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Enhancement of immobility in mouse forced swimming test by treatment with human interferon

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Abstract

We investigated the depression induced by human interferons using the forced swimming test in mice. Intravenous (i.v.) administration of interferon-α s (natural interferon-α, recombinant interferon-α-2a and recombinant interferon-α-2b, 600–60 000 IU/kg) increased the immobility time in the forced swimming test in a dose-dependent manner, but natural interferon-β and recombinant interferon-γ-1a did not affect the immobility time. The increase in the immobility time induced by recombinant interferon-α-2b peaked at 15 min after dosing. Administration of recombinant interferon-α-2b (6000 IU/kg, i.v.) once daily for 7 consecutive days increased the immobility time, but natural interferon-β and recombinant interferon-γ-1a did not. Recombinant interferon-α-2b in combination with the anti-depressants imipramine (10 mg/kg, i.p.) and mianserin (20 mg/kg, i.p.) did not increase the immobility time. These results suggest that interferon-α has a greater potential for inducing depression than interferon-β and -γ, and that anti-depressants are effective against interferon-α-induced depression.

Keywords: Interferon; Depression; Forced swimming test; Antidepressant

1. Introduction

Interferons are among the cytokines that are involved in the host defense against viral infections. There are three major classes of human interferons: interferon-α produced by leukocytes, interferon-β produced by fibroblasts and interferon-γ produced by T cells. Interferon-α and interferon-β bind to a common interferon-α/β receptor, whereas interferon-γ binds to a separate specific receptor. Interferons produced by infected cells prevent the multiplication of viruses and further induce the immune-mediated clearance of viruses (Langer and Pestka, 1988; Sen and Lengyel, 1992).

Hoofnagle et al. (1986) reported that interferon therapy is effective in patients with non-A and non-B types of chronic hepatitis, and the number of patients treated with interferon in Japan increased markedly after the Health and Welfare Ministry approved interferon treatment for chronic active hepatitis type C.

Side effects of interferons on the central nervous system (CNS), the respiratory and cardiovascular systems, renal function and autoimmune disease have been observed (Quesada et al., 1986; Vial and Descotes, 1994). In particular, effects on the CNS, such as drowsiness, schizophrenia, sensory hypersensitivity, motility disorder, hallucination and depression, have been reported (Rohatiner et al., 1983; Smedley et al., 1983; Adams et al., 1988). Interestingly, the incidence of the CNS side effects, especially psychosis, of interferon-α is supposed to be higher than that of interferon-β or -γ (Bocci, 1988; Vial and Descotes, 1994; Takagi, 1995). In most patients with psychosis during interferon therapy, the electroencephalogram (EEG) is modified and there is slowing of the dominant α-rhythms and occasional appearance of diffuse δ- or intermittent θ-activity (Mattson et al., 1983; Rohatiner et al., 1983; Suter et al., 1984). Furthermore, Krueger et al. (1987) showed that human interferon-α enhanced EEG slow-wave activity in rabbits, and Birmanns et al. (1990) showed that human interferon-α modified cortical EEG activity and increased EEG synchronization in rats dose dependently. These clinical reports and animal experiments suggest that interferon-α influences the CNS, but the mechanisms by which interferon-α induces the CNS side effects are not clear.

Depression is a serious CNS side effect which sometimes leads patients to commit suicide during interferon

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therapy (Prasad et al., 1992; Renault et al., 1987), but there is little documentation on the evaluation of depression in animals. The forced swimming test is considered to be a behavioral screening method for anti-depressants (Borsini and Meli, 1988). An immobile posture observed in this test indicates 'behavioral despair' and can be an animal model of depression (Porsolt et al., 1977, 1978). Because anti-depressants decrease the immobility time in this test without stimulating motor activity, we postulated that drugs which increase the immobility time without decreasing motor activity have a potential for inducing depression.

In the present study, we evaluated the effects of human interferon-α, -β and -γ on immobility time in the forced swimming test and on the spontaneous locomotor activity of mice. Furthermore, we tested the effects of anti-depressants on the activity of interferons.

2. Materials and methods

2.1. Animals

Male Slc:ddY mice (Japan SLC, Hamamatsu, Japan) weighing 24–30 g were used. The mice were housed in an animal room under the following conditions: room temperature 23 ± 2°C, relative humidity 55 ± 15%, with a 12-h/12-h light–dark cycle (lights on at 0800). Each mouse was fed on a mouse/rat diet (F-2, pelleted form, Funabashi Farm, Funabashi, Japan) and allowed tap water ad libitum.

