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Pharmacological studies on YM992, a novel antidepressant with selective serotonin re-uptake inhibitory and 5-HT_{2A} receptor antagonistic activity

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Abstract

YM992 ((*S*)-2-[[(7-fluoro-4-indanyl)oxy]methyl]morpholine monohydrochloride) is a novel compound that has selective serotonin (5-hydroxytryptamine, 5-HT) re-uptake inhibition and 5-HT_{2A} receptor antagonistic activity in vivo. YM992, fluoxetine and citalopram showed 5-HT uptake inhibition activity in *l*-5-hydroxy-tryptophan (*l*-5-HTP)-treated mice. YM992 and trazodone attenuated 5-$HT_{2A/2C}$ receptor agonist-induced head-twitches in mice, indicating that these drugs had 5-HT_{2A} receptor antagonistic activity. YM992 and amitriptyline were highly active in the mouse tail suspension test. In contrast, fluoxetine and citalopram showed only a tendency to reduce the immobility time. Single treatment with YM992 as well as trazodone and fluoxetine ameliorated the learning deficit of olfactory-bulbectomized rats, whereas citalopram and amitriptyline showed an ameliorative effect only after chronic treatment. Although YM992 has moderate affinity for α_1-adrenoceptors, α_1-adrenoceptor antagonism of YM992 in vivo was 10 times weaker than that of trazodone. These results demonstrate that YM992 has 5-HT uptake inhibition and 5-HT_{2A} receptor antagonistic activity in vivo, and suggest that YM992 may be a novel antidepressant with high efficacy in clinical use. © 1997 Elsevier Science B.V.

Keywords: YM992; Antidepressant; 5-HT (5-hydroxytryptamine, serotonin) re-uptake inhibition; 5-HT_{2A} receptor antagonistic activity; Tail suspension test; Olfactory bulbectomized rat

1. Introduction

There is growing evidence that the serotonin (5-hydroxytryptamine, 5-HT) system is involved in the pathogenesis and treatment of depression. Several clinical studies have reported a decrease in the cerebrospinal fluid (CSF) concentration of 5-HT metabolites in patients with depression (Leonard, 1995), suggesting a dysfunction of the 5-HTergic system. Moreover, selective 5-HT re-uptake inhibitors, which selectively block re-uptake of 5-HT and have no interaction with a variety of receptors (Johnson, 1991), are widely prescribed and are effective antidepressants.

Many studies examining the relationship between long-term antidepressant treatment and the 5-HT system have therefore been conducted. Recent findings have shown that long-term antidepressant treatment, including tricyclic antidepressants, monoamine oxidase inhibitors, electroconvulsive shocks and selective 5-HT re-uptake inhibitors, enhances 5-HTergic neurotransmission, in particular that mediated by postsynaptic 5-HT_{1A} receptors (Blier and De Montigny, 1994). Long-term treatment with tricyclic antidepressants or electroconvulsive shocks induces the up-regulation of postsynaptic 5-HT_{1A} receptors or the enhancement of the inhibitory effects of 5-HT on neuronal firing, which is mediated by 5-HT_{1A} receptors, in rat forebrain areas (Chaput et al., 1991; Hayakawa et al., 1993; Welner et al., 1989). Long-term treatment with selective 5-HT re-uptake inhibitors or monoamine oxidase inhibitors also enhances the inhibitory effects of 5-HT on neuronal firing in rat hippocampus, by causing desensitization of somatodendritic 5-HT_{1A} receptors in the dorsal raphe (Blier et al., 1990).

Further, it has also been suggested that the interaction between 5-HT_{1A} and 5-HT_2 receptors may be another

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Table 1
Comparison of the binding profiles of YM992 and other antidepressants

Binding site	Tissue	Ligand	K_i (nM)				
			YM992	Trazodone	Fluoxetine	Citalopram	Amitriptyline
5-HT uptake site	Rat cortex	[^{3}H]Citalopram	21	140	9.3	0.46	57
5-HT$_{2A}$ receptor	Rat frontal cortex	[^{3}H]Ketanserin	86	38	1 700	> 1 000	20
Adrenaline α_1 receptor	Rat cortex	[^{3}H]Prazosin	200	37	3 100	857	17
Dopamine D$_2$ receptor	Rat striatum	[^{3}H]Spiperone	> 10 000	400	7 800	> 1 000	150
Histamine H$_1$ receptor	Rat cortex	[^{3}H]Pyrilamine	2 500	340	6 300	–	5.1
Muscarine M$_1$ receptor	Rat cortex	[^{3}H]Pirenzepine	4 100	> 10 000	2 000	–	6.2
Muscarine M$_2$ receptor	Rat heart	[^{3}H]QNB	> 10 000	> 10 000	–	–	40

Referenced from Hatanaka et al. (1996).

potential mechanism of the antidepressant effect and is consistent with the above findings. It is reported that 5-HT$_2$ receptor antagonists enhance 5-HT$_{1A}$ receptor agonist-induced behavior (Backus et al., 1990). Ketanserin, which has more potent affinity for 5-HT$_{2A}$ receptors than for 5-HT$_{2C}$ receptors, enhances the inhibitory effects of 5-HT in forebrain areas (Lakoski and Aghajanian, 1985). On this basis, compounds having both 5-HT uptake inhibition and 5-HT$_{2A}$ receptor antagonistic activity are expected to enhance 5-HTergic neurotransmission, in particular that mediated by 5-HT$_{1A}$ receptors, more efficiently than other antidepressants.

