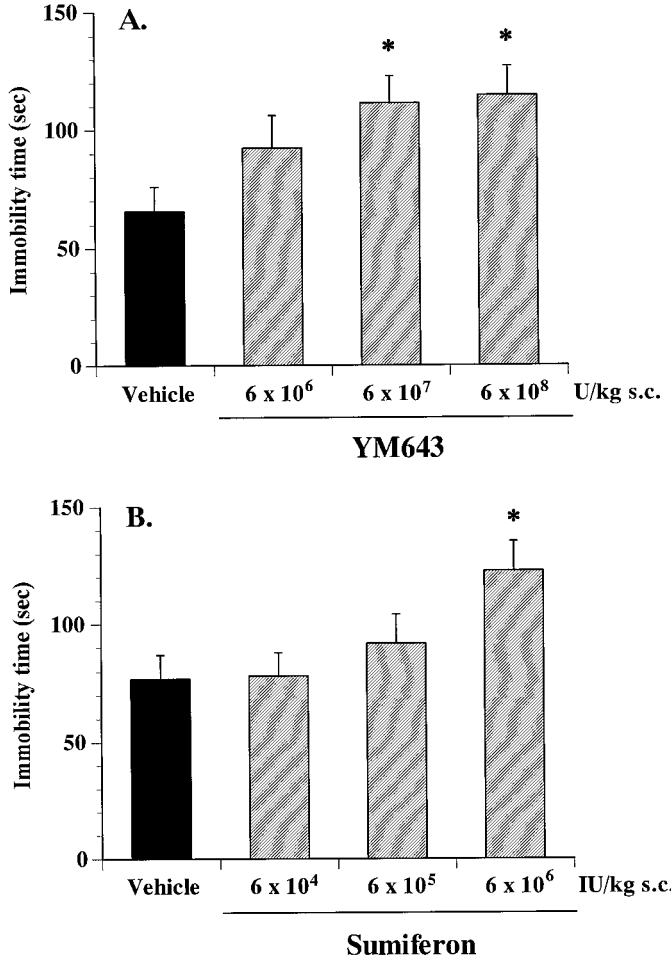

Fig. 2. Effect of repeated treatment of YM643 (A) and sumiferon (B) on immobility time in the mouse tail-suspension test. Drugs were s.c. injected into mice once a day for 7 days. The test was carried out 30 min after last drug injection. Each column represents the mean ± S.E. of total immobility time during 6 min calculated from 20 animals. $^{*}P < .05$ versus vehicle-treated group (Dunnett's test).

Effects on Locomotor Activity. Intravenously injected YM643 (2×10^9 U/kg) and sumiferon (2×10^7 I.U./kg) had no effect on locomotor activity in mice 0.25, 0.5, 1, and 2 h after the injection (data not shown; $n = 12$).

Discussion

In this study, both YM643 and sumiferon dose dependently increased immobility time as measured by the mouse tail-suspension test. Neither YM643 nor sumiferon affected locomotor activity, suggesting that IFN-α induces depression-like behavior in mice as well as humans. Makino et al. (1997, 1998) also suggested that natural IFN-α, recombinant IFN-α-2a, and IFN-α-2b enhanced immobility in the mouse forced swimming test, indicating that our results are consistent with their findings.

To investigate the mechanism of IFN-α-induced depression, the involvement of endogenous PGs, the opioid system, and CRH_1 receptors also were examined in YM643- or sumiferon-induced depression-like behavior in mice. IFN-α was reported to increase PG release in mice (Ohdo et al., 1997). In cats, i.c.v. injected PGs showed CNS depressant effects such as immobility (Holmes and Trim, 1985). YM643- or sumiferon-induced depression-like behavior, however, was not inhibited by pretreatment with indomethacin in this study. Although fever or anorexia attributable to IFN-α were reported to be mediated via PGs (Crnic and Segall, 1992), our results suggest that behavioral effects of IFN-α, such as depression-like behavior in mice, are not mediated by the release of PGs. Concerning the opioid system, it was reported that IFN-α bound to the opioid receptor (Menzies et al., 1992), and naltrexone, a opioid receptor antagonist, ameliorated IFN-α-induced neurotoxic side effects in patients (Valentine et al., 1995). Amir (1982) also reported that naloxone decreased the immobility time as measured by the mouse forced swimming test, suggesting the involvement of endogenous opioids in depression-like behavior. IFN-α-stimulated immobility in the mouse forced swimming test also was inhibited by pretreatment with naloxone (Makino et al., 1997). In our study, pretreatment with naloxone at 3 mg/kg s.c., which was reported sufficient to block opioid receptors (Serrano et al., 1998), did not inhibit either YM643- or sumiferon-induced increased immobility time as measured by the mouse tail-suspension test. Furthermore, naloxone tended to increase immobility time observed in vehicle-treated mice. These results indicate that the opioid system does not participate in IFN-α-induced depression-like behavior in mice as