2.2. Drugs and treatments

The following drugs were used: natural interferon-α (Sumiferon®, Sumitomo Pharmaceutical, Osaka, Japan), recombinant interferon-α-2a (Canferon A®, Takeda Yakuhin Kogyo, Osaka, Japan), recombinant interferon-α-2b (Intron A®, Yamanouchi Pharmaceutical–Schering Plough, Tokyo, Japan), natural interferon-β (Feron®, Daiichi Pharmaceutical, Tokyo, Japan), recombinant interferon-γ-1a (Imunomax-γ®, Shionogi Pharmaceutical, Osaka, Japan), imipramine hydrochloride (Sigma, St. Louis, MO, USA) and mianserin (Sigma, St. Louis, MO, USA). The drugs were dissolved in 0.9% physiological saline (Fuso Yakuhin Kogyo, Osaka, Japan). Interferons were administered intravenously 15 min before testing, except for the time course study. Imipramine and mianserin were given intraperitoneally 30 min before testing. The animals in the control group were administered 0.9% physiological saline. In the chronic study, saline or interferons were administered once daily for 7 consecutive days, and mice were tested 15 min after the final administration.

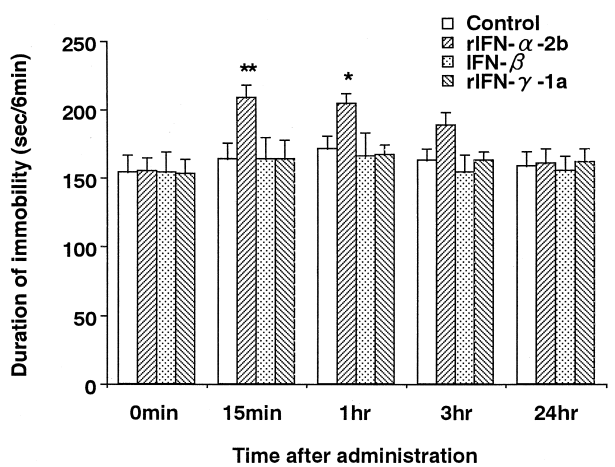

Fig. 1. Effects of recombinant interferon-α-2b (rIFN-α-2b), natural interferon-β (IFN-β) and recombinant interferon-γ-1a (rIFN-γ-1a) on the immobility time of mice in the forced swimming test. Interferons (60 000 IU/kg, i.v.) were administered just before (0 min) and 15 min, 1 h, 3 h and 24 h before the measurement of immobility time. Each result represents the mean ± S.E. ($n = 10$). $*\ P < 0.05$, $**\ P < 0.01$ vs. control group (Dunnett's multiple comparison test).