YM992 ((*S*)-2-[[(7-fluoro-4-indanyl)oxy]methyl]morpholine monohydrochloride) was synthesized with the view of developing an antidepressant that would inhibit the re-uptake of 5-HT and block 5-HT$_{2A}$ receptors. The biochemical profile of YM992 has been reported previously (Hatanaka et al., 1996). YM992 showed high affinity for both 5-HT uptake sites and 5-HT$_{2A}$ receptors (K_i value = 21 and 86 nM, respectively; see Table 1). In the present study, we examined the in vivo blockade of 5-HT uptake and of 5-HT$_{2A}$ receptors by this compound, and its antidepressant activity in several animal models in comparison with the effects of other antidepressants.

2. Materials and methods

2.1. Animals

Male ICR mice (SLC, Japan) weighing 25–35 g and male Wistar rats (SLC, Japan) weighing 200–250 g were used.

2.2. Drugs

YM992 was synthesized in our laboratory. The following drugs were obtained commercially: trazodone hydrochloride (Kanebo, Tokyo, Japan), citalopram hydrobromide (H. Lundbeck, Copenhagen, Denmark), fluoxetine hydrochloride (Eli Lilly, Indianapolis, IN, USA), amitriptyline hydrochloride (Sigma, St. Louis, MO, USA), *l*-5-hydroxy-tryptophan (*l*-5-HTP) (Tokyo Kasei Kogyo, Tokyo, Japan). (±)-1-(2,5-Dimethoxy-4-iodophenyl)2-amino-propane (DOI) hydrochloride, phenylephrine hydrochloride, oxotremorine sesquifumarate were obtained from Research Biochemicals International (Natick, MA, USA). All compounds were dissolved in saline or distilled water.

2.3. l-5-HTP potentiation

Mice were dosed orally at 48 min (fluoxetine, citalopram and amitriptyline) or 30 min (others) before administration of *l*-5-HTP (90 mg/kg, i.v.) according to the method of Bogdanski et al. (1958). This dose of *l*-5-HTP by itself causes no clear behavioral effects, but in mice treated with 5-HT re-uptake inhibitors it produces syndromes including tremors, head-twitches and hind-limb abduction. The mice were rated for the presence of each symptom at 5–10 min after *l*-5-HTP treatment. The ED$_{50}$ values of drugs for inducing each symptom in *l*-5-HTP-treated mice were calculated by Probit analysis.

2.4. Effects on DOI-induced head-twitches

Mice were dosed orally with drugs at 50 min (fluoxetine, citalopram and amitriptyline) or 30 min (others) before DOI (2.5 mg/kg, i.p.). The number of head-twitches was counted at 5–10 min after DOI treatment. The ID$_{50}$ values of drugs for inhibiting head-twitches were calculated by linear regression.

2.5. Tail suspension test

The tail suspension test is based on the method of Steru et al. (1985). Mice were dosed orally at 48 min (fluoxetine, citalopram and amitriptyline) or 30 min (others) before the test. Mice were suspended by the tail for 6 min, and the duration of immobility was measured by an observer who was blinded to drug treatment.

2.6. Effects on the learning deficit and locomotor activity in olfactory-bulbectomized rats

Rats were olfactory bulbectomized by the method of Cairncross et al. (1978). In brief, a rat was anaesthetized

with sodium pentobarbital (50 mg/kg, i.p.) and placed on a stereotaxic frame. Two holes 5 mm anterior to the bregma and 2 mm lateral to the midline were drilled through the skull. The underlying olfactory bulbs were aspirated using a water suction pump. At least 1 week was allowed for recovery from surgery before the initiation of the study. All animals were tested on a step-through passive avoidance task. In this study, the test was conducted in a two-compartment passive avoidance apparatus (O'hara, Tokyo, Japan). When the rat entered the dark compartment from the light compartment, a foot-shock (40–60 V AC) was applied for 1 s through the metal grid of the floor. The procedure was repeated until the rat remained in the light compartment for at least 180 s. The number of trials needed by each rat to reach this learning criterion was recorded. In the single-treatment study, drugs were dosed intraperitoneally (i.p.) 60 min before the test. In the repeated-treatment study, drugs were dosed i.p. daily for 7 or 14 days, and the test was conducted 60 min after the last treatment.

The locomotor activity of the animals was studied in an 'open-field' apparatus. The animals were placed singly in the center of the 'open-field' apparatus. The number of times the animals crossed the partitions on the surface of the apparatus in a 3-min period was recorded.