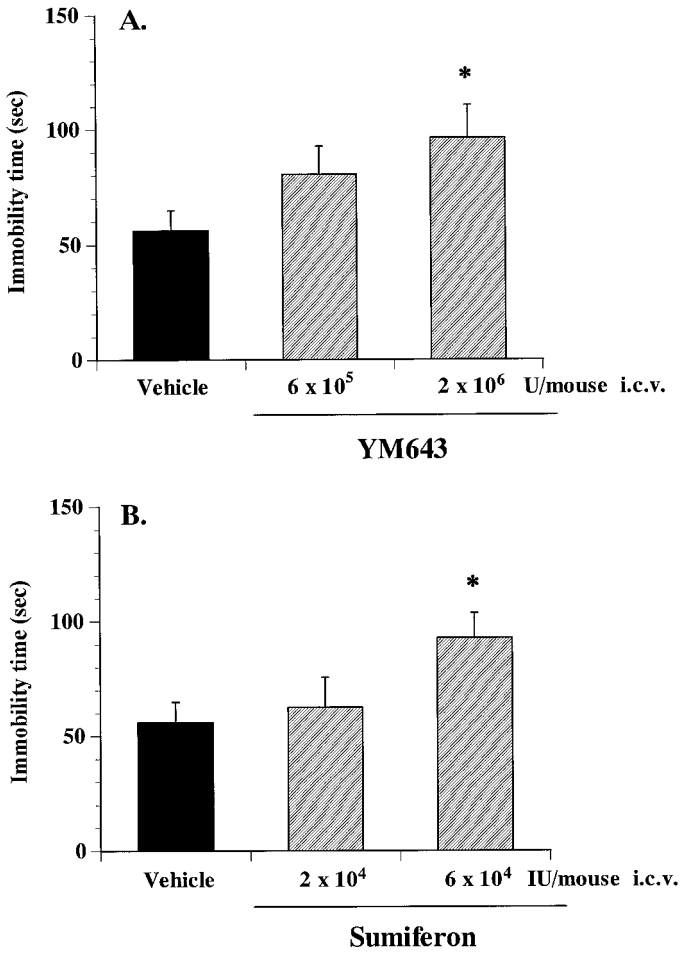

Fig. 3. Effect of centrally injected YM643 (A) and sumiferon (B) on immobility time in the mouse tail-suspension test. Drugs were i.c.v. injected into mice 15 min before the test. Each column represents the mean ± S.E. of total immobility time during 6 min calculated from 10 animals. $^{*}P < .05$ versus vehicle-treated group (Dunnett's test).