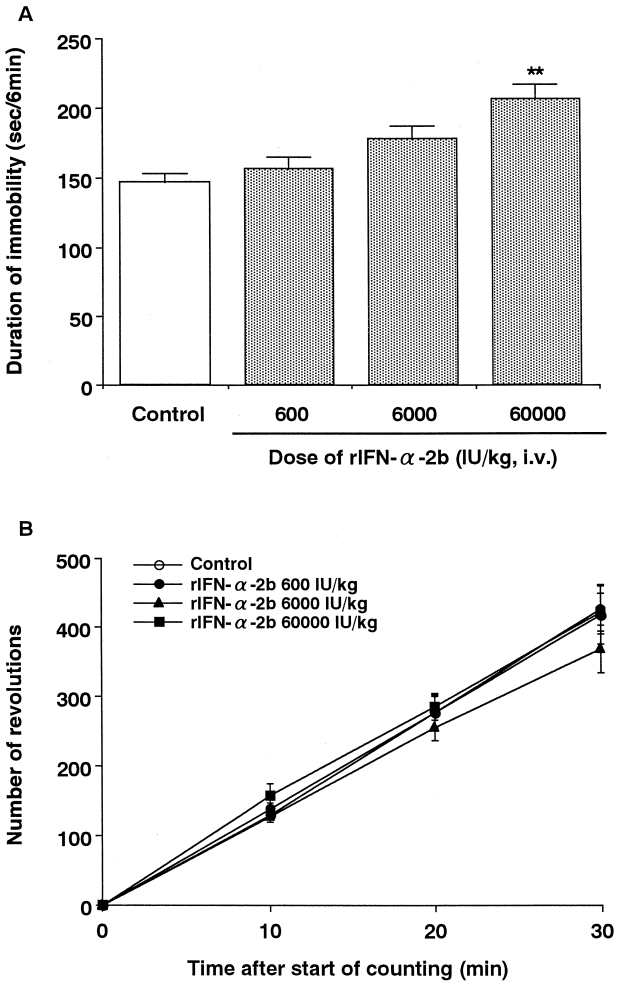

Fig. 2. Effects of recombinant interferon-α-2b (rIFN-α-2b) on the immobility time of mice in the forced swimming test (A) and on the spontaneous locomotor activity of mice (B). rIFN-α-2b (600–60 000 IU/kg, i.v.) was administered 15 min before the measurement of immobility time and locomotor activity. Each result represents the mean ± S.E. ($n = 10$). $**\ P < 0.01$ vs. control group (Dunnett's multiple comparison test).

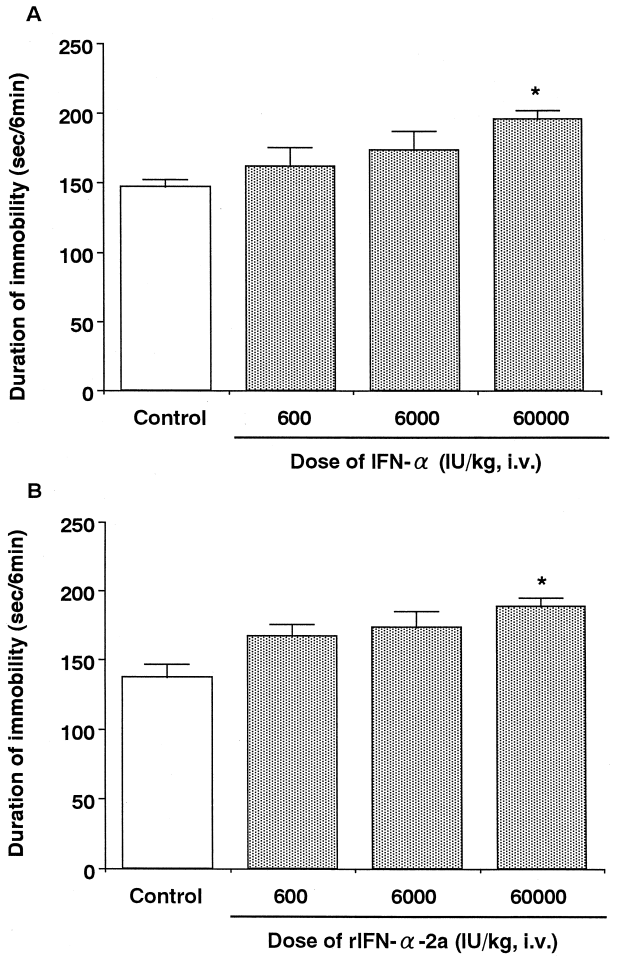

Fig. 3. Effects of natural interferon-α (IFN-α) (A) and recombinant interferon-α-2a (rIFN-α-2a) (B) on the immobility time of mice in the forced swimming test. Both interferons (600–60 000 IU/kg, i.v.) were administered 15 min before the measurement of immobility time. Each result represents the mean ± S.E. ($n = 10$). $*$ $P < 0.05$ vs. control group (Dunnett's multiple comparison test).

2.3. Forced swimming test

The procedure was used described by Porsolt et al. (1977), with some modification. Mice were forced to swim for 6 min inside a vertical glass cylinder (height, 25 cm; diameter, 12 cm) containing water about 15 cm deep at 20°C. The total duration of immobility during the 6 min was measured. We used separate group of mice in each study, and each mouse was used only one time in the time course study.

2.4. Spontaneous locomotor activity test

Mice were placed individually in a wheel cage (MIP-012, Muromachi Kikai, Tokyo, Japan). The number of rotations of the cage was measured as an index of spontaneous locomotor activity. Mice which rotated the cage more than 200 times in a 30-min period were selected for the study 24 h prior to the experiment. The spontaneous locomotor activity was measured at 10-min intervals for a period of 30 min. We used separate group of mice in each study.