2.7. Effects on the vasopressor response to phenylephrine in pithed rats

Rats were anaesthetized with ether and pithed by inserting a steel rod (1.5 mm in diameter) through the orbit and foramen magnum down into the spinal canal. Systemic arterial blood pressure was measured at the left carotid artery via a pressure transducer (TP-400T, Nihon Kohden, Tokyo, Japan) and recorded on a blood pressure amplifier (AP-641G, Nihon Kohden). Heart rate was measured with a heart rate counter (AT-601G, Nihon Kohden) triggered by the pulse pressure. The postsynaptic vascular α_1-adrenoceptor-blocking activities were assessed by antagonism of the α_1-adrenoceptor-mediated vasopressor effect of phenylephrine (Honda et al., 1986). Phenylephrine was injected into the right femoral vein through a cannula at intervals of approximately 5–10 min. The dose-response curves for phenylephrine were made before and 15 min after i.v. treatment with each dose of antagonist. The dose of antagonist required to produce an agonist dose ratio of 2 (DR_2) was calculated by the method of Arunlakshana and Schild (1959).

2.8. Effects on oxotremorine-induced tremors

Mice were dosed i.p. with drugs at 30 min before oxotremorine administration (1 mg/kg, i.p.). The number of mice in which tremor was elicited was counted at 5–10 min after oxotremorine treatment, and ID_{50} values for inhibition of tremor were calculated by Probit analysis.

2.9. Statistics

The results of the tail suspension test were analyzed by the Kruskal-Wallis *H*-test followed by the Wilcoxon multiple-comparison test. The learning deficit and spontaneous locomotor activity rate of olfactory-bulbectomized rats were analyzed by Kruskal-Wallis *H*-test followed by the Mann-Whitney *U*-test.

3. Results

3.1. l-5-HTP potentiation

YM992, fluoxetine and citalopram strongly potentiated *l*-5-HTP-induced behavioral effects in mice. The potency of YM992 was almost equivalent to that of fluoxetine (Table 2). The ED_{50} values of YM992 for inducing tremor, head-twitch and hind-limb abduction were 18.6, 27.9, 30.0 mg/kg (p.o.), respectively. This result indicates that YM992 shows 5-HT uptake inhibition activity in vivo. Trazodone, which has weak 5-HT uptake inhibition and potent $5\text{-}HT_{2A}$ receptor antagonistic activity, showed no potentiating effect even at a dose of 60 mg/kg (p.o.).

3.2. Effects on DOI-induced head-twitches

YM992 reduced the number of head-twitches induced by DOI. The ID_{50} value of YM992 for reducing the

Table 2
Potentiation of *l*-5-HTP symptoms by YM992 and other antidepressants

Compound	ED_{50} (mg/kg, p.o.) and 95% CL for causing the following symptoms in *l*-5-HTP-treated mice		
	Tremors	Head-twitches	Hind-limb abduction
YM992	18.6 (13.6–24.1)	27.9 (19.8–52.8)	30.0 (24.3–37.7)
Fluoxetine	23.0 (2.3–40.3)	30.8 (17.1–51.6)	39.1 (29.7–65.9)
Citalopram	4.6 (3.5–5.9)	4.3 (3.1–5.8)	7.6 (6.0–9.5)
Trazodone	> 60	> 60	> 60
Amitriptyline	> 60	> 60	> 60

l-5-HTP (90 mg/kg, i.v.) was administered 48 min (fluoxetine, citalopram and amitriptyline) or 30 min (others) after the injection of antidepressants. Symptoms including tremors, head-twitch and hind-limb abduction were evaluated from 5 to 10 min later in groups of 8 mice.

Table 3
Effects of YM992 and other antidepressants on DOI-induced head-twitches and oxotremorine-induced tremors

Compound	Inhibition of head-twitches in DOI-treated mice ID_{50} (mg/kg, p.o.) and 95% CL	Inhibition of tremors in oxotremorine-treated mice ID_{50} (mg/kg, i.p.) and 95% CL
YM992	20.6 (25.3–16.9)	> 100
Fluoxetine	> 60	> 60
Citalopram	> 60	> 100
Trazodone	2.0 (3.4–1.2)	> 100
Amitriptyline	11.2 (16.1–8.4)	13.6 (21.0–6.2)

DOI (2.5 mg/kg, i.p.) was administered 48 min (fluoxetine, citalopram and amitriptyline) or 30 min (others) after the injection of antidepressants. The number of head-twitches was counted from 5 to 10 min later in groups of 8 mice. Oxotremorine (1 mg/kg, i.p.) was administered 30 min after the injection of antidepressants. Tremors were evaluated 10-15 min later in groups of 8 mice.

number of head-twitches was 20.6 mg/kg (p.o.) (Table 3). This result indicates that YM992 shows 5-HT_{2A} receptor antagonistic activity in vivo. Fluoxetine and citalopram showed no 5-HT_{2A} receptor antagonistic activity even at a dose of 60 mg/kg (p.o.).