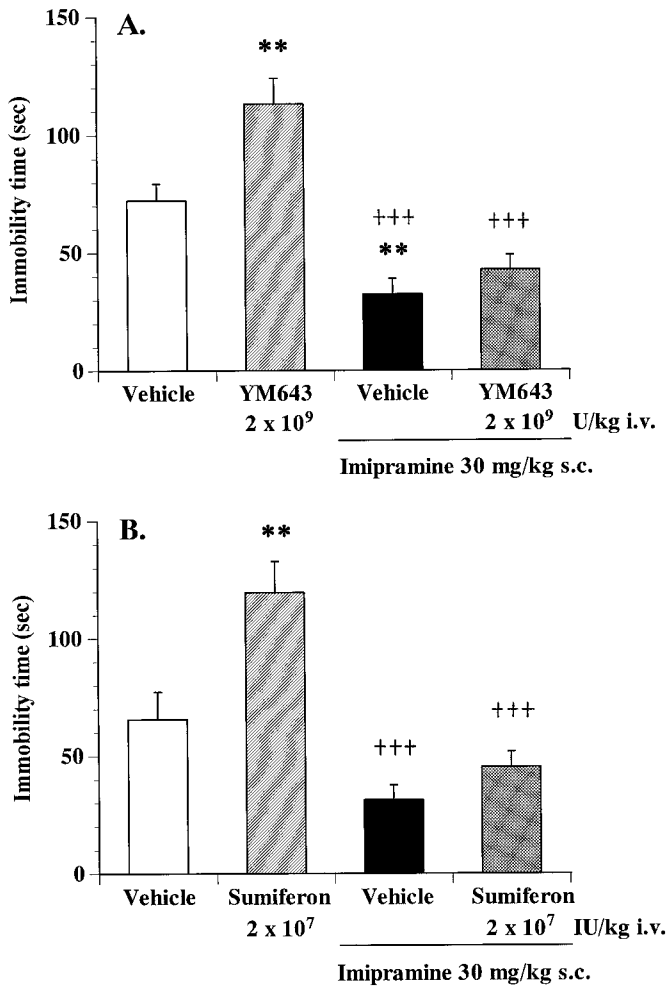

Fig. 4. Inhibitory effect of imipramine on YM643 (A)- and sumiferon (B)-induced increases in immobility time in the mouse tail-suspension test. Imipramine (30 mg/kg) was s.c. injected into mice 30 min before IFN-α administration. YM643 (2×10^9 U/kg) or sumiferon (2×10^7 I.U./kg) was i.v. injected into mice 15 min before the test. Each column represents the mean ± S.E. of total immobility time during 6 min calculated from 20 animals. $^{**}P < .01$ versus vehicle-treated group, $^{+++}P < .001$ versus IFN-α-treated group (Tukey's test).

measured by the tail-suspension test. As to the reason why our results are inconsistent with previous findings, cold stress, which is reported to induce opiate release (Grisel et al., 1993; Mogil et al., 1996), may be a complicating factor in the forced swimming test.

CRH levels are known to change in patients with depression (Catalan et al., 1998; Mitchell, 1998). Recent post-mortem findings and dynamic endocrine studies suggested that both hypothalamic and extrahypothalamic concentrations of CRH were moderately elevated in patients with depression, and that antidepressant treatment tended to normalize this elevation (Mitchell, 1998). IFN-α was reported to stimulate the hypothalamic-pituitary-adrenal axis of rats and CRH release in isolated rat brains (Gisslinger et al., 1993; Raber et al., 1997). CRH receptors have been classified into at least two subtypes: CRH_1 and CRH_2 (Lovenberg et al., 1995). CP-154,526 is the selective CRH_1 receptor antagonist and reported to have very low affinity to other receptors, including the CRH_2 receptor (Schulz et al., 1996). CRH_1 receptors are located mainly in the CNS (Primus et al., 1997) and CP-154,526 shows antidepressant-like effects in rats with stress-induced depression-like behavior (Mansbach et al., 1997). In the present study, CP-154,526 dose dependently inhibited the increase in immobility time induced either by YM643 or sumiferon. Based on the ID_{50} value, the inhibitory effect of CP-154,526 on YM643- and sumiferon-induced depression-like behavior is almost equal. Antidepressant activity of CP-154,526 in this study is almost equipotent as its CRH_1 receptor-blocking activities against CRH-induced responses in rats (Lundkvist et al., 1996; Schulz et al., 1996). Furthermore, CP-154,526 almost completely abolishes increased immobility time induced by both YM643 and sumiferon, indicating that activation of the CRH_1 receptor via IFN-α-induced CRH release is involved in IFN-α-induced depression-like behavior in mice. In contrast, CP-154,526 up to 30 mg/kg s.c. did not affect immobility time in vehicle-treated mice (data not shown; $n = 10$). These findings may suggest that endogenous CRH does not participate in depression-like behavior induced by tail-suspension-stress.

Monoamine and catecholamine release deficiency in the brain is known to contribute to the development of depression. The inhibitory effect of imipramine, which inhibits monoamine and catecholamine reuptake, on IFN-α-induced depression-like behavior also was examined. Pretreatment