2.5. Statistical analysis

Data from the forced swimming test and the spontaneous locomotor activity were analyzed by the one-way layout and multiple comparison method of Dunnett. Data for the combination of anti-depressant and interferon in the forced swimming test were analyzed by a two-way analysis of variance (ANOVA).

3. Results

3.1. Time course studies of the effect of interferons

Recombinant interferon-α-2b (60 000 IU/kg, i.v.) did not change the immobility time immediately after dosing

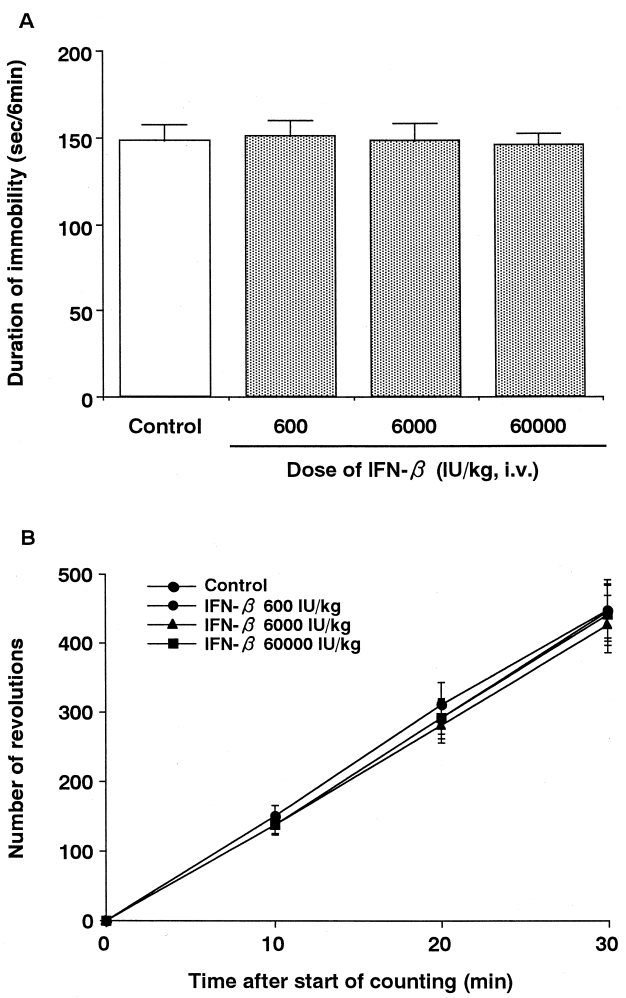

Fig. 4. Effects of natural interferon-β (IFN-β) on the immobility time of mice in the forced swimming test (A) and on the spontaneous locomotor activity of mice (B). IFN-β (600–60 000 IU/kg, i.v.) was administered 15 min before the measurement of immobility time and locomotor activity. Each result represents the mean ± S.E. ($n = 10$).