3.3. Tail suspension test

YM992 and amitriptyline were highly active in the mouse tail suspension test. These drugs decreased the immobility time in a dose-dependent manner, and these

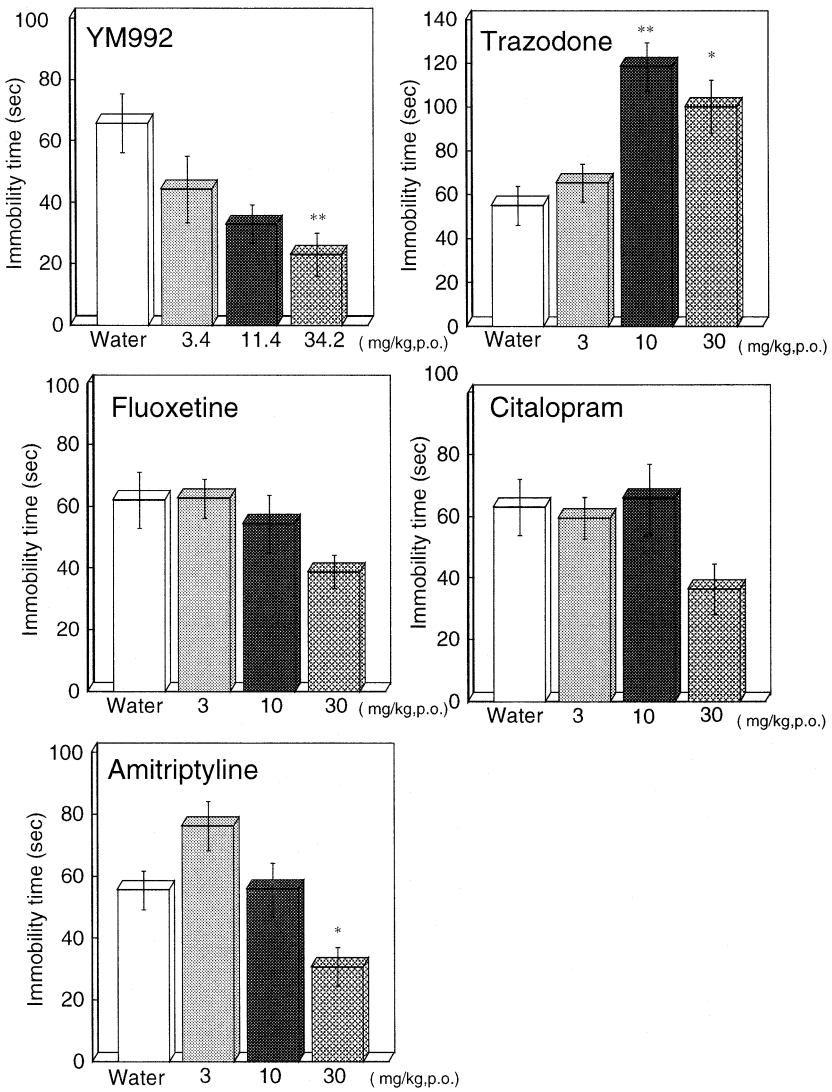

Fig. 1. Effects of YM992 and other antidepressants on immobility time in the mouse tail suspension test. Mice were dosed with drugs 48 min (fluoxetine and citalopram) or 30 min (others) before the test. Each value represents the mean ± S.E.M. ($n = 20$) of total immobility time (s). * $P < 0.05$, ** $P < 0.01$ versus water (Kruskal-Wallis H-test followed by Wilcoxon multiple-comparison test).

effects were statistically significant at a dose of 34.2 and 30 mg/kg (p.o.), respectively (Fig. 1). Citalopram and fluoxetine showed a tendency to reduce the immobility time. In contrast, trazodone significantly prolonged the immobility time.

3.4. Effects on learning deficit in olfactory-bulbectomized rats

Olfactory-bulbectomized rats required a significantly greater number of trials to reach the learning criterion than did sham-operated rats, indicating a learning deficit in olfactory-bulbectomized rats in a step-through passive avoidance task. Single treatment with YM992, fluoxetine and trazodone ameliorated this learning deficit (Fig. 2). Trazodone, but not YM992 and fluoxetine, significantly decreased the spontaneous activity of olfactory-bulbectomized rats at this dose (Fig. 3). The effect of a single treatment with fluoxetine disappeared after a 7- or 14-day treatment. The other antidepressants, citalopram and amitriptyline, were effective only after a 14-day treatment.