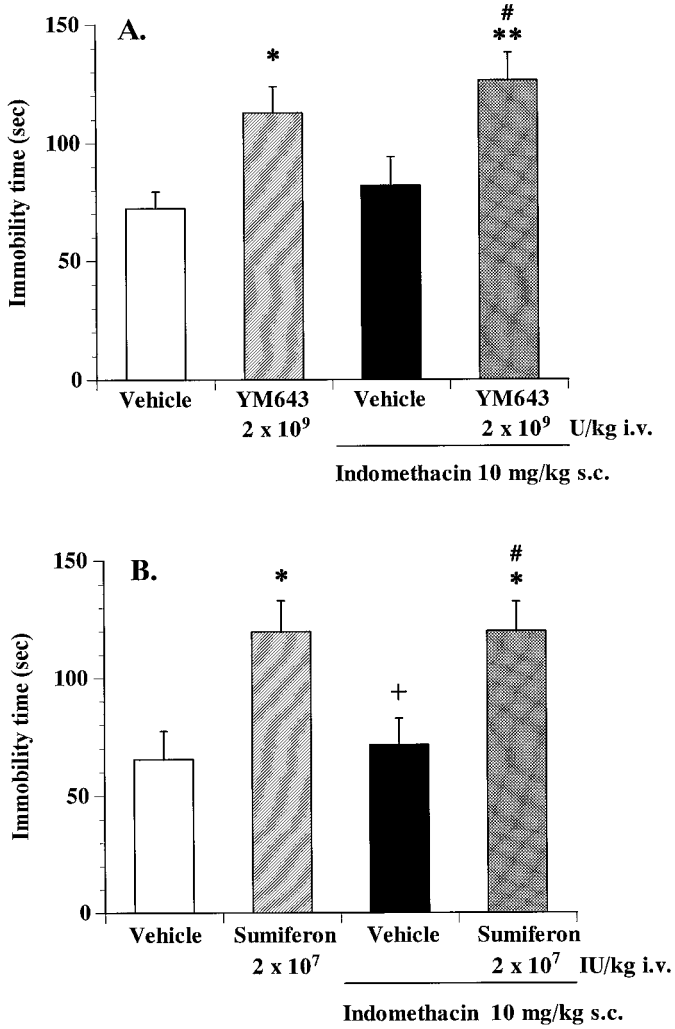

Fig. 5. Effect of indomethacin on YM643 (A)- and sumiferon (B)-induced increases in immobility time in the mouse tail-suspension test. Indomethacin (10 mg/kg) was s.c. injected into mice 30 min before IFN-α administration. YM643 (2×10^9 U/kg) or sumiferon (2×10^7 I.U./kg) was i.v. injected into mice 15 min before the test. Each column represents the mean ± S.E. of total immobility time during 6 min calculated from 20 animals. $^{*}P < .05$, $^{**}P < .01$ versus vehicle-treated group, $^{+}P < .05$ versus IFN-α-treated group, $^{\#}P < .05$ versus indomethacin-treated group (Tukey's test).

