The 5-HT2 Receptor Antagonist Reduces Immobility of Mice Treated with the Atypical Antidepressant Mianserin in the Forced Swimming Test

Yumi Sugimoto, Shizuo Yamada, and Jun Yamada


Forced swimming test is widely used as the screening model for assessments of antidepressants.1,2) Most antidepressants reduce immobility time in both mice and rats and the mechanisms of antidepressants have been investigated using this model.1—3) It is well recognized that depression is associated with the noradrenergic and serotonergic systems. Drugs inhibiting noradrenaline (NA) and/or 5-HT reuptake at nerve terminals, or inhibiting metabolism of these amines (monoamine oxidase inhibitors) improve depression.4—6)

We previously demonstrated that the tricyclic antidepressant imipramine which inhibits reuptake of both 5-HT and NA, induces anti-immobility effects and that blockade of the 5-HT1 receptor leads to potentiation of the antidepressant effects of imipramine.7) Furthermore, it was found that the 5-HT2 receptor antagonist reduces immobility time in mice treated with NA reuptake inhibitors, but not with selective serotonin reuptake inhibitors (SSRIs).8) These results indicate that the blockade of the 5-HT2 receptor selectively potentiate antidepressant effects of drugs that inhibit NA reuptake and that this receptor may participate in antidepressant effects by modifying NA transmission.

Mianserin is an atypical antidepressant, which inhibits α2 adrenoceptor located in nerve terminals of noradrenergic neurons, resulting in facilitating NA release and increasing NA levels in the synaptic cleft.9) As described above, the blockade of the 5-HT2 receptor enhances the anti-immobility effects of NA reuptake inhibitors. Since mianserin increases NA release, the 5-HT2 receptor antagonist may affect the immobility time of mice treated with mianserin. In the present paper, we examined the immobility time following co-administration of the 5-HT2 receptor antagonist LY 53857 and mianserin.

MATERIALS AND METHODS

Male ddY mice weighing 25—30 g were purchased from SLC Japan Inc. (Japan). The mice were given free access to food and water and were housed under a controlled 12-h/12-h light–dark cycle (light from 7:00 a.m. to 7:00 p.m.), with room temperature 23 ± 1 °C and humidity 55 ± 5%.

Mianserin HCl and 4-isopropyl-7-methyl-9-(2-hydroxy-1-methyl-propoxy carbonyl)-4,6A,7,8,9,10,10A-octahydro-indol[4,3-FG]quinolone maleate (LY 53857) were obtained from Research Biochemicals Inc. (U.S.A.) and dissolved in saline. Mianserin was given i.p. LY 53857 was administered i.p. 30 min before the injection of mianserin.

The forced swimming test was performed according to the methods described by Porsolt et al.1) Each mouse was placed in a 25 cm glass cylinder (10 cm diameter) containing 10 cm of water maintained at 23 ± 1 °C. Immobility was recorded during a 6-min swimming test.

Locomotor activity for 10 min was measured by a digital counter with an infrared sensor (Neuroscience Inc., Japan) 30 min after the injection of mianserin.

Dose-related effects of mianserin on immobility were evaluated by one-way analysis of variance (ANOVA) followed by Dunnett’s test. Other results were analyzed by two-way ANOVA followed by Tukey’s test.

RESULTS

Effects of Mianserin on Immobility in Forced Swimming Test

Figure 1 shows effects of mianserin on immobility in mice. Mianserin at doses ranging from 1—10 mg/kg did not affect immobility time. At 20 mg/kg, mianserin reduced immobility time significantly.

Fig. 1. Effects of Mianserin on Immobility in Forced Swimming Test

Results are shown as mean ± S.E. (n=6—9). Mianserin was given i.p. ***p < 0.001.
Mianserin does not affect locomotor activity. Furthermore, co-administration of LY 53857 and mianserin did not alter locomotor activity, either. These results indicate that the enhancement of anti-immobility effects elicited by LY 53857 is not related to changes in locomotor activity.

The mechanisms for the antidepressant effects of mianserin have been suggested to be involved in enhancing noradrenergic neurotransmission based on its blockade of α2 receptors. Our previous reports indicated that the 5-HT2 receptor antagonist LY 53857 reduced immobility in mice treated with antidepressants inhibiting reuptake of NA but not those of SSRIs. For example, treatment with LY 53857 and a subactive dose of the selective NA reuptake inhibitor maprotiline induces apparent anti-immobility effects, although LY 53857 did not alter the duration of immobility of mice treated with the SSRI fluoxetine. It indicates that the 5-HT2 receptor may participate in antidepressant effects by modifying NA transmission.

Our results demonstrated that treatment with LY 53857 and subactive dose of mianserin reduced immobility similar to that by maprotiline. Since mianserin increases NA release through α2 receptor inhibition, augmentation of anti-immobility effects elicited by LY 53857 may be associated with the noradrenergic system. This result confirms that LY 53857 enhances anti-immobility effects by modulating NA transmission.

It has been reported that LY 53857 has a high affinity with the 5-HT2A/2B/2C receptor subtypes. The dose of LY 53857 in the present study was sufficient to inhibit 5-HT2A and 5-HT2C receptor-mediated head-shake responses and hypophagia in rats. The presence of an interaction between 5-HT2 receptors and catecholaminergic neurons has been suggested. It was reported that the 5-HT2A receptor activation may enhance NA release from nerve terminals of rat brain. Recent findings suggested that the blockade of 5-HT2C receptor increases noradrenaline or dopamine release in the brain, as measured by microdialysis in rats. Since mianserin increases NA release by blocking α2 receptors, blockade of the 5-HT2C receptor by LY 53857 may lead to increased potentiation of noradrenergic transmission, which results in apparent anti-immobility effects.

It has been suggested that mianserin itself is a 5-HT2A/2C receptor antagonist. Hand et al. demonstrated that antidepressant effects of mianserin are associated with the 5-HT2 receptor antagonism. Therefore, because mianserin antagonizes 5-HT1 receptor, probably the 5-HT2C receptor, in addition to α2 receptors, co-administration of LY 53857 with mianserin may appear apparent anti-immobility effects. Recent evidence has shown that the 5-HT2C receptor inverse agonist may be effective in depression. Thus, inhibition of the 5-HT2C receptor activity may lead to antidepressant effects.

In summary, our results demonstrated that inhibition of the 5-HT2 receptor by LY 53857 enhances the anti-immobility effects of mianserin. Since LY 53857 potentiates anti-immobility effects of NA reuptake inhibitors, the results obtained...
with mianserin further support the postulation that the 5-HT₂ receptor antagonism may increase the sensitivity to antidepressants by moderating the noradrenergic system.

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REFERENCES

8) Yamada J., Sugimoto Y., Brain Res. in press.