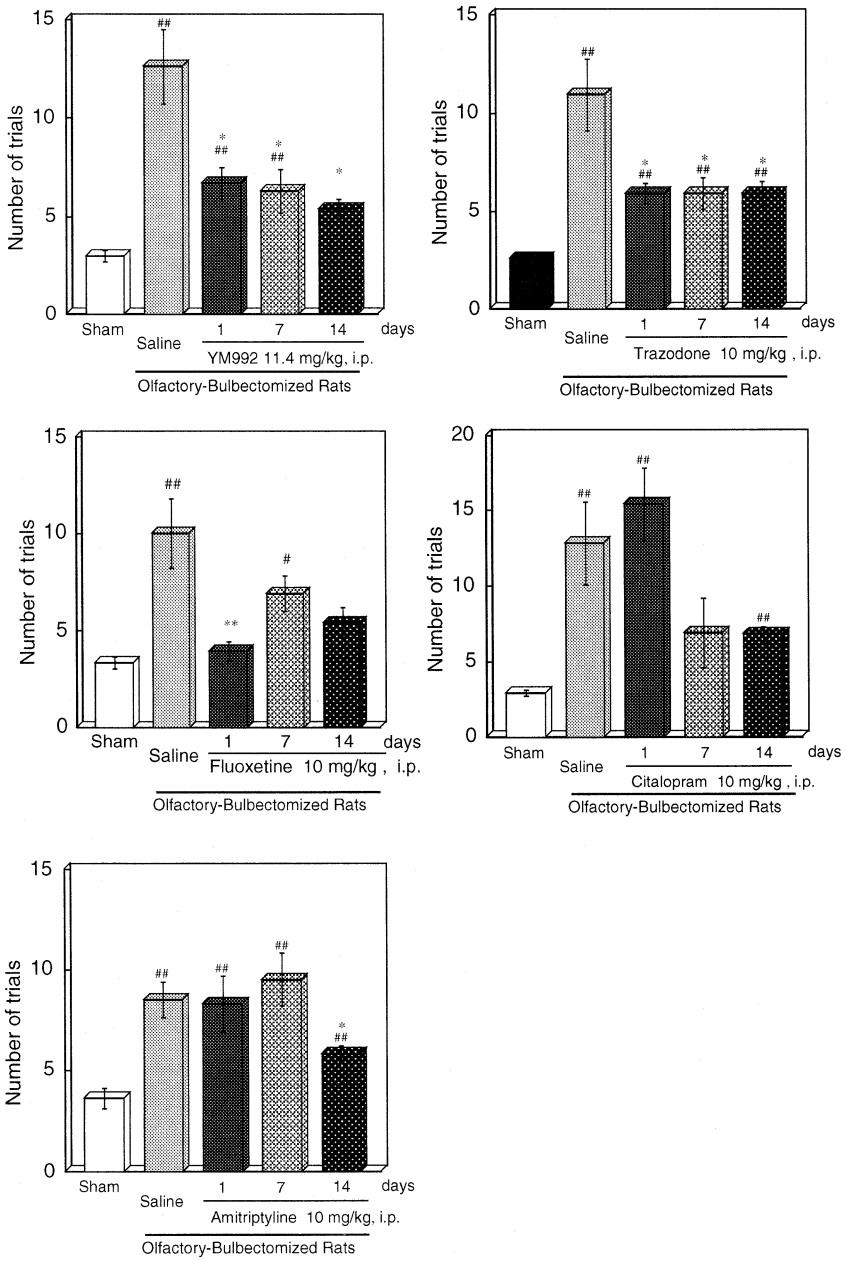

Fig. 2. Effects of YM992 and other antidepressants on the learning deficit of olfactory-bulbectomized rats in the passive avoidance task. Rats were dosed with drugs once or daily for 7 or 14 days, and the test was conducted at 60 min after the last treatment. Each value represents the mean ± S.E.M. ($n = 6–10$) of the number of trials needed to reach the criterion (the rat remained in the light compartment for 180 s). $^{\#}$ $P < 0.05$, $^{\#\#}$ $P < 0.01$ versus sham, * $P < 0.05$, ** $P < 0.01$ versus saline (Kruskal-Wallis H-test followed by Mann-Whitney U-test).

3.5. Effects on the vasopressor response to phenylephrine in pithed rats

YM992 and trazodone produced a dose-dependent and parallel shift of the log dose-response curve with respect to the increase in diastolic pressure elicited by phenylephrine. Based on DR_2 values obtained from Schild plots, YM992 ($DR_2 = 22.4$ mg/kg, i.v.) was approximately 10 times less potent than trazodone ($DR_2 = 2.2$ mg/kg, i.v.) (Fig. 4).