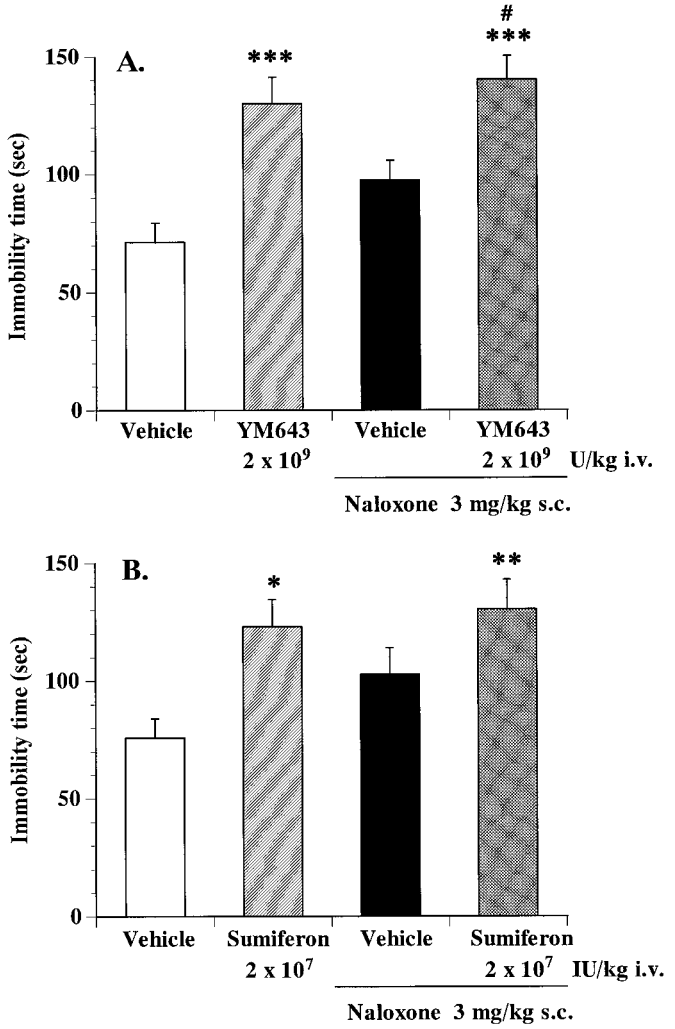

Fig. 6. Effect of naloxone on YM643 (A)- and sumiferon (B)-induced increases in immobility time in the mouse tail-suspension test. Naloxone (3 mg/kg) was s.c. injected into mice 30 min before IFN-α administration. YM643 (2×10^9 U/kg) or sumiferon (2×10^7 I.U./kg) was i.v. injected into mice 15 min before the test. Each column represents the mean ± S.E. of total immobility time during 6 min calculated from 20 animals. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$ versus vehicle-treated group, $^{\#}P < .05$ versus naloxone-treated group (Tukey's test).

with imipramine inhibited the increased immobility time induced by both YM643 and sumiferon in mice. It was reported that IFN-α-induced depression in patients with hepatitis C was successfully treated with antidepressants such as imipramine, amitriptyline, fluoxetine, and mianserin (Levenson and Fallon, 1993; Otsubo et al., 1997). Imipramine down-regulates the activity of the hypothalamic-pituitary-adrenal axis in experimental animals and healthy humans (Gold et al., 1995). Chronic treatment with antidepressants decreased basal CRH levels in the hypothalamus or the extrahypothalamic areas and stress-induced CRH release in the locus ceruleus (Curtis and Valentino, 1994; Fadda et al., 1995). Collectively, these results show antidepressants may alleviate IFN-α-induced depression due to their inhibition of IFN-α-induced CRH release. Additionally, repeated administration of IFN-α was reported to decrease dopaminergic neural activity and the number of serotonin-positive neurons in the animal brain (Shuto et al., 1997; Tanaka et al., 1997). In an in vitro study, IFN-α reduced catecholamine secretion from bovine adrenal chromaffin cells (Tachikawa et al., 1997). Therefore, direct inhibition of monoamine and catecholamine functions also might be involved in IFN-α-induced depression.

The antiviral and antiproliferative activity of consensus IFN-α was the same as that of natural IFN-α on a unit basis (Blatt et al., 1996). Interestingly, the potency of sumiferon in inducing depression-like behavior was ~10 to 100 times more potent than that of YM643 in this study. This difference in potency may be due to differences in their blood-brain barrier permeability. Doses of i.c.v.-injected YM643 and sumiferon that induced depression-like behavior corresponded to ~3 and 10%, respectively, of doses eliciting this effect after i.v. injection. Therefore, the ratio of YM643 and sumiferon doses able to induce depression-like behavior after i.c.v. injection was almost the same as that after i.v. injection in the present study. These results suggest that the difference in potency of