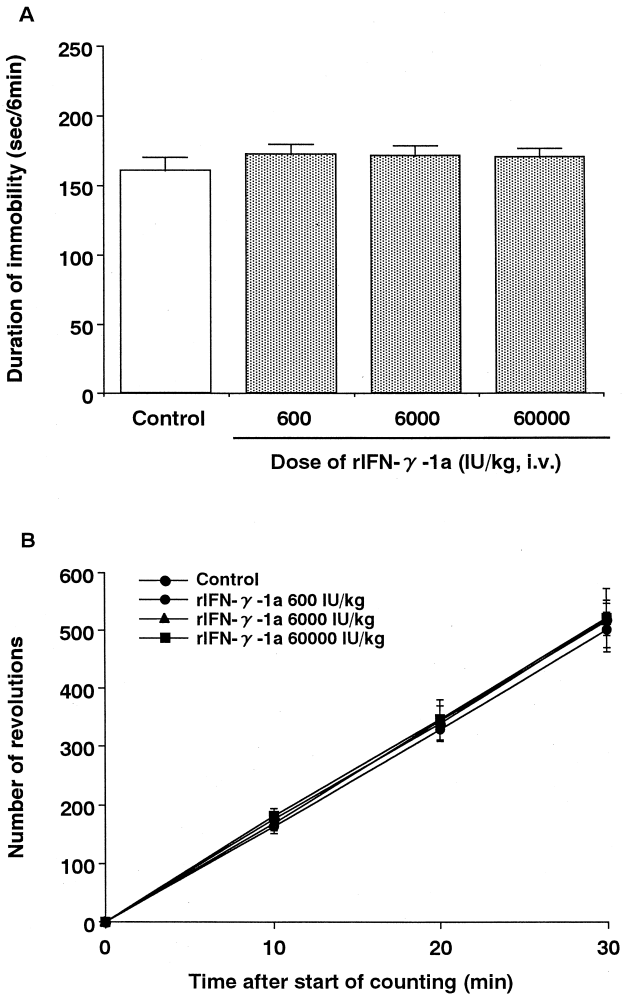

Fig. 5. Effects of recombinant interferon-γ-1a (rIFN-γ-1a) on the immobility time of mice in the forced swimming test (A) and on the spontaneous locomotor activity of mice (B). rIFN-γ-1a (600–60 000 IU/kg, i.v.) was administered 15 min before the measurement of immobility time and locomotor activity. Each result represents the mean ± S.E. ($n = 10$).

(0 min) but significantly increased the immobility time at both 15 and 60 min after dosing. The effect of recombinant interferon-α-2b was partially reversed at 3 h after dosing and completely disappeared at 24 h after dosing. Natural interferon-β and recombinant interferon-γ-1a (60 000 IU/kg, i.v.) did not change the immobility time at any time (Fig. 1). None of these interferons (60 000 IU/kg, i.v.) changed the spontaneous locomotor activity (data not shown). Based on these results, we evaluated the effect of interferon-α at 15 min after dosing in the following study.

3.2. Effects of single administration of interferons

Recombinant interferon-α-2b (600–60 000 IU/kg, i.v.) increased the immobility time in a dose-dependent manner, and the effect was statistically significant at 60 000 IU/kg (Fig. 2). Recombinant interferon-α-2b (600–60 000 IU/kg, i.v.), however, did not change the spontaneous locomotor activity (Fig. 2).

Both natural interferon-α and recombinant interferon-α-2a (600–60 000 IU/kg, i.v.) increased the immobility time in a dose-dependent manner, an effect that was statistically significant at a dose of 60 000 IU/kg (Fig. 3). Neither of the interferon-αs (60 000 IU/kg, i.v.) changed the spontaneous locomotor activity (data not shown).

Natural interferon-β and recombinant interferon-γ-1a (600–60 000 IU/kg, i.v.) did not change the immobility time or the spontaneous locomotor activity (Figs. 4 and 5).

3.3. Effects of 7 consecutive days administration of interferons

As shown in Fig. 6, recombinant interferon-α-2b (6000 IU/kg, i.v.) induced a statistically significant increase in