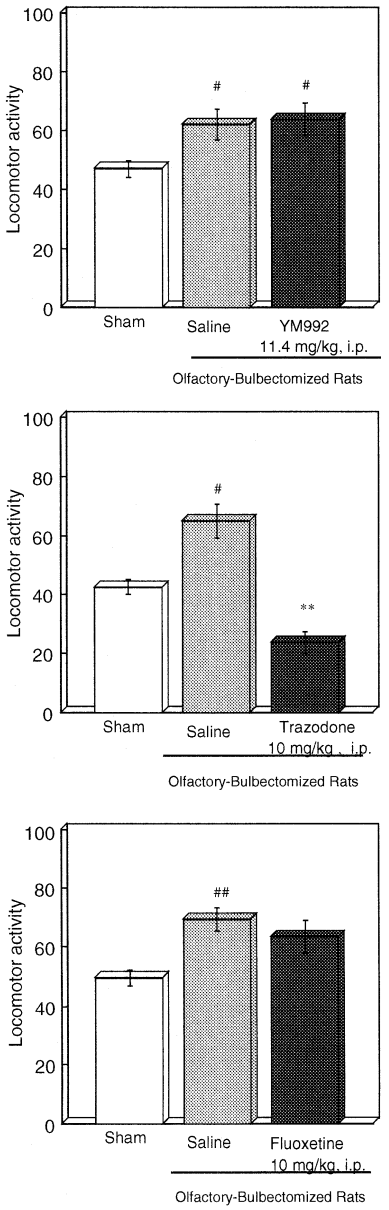

Fig. 3. Effects of YM992, fluoxetine and trazodone on the locomotor activity of olfactory-bulbectomized rats in the open-field apparatus. Rats were dosed with drugs 30 min before the test. Each value represents the mean ± S.E.M. ($n = 8$) of the number of line crossings in the open field. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ versus sham, $^{**}P < 0.01$ versus saline (Kruskal-Wallis *H*-test followed by Mann-Whitney *U*-test).

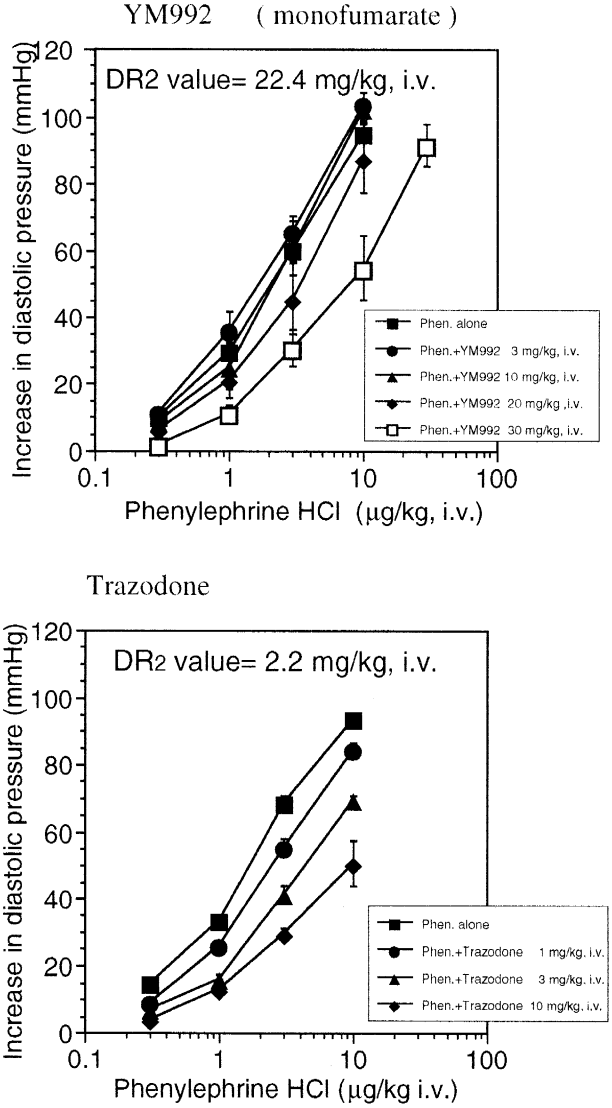

Fig. 4. Effects of YM992 and trazodone on the phenylephrine-induced vasopressor response in pithed rats. Each value represents the mean ± S.E.M. ($n = 3$–4).

3.6. Effects on oxotremorine-induced tremors

Neither YM992 nor other selective 5-HT re-uptake inhibitors showed any inhibiting effect on tremors induced by oxotremorine, even at a high dose. In contrast, amitriptyline inhibited oxotremorine-induced tremor, with an ID_{50} value of 13.6 mg/kg (i.p.) (Table 3).

4. Discussion

In the *l*-5-HTP potentiation study, YM992 as well as other selective 5-HT re-uptake inhibitors such as citalopram and fluoxetine showed 5-HT uptake inhibition activity. Their order of potency was correlated with their binding affinity for 5-HT uptake sites. In contrast, trazodone

showed no effect in this study even at a high dose. It is reported that monoamine uptake inhibitors with antagonistic activity on other receptors, especially on 5-HT_2 receptors, block *l*-5-HTP-induced behaviors (Lucki et al., 1984). However, YM992, which also has potent affinity for 5-HT_2 receptors, potentiated these behaviors. Thus the insufficient effect of trazodone may be due to its lower affinity for 5-HT uptake sites than that of YM992. In fact, it has been reported that the inhibitory activity of trazodone on 5-HT uptake sites is weaker than that of desmethylimipramine, which is well known as a selective norepinephrine re-uptake inhibitor (Riblet et al., 1979).