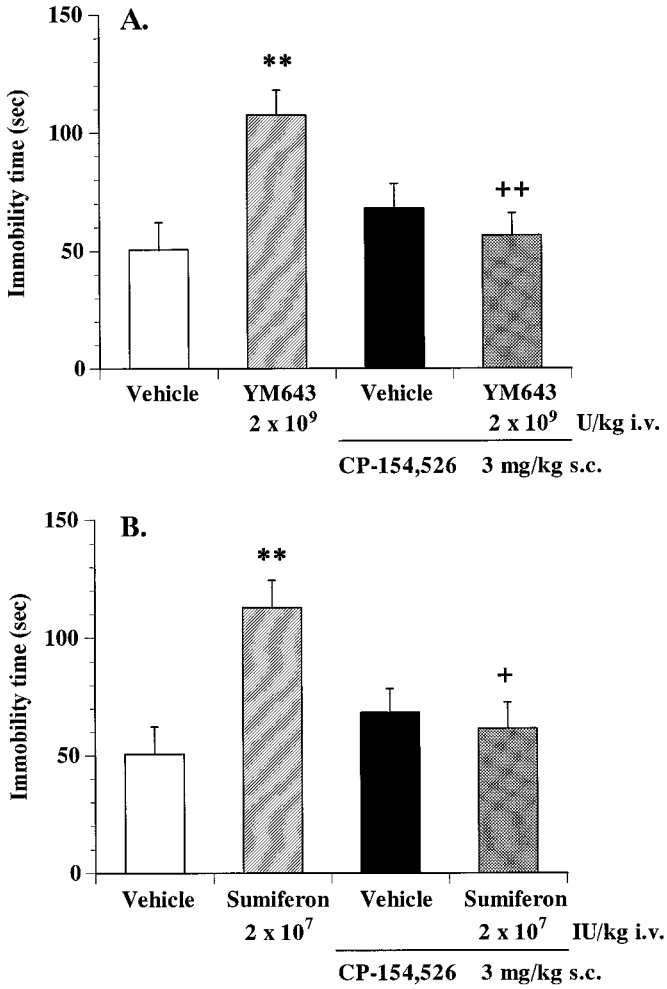

Fig. 7. Inhibitory effect of CP-154,526 on YM643 (A)- and sumiferon (B)-induced increases in immobility time in the mouse tail-suspension test. CP-154,526 (3 mg/kg) was s.c. injected into mice 30 min before IFN-α administration. YM643 (2×10^9 U/kg) or sumiferon (2×10^7 I.U./kg) was i.v. injected into mice 15 min before the test. Each column represents the mean ± S.E. of total immobility time during 6 min calculated from 15 animals. $^{**}P < .01$ versus vehicle-treated group, $^{+}P < .05$, $^{++}P < .01$ versus IFN-α-treated group (Tukey's test).

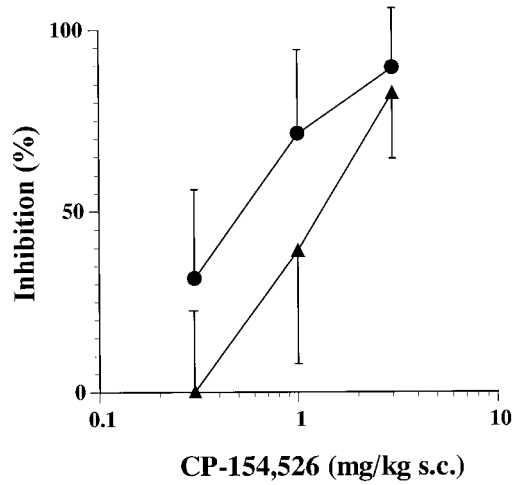

Fig. 8. Dose-response curves of the inhibitory effect of CP-154,526 on YM643 (●)- and sumiferon (▲)-induced increases in immobility time in the mouse tail-suspension test. CP-154,526 (0.3–3 mg/kg) was s.c. injected into mice 30 min before IFN-α administration. YM643 (2×10^9 U/kg) or sumiferon (2×10^7 I.U./kg) was i.v. injected into mice 15 min before the test. Each point represents the mean ± S.E. of the inhibitory percentage calculated from 10 or 15 animals.

their depression-like behavior-inducing effects is not related to blood-brain barrier permeability.

Consensus IFN-α has a higher affinity for type I interferon receptors than natural IFN-α, although it was shown to be a less potent inducer of interleukin-1β (IL-1β) compared with natural IFN-α (Blatt et al., 1996). Maes et al. (1993) reported that the increase in IL-1β production might produce major depression in humans via hypothalamic-pituitary-adrenal axis hyperactivity. Tricyclic antidepressants (e.g., imipramine) are reported to inhibit IL-1β release in human blood monocytes (Xia et al., 1996). Together, these observations may indicate IFN-α produces depression through IL-1β release, which in turn is responsible for CRH release in the brain. The difference in potency of depression-like behavior-inducing effects between consensus IFN-α YM643 and the natural IFN-α sumiferon therefore may be explained by their IL-1β-releasing activities.

The depression-inducing effects of YM643 and sumiferon after repeated s.c. injection were ~3 to 30 times more potent than those after a single i.v. injection. These results show that IFN-α-induced depression-like behavior is enhanced by chronic treatment. Similarly, their antitumor activities also were enhanced by repeated injection to mice (Altrock et al., 1986).

In conclusion, IFN-α induces depression-like behavior by acting on the brain in mice. This depression-like behavior can be alleviated with imipramine and other antidepressants. The results indicate that activation of CRH_1 receptors is involved in IFN-α-induced depression-like behavior, but PGs and opioid systems do not participate in this process.

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