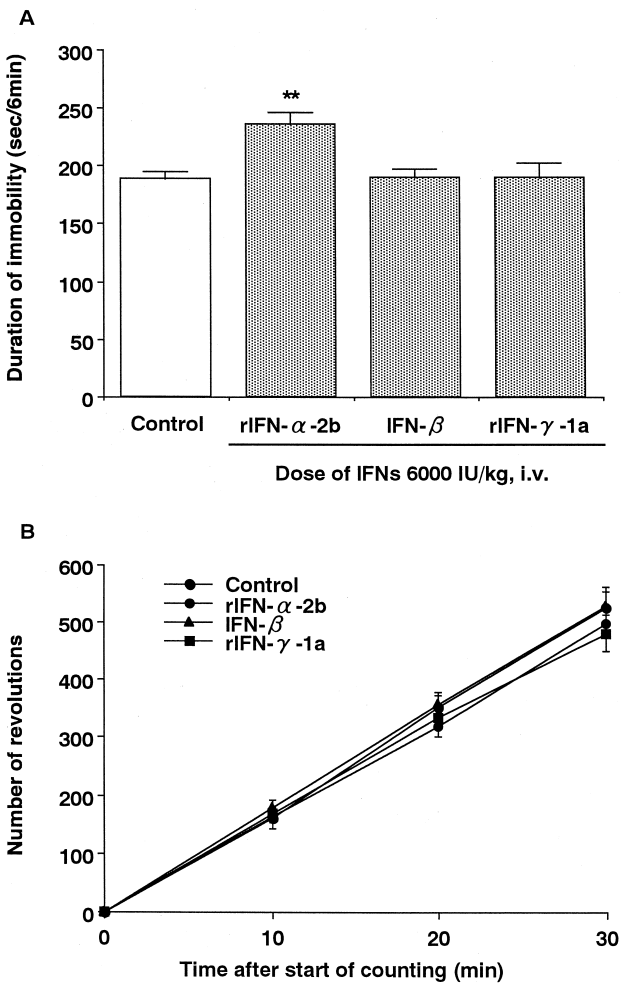

Fig. 6. Effects of repeated administration of recombinant interferon-α-2b (rIFN-α-2b), natural interferon-β (IFN-β) and recombinant interferon-γ-1a (rIFN-γ-1a) on the immobility time of mice in the forced swimming test (A) and on the spontaneous locomotor activity of mice (B). Interferons (6000 IU/kg, i.v.) were administered daily for 7 consecutive days. The measurement of immobility time and locomotor activity was performed 15 min after the final administration of interferon. Each result represents the mean ± S.E. ($n = 10$). $**P < 0.01$ vs. control group (Dunnett's multiple comparison test).

the immobility time after 7 consecutive days' administration. Natural interferon-β and recombinant interferon-γ-1a (6000 IU/kg, i.v.) did not change the immobility time.

None of these interferons (6000 IU/kg, i.v.) changed the spontaneous locomotor activity (Fig. 6).

3.4. Effects of anti-depressants on the activity of interferon-α

Imipramine (10 mg/kg, i.p.) by itself significantly decreased the immobility time and the spontaneous locomotor activity. Recombinant interferon-α-2b (60 000 IU/kg, i.v.) in combination with imipramine did not increase the immobility time, which was the same as that of the control group, in spite of decrease in spontaneous locomotor activity (Fig. 7). No significant effects were found for any of the interactions between recombinant interferon-α-2b and imipramine (ANOVA 2×2 values were $F(1,36) = 1.73$, $P > 0.05$).

Mianserin (20 mg/kg, i.p.) by itself tended to decrease the immobility time. Recombinant interferon-α-2b (60 000 IU/kg, i.v.) in combination with mianserin did not increase the immobility time (Fig. 8). No significant effects were found for any of the interactions between recombinant interferon-α-2b and mianserin (ANOVA 2×2 values were $F(1,36) = 0.43$, $P > 0.05$).