YM992 as well as trazodone inhibited DOI-induced head-twitches. In contrast, fluoxetine and citalopram showed no 5-HT_{2A} receptor antagonistic activity. This finding reflects the lack of affinity of these drugs for 5-HT_2 receptors. Although DOI is a 5-$HT_{2A/2C}$ agonist, it is reported that head-twitch is induced by stimulation of the 5-HT_{2A} subtype (Darmani et al., 1994), indicating that YM992 acts on 5-HT_{2A} receptors as an antagonist in vivo. These results demonstrated that YM992, unlike the selective 5-HT re-uptake inhibitors and trazodone, possesses both 5-HT uptake inhibition and 5-HT_{2A} receptor antagonistic activity in vivo. In vitro assays have demonstrated that YM992 possesses selective 5-HT uptake inhibition and 5-HT_{2A} receptor antagonistic activity (Hatanaka et al., 1996).

YM992 as well as amitriptyline were highly active in the mouse tail suspension test. This model is one of the widely used screening models in which positive results are generally indicative of antidepressant activity in clinical use (Steru et al., 1985). Fluoxetine and citalopram showed a tendency to reduce the immobility time, but their effects were not significant. This result suggests that, in addition to its 5-HT uptake inhibition activity, the 5-HT_{2A} receptor antagonistic activity of YM992 may contribute to its high efficacy. Although trazodone has potent affinity for 5-HT_{2A} receptors, it significantly prolonged the immobility time. This prolongation effect of trazodone is probably due to its low affinity for 5-HT uptake sites and/or a sedative effect based on its α_1-adrenoceptor antagonistic activity.

It is well known that many behavioral and endocrine changes in olfactory-bulbectomized rats, such as aggressiveness, hyperactivity, anhedonia, passive avoidance deficit and increase in serum corticosterone level, can be reversed by either acute or chronic administration of antidepressants (Cairncross et al., 1979; Jesberger and Richardson, 1986). These changes are considered to relate to abnormalities in 5-HTergic neurotransmission in the olfactory-bulbectomized rat (Janscar and Leonard, 1981; Neckers et al., 1975). Because the reversal of the passive avoidance deficit in olfactory-bulbectomized rats is specific to antidepressants, the behavior of these rats is useful as an antidepressant screening model (Jesberger and Richardson, 1986). In the present study YM992 and trazodone, unlike citalopram and amitriptyline, reversed the passive avoidance deficit in olfactory-bulbectomized rats after single as well as after 14-day treatment. The effect of trazodone may be attributable to its sedative effect, which derives from its α_1-adrenoceptor antagonistic activity, because only trazodone significantly reduced the locomotor activity of olfactory-bulbectomized rats. However, the 5-HT uptake inhibition and 5-HT_{2A} receptor antagonistic activity of these drugs would be expected to contribute to this acute amelioration. Indeed, the 5-HT uptake inhibition of trazodone is much weaker than that of YM992, but there is the possibility that the weak inhibition of trazodone plays an important role in this model, in which the hypofunction of the 5-HTergic system is observed. Although amitriptyline also possesses both 5-HT uptake inhibition and potent 5-HT_{2A} receptor antagonistic activity, its potent anticholinergic or antihistaminergic activity, which decreases with chronic treatment, would counteract its acute ameliorative effect. Single treatment with fluoxetine also ameliorated this deficit, but the effect disappeared with chronic treatment. The disappearance of amelioration may be involved with the up-regulation of 5-HT_2 receptors observed after chronic treatment with this drug (Hrdina and Vu, 1993). From these results the amelioration produced by these antidepressants may be related to the facilitation of 5-HTergic neurotransmission and/or antagonism of 5-HT_{2A} receptors. Combination treatment with selective 5-HT re-uptake inhibitors and selective 5-HT_{2A} receptor antagonists will be needed to examine this hypothesis. Different from fluoxetine, citalopram ameliorated the deficit only after chronic treatment. The reason for this difference is unknown. However, it is reported that olfactory bulbectomy in the rat decreases the norepinephrine levels and turnover in various brain areas (Jesberger and Richardson, 1986). The selectivity of fluoxetine for 5-HT uptake compared to norepinephrine uptake is much less than that of citalopram, which is the most selective 5-HT re-uptake inhibitor (Johnson, 1991). The difference in selectivity for monoamine uptake between these drugs may be related to the acute ameliorating effect of fluoxetine.