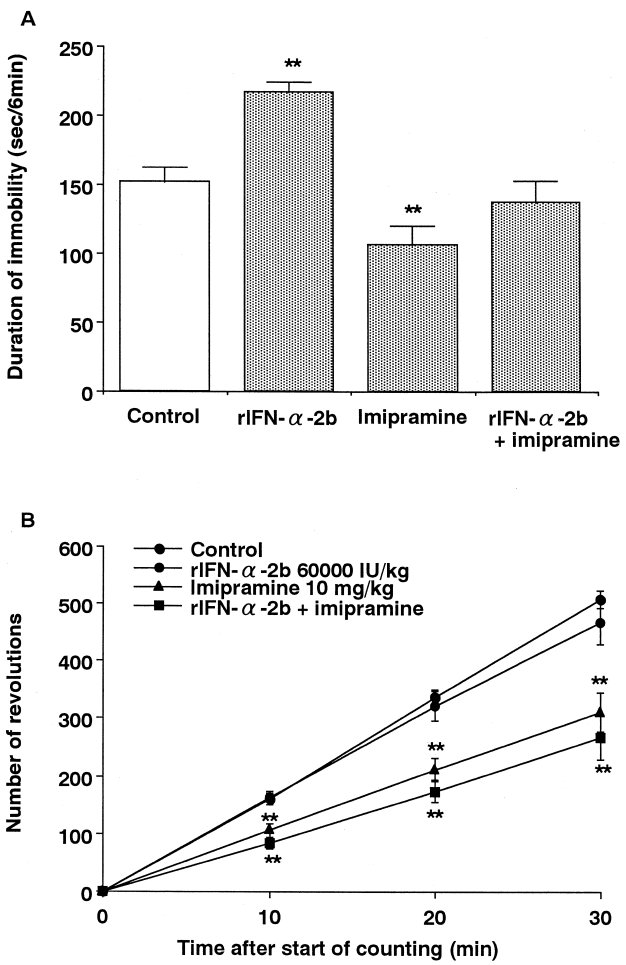

Fig. 7. Effects of imipramine on the recombinant interferon-α-2b (rIFN-α-2b)-induced increase in the immobility time of mice in the forced swimming test (A) and on the spontaneous locomotor activity of mice (B). Imipramine (10 mg/kg, s.c.) was administered 15 min before treatment of rIFN-α-2b (60 000 IU/kg, i.v.). The measurement of immobility time and locomotor activity was performed 15 min after drug administration. Each result represents the mean ± S.E. ($n = 10$). (A) ANOVA 2×2 values were $F(1,36) = 1.73$, $P < 0.01$, $F(1,36) = 23.81$ $** P < 0.01$ for rIFN-α-2b and $F(1,36) = 39.19$, $** P < 0.01$ for imipramine. (B) $** P < 0.01$ vs. control group (Dunnett's multiple comparison test).

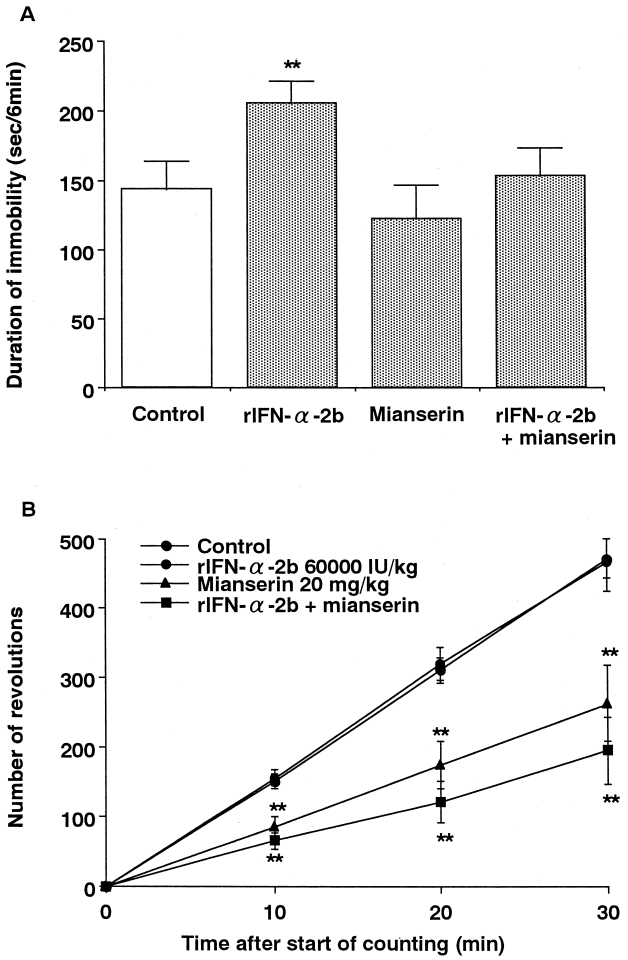

Fig. 8. Effects of mianserin on the recombinant interferon-α-2b (rIFN-α-2b)-induced increase in the immobility time of mice in the forced swimming test (A) and on the spontaneous locomotor activity of mice (B). Mianserin (20 mg/kg, s.c.) was administered 15 min before treatment with rIFN-α-2b (60 000 IU/kg, i.v.). The measurement of immobility time and locomotor activity was performed 15 min after drug administration. Each result represents the mean ± S.E. ($n = 10$). (A) ANOVA 2×2 values were $F(1,36) = 0.43$, $P > 0.05$, $F(1,36) = 5.34$ $** P < 0.05$ for rIFN-α-2b and $F(1,36) = 2.84$, $P > 0.05$ for mianserin. (B) $** P < 0.01$ vs. control group (Dunnett's multiple comparison test).