Among 5-HT receptor subtypes, 5-HT_{1A} and 5-HT_{2A} receptors are especially considered to be involved in the pathogenesis of depression and the effect of antidepressant treatments. A decrease in the endocrine response to 5-HT_{1A} agonists in depressive patients (Lesch et al., 1990) and an increase in the number of 5-HT_{2A} receptors in the frontal cortex of suicide victims have been reported (Mann et al., 1990). Long-term treatment with tricyclic antidepressants or electroconvulsive shocks induces the up-regulation of postsynaptic 5-HT_{1A} receptors (Chaput et al., 1991; Hayakawa et al., 1993; Welner et al., 1989). Moreover, it is well known that chronic treatment with many antidepressants induces the down-regulation of 5-HT_{2A} receptors (Cowen, 1990, 1991). Chronic treatment with selective 5-HT re-uptake inhibitors is also reported to enhance 5-HTergic neurotransmission, in particular that mediated by postsynaptic 5-HT_{1A} receptors (Blier and De Montigny,

1994). Although 5-HT uptake inhibition is observed after acute treatment with selective 5-HT re-uptake inhibitors in vitro, these compounds also take several weeks to alleviate the symptoms of depression. This is probably explained by the fact that an increase in 5-HT concentration in the postsynaptic area, such as the frontal cortex or hippocampus, is produced only after chronic treatment with selective 5-HT re-uptake inhibitors, which causes the desensitization of 5-HT autoreceptors (Blier et al., 1990; Chaput et al., 1991).

In addition, recent studies have demonstrated an interaction between 5-HT_{1A} and 5-HT_2 receptors, in which 5-HT_2 antagonists electrophysiologically, biochemically and behaviorally potentiate 5-HT_{1A}-mediated responses (Backus et al., 1990; Blier et al., 1990; Lakoski and Aghajanian, 1985; Weiss et al., 1986). Therefore, YM992, which has both 5-HT uptake inhibition and 5-HT_{2A} receptor antagonistic activity, would ameliorate abnormalities of 5-HTergic neurotransmission more efficiently than selective 5-HT re-uptake inhibitors, especially those mediated by postsynaptic 5-HT_{1A} receptors. This property of YM992 would contribute to its high efficacy in the animal models examined in this study and its antidepressant effect in clinical use.

The major advantage of selective 5-HT re-uptake inhibitors over tricyclic antidepressants is that they are largely devoid of the severe side effects seen with tricyclic antidepressants, such as dry mouth, drowsiness and orthostatic hypotension. This low propensity of selective 5-HT re-uptake inhibitors to cause adverse effects is mainly due to their lack of effect on acetylcholine and histamine receptors and adrenoceptors. Although YM992 has moderate affinity for α_1-adrenoceptors (Hatanaka et al., 1996), which is associated with orthostatic hypotension or sedation in clinical use, the intrinsic α_1-adrenoceptor antagonistic activity of YM992 in pithed rats was much weaker than that of trazodone. In addition, YM992 lacked an anticholinergic effect in mice. These data, therefore, indicate that YM992, like selective 5-HT re-uptake inhibitors, will be a much safer antidepressant than tricyclic antidepressants.

In conclusion, the data reported in the present study indicate that the pharmacological profile of YM992 is different from that of tricyclic antidepressants and selective 5-HT re-uptake inhibitors, and that YM992 has high efficacy in various tests, some of which predict the antidepressant activity of drugs. It is therefore suggested that YM992 represents a new type of antidepressant and may have a potent antidepressant effect in clinical use.

References

Arunlakshana, O., Schild, H.O., 1959. Some quantitative uses of drug antagonists. Br. J. Pharmacol. 14, 46–58.

Backus, L.I., Sharp, T., Grahame-Smith, D.G., 1990. Behavioral evidence for a functional interaction between central 5-HT_2 and 5-HT_{1A} receptors. Br. J. Pharmacol. 100, 793–799.

Blier, P., De Montigny, C., 1994. Current advances and trends in the treatment of depression. Trends Pharmacol. Sci. 15, 220–225.

Blier, P., De Montigny, C., Chaput, Y., 1990. A role for the serotonin system in the mechanism of action of antidepressants. J. Clin. Psychiatry 51 (Suppl. 1), 14–20.

Bogdanski, D.F., Weissbach, H., Udenfriend, S., 1958. Pharmacological studies with the serotonin precursor, 5-hydroxytryptophan. J. Pharmacol. Exp. Ther. 122, 182–194.

Cairncross, K.D., Cox, B., Forster, C., Wren, A.F., 1978. A new model for the detection of antidepressant drugs: olfactory bulbectomy in the rat compared with exiting models. J. Pharmacol. Methods 1, 131–143.

Cairncross, K.D., Wren, A., Foster, C., Cox, B., Schnieden, H., 1979. The effect of psychoactive drugs on plasma corticosterone levels and behavior in the bulbectomized rat. Pharmacol. Biochem. Behav. 10, 353–359.

Chaput, Y., De Montigny, C., Blier, P., 1991. Presynaptic and postsynaptic modification of the serotonin system by long-term administration of antidepressant treatments. An in vivo electrophysiologic study in the rat. Neuropsychopharmacology 5, 219–229.

Cowen, P.J., 1990. Antidepressant: current concepts of mode of action. Int. Clin. Psychopharmacol. 5 (Suppl. 3), 45–55.

Cowen, P.J., 1991. Serotonin receptor subtypes: implications for psychopharmacology. Br. J. Psychiatry 159 (Suppl. 12), 7–14.

Darmani, N.A., Mock, O.B., Towns, L.C., Gerdes, C.F., 1994. The head-twitch response in the least shrew (*Cryptotis parva