4. Discussion

The purpose of our study was to evaluate whether interferons have the potential to induce depression. The forced swimming test used in this study is regarded as a valuable screening model for anti-depressants (Borsini and Meli, 1988) because anti-depressants, unlike CNS stimulants, decrease immobility time without stimulating motor activity (Porsolt et al., 1977, 1978; Shimazoe et al., 1987). We confirmed that anti-depressants, such as imipramine and mianserin, decreased the immobility time despite decreasing the spontaneous locomotor activity in mice. We hypothesized that drugs that increase immobility time in this test have the potential to induce depression. In general, two trials, before and after anti-depressant treatment, were performed to evaluate anti-depressant activity. However, we performed only one trial of the forced swimming test to clarify the ability of the drugs to increase the immobility time, because animals rapidly become immobile during multiple trials (Porsolt et al., 1978; Shimazoe et al., 1987). Furthermore, because drugs that cause motor dysfunction, including decreased locomotor activity and ataxia, apparently increase the immobility time, the effects on motor activity of the drugs were evaluated under the same treatment regimen and conditions as those used in the forced swimming test. In this study, none of the interferons affected the spontaneous locomotor activity of mice, suggesting that the increasing effect of interferon-αs on the immobility time was due to its depressant activity, and was not due to the motor dysfunction. In previous studies, Blalock and Smith (1981) reported that interferon-α caused inhibition of spontaneous movement and catalepsy in mice, and Dunn and Crnic (1993) also reported that recombinant interferon-α A/D caused a reduction in locomotor activity in mice, results which differ from our results. The reason for the discrepancy might be due to the differences between the types and sources of interferon-α, or to the times and routes of injection and timing of the test.

Interferon-α s (both natural and recombinant types) increased the immobility time in the forced swimming test in a dose-dependent manner, whereas interferon-β and -γ had no effect. These findings are consistent with those of clinical studies showing no difference in psychotic effects in patients receiving either type of interferon-α (Vial and Descotes, 1994). The increase in the immobility time induced by recombinant interferon-α-2b was maintained even at 3 h after dosing, but disappeared by 24 h. However, this effect of recombinant interferon-α-2b was pronounced after 7 consecutive days of drug administration. Even a lower dose (6000 IU/kg, i.v.; comparable to its therapeutic dose) which tended to induce depression after a single administration significantly increased the immobility time on repeated administration. Furthermore, we confirmed that recombinant interferon-α-2b did not increase the immobility time 24 h after the final dose of the 7-day administration regimen (data not shown). These findings indicate that the ability of interferon-α to increase the immobility time was reversible but that repeated treatment might increase the susceptibility of animals to interferon-α.

According to Willner (1984), the potency of anti-depressants in the forced swimming test significantly correlates with their clinical efficacy. In this study, interferon-α in combination with the anti-depressants, imipramine and mianserin, did not increase the immobility time, which was the same as that of the control group. Although these anti-depressants did not antagonize the effect of interferon-α because there was no interaction between interferon-α and anti-depressant, the results of the present study suggest that anti-depressants would be effective against interferon-α-induced depression. Indeed, the clinical efficacy of anti-depressants for interferon-induced depression has been reported (Otubo et al., 1997). We conclude that the increase in the immobility time induced by interferon-αs in the present study reflects their potential for inducing depression.

The mechanisms by which interferons induce psychosis have yet to be elucidated. Possible mechanisms of neurotoxicity induced by interferons are suggested below. Based on clinical studies and EEG changes, toxic neurasthenia and neuropsychological abnormalities may be the result of a predominant interferon-α effect on front-subcortical functions (Adams et al., 1984; Iivanainen et al., 1985; Meyers et al., 1991), although a direct effect of interferons on the transendothelial passage has been speculated (Bocci, 1988, 1994). Other indirect mechanisms may also be involved. Interferons are known to induce the production of various cytokines, such as interleukin-1 and tumor necrosis factor, which also induce neurotoxicity (Arenzana-Seisdedos and Virelizier, 1983), change the secretion of neuroendocrine hormones, such as adrenocorticotropic hormone (Blalock and Smith, 1980; Blalock and Stanton, 1980; Nolten et al., 1993), and increase cortisol levels (Gisslinger et al., 1993; Nolten et al., 1993). Furthermore, interferon-α has also been shown to have opiate-like activity (Blalock and Smith, 1981), and the diencephalic areas in which interferon-α has been shown to cause neuronal excitability coincide with opiate receptor-rich areas (Dafny et al., 1988). Interferon-α is also reported to inhibit naloxone binding to rat brain membranes (Menzies et al., 1992). These speculations, however, do not explain why the incidence of CNS side effects of interferon-α is higher than that of interferon-β or -γ, and why interferon-αs, but not interferon-β or -γ, had depressant activity in the present study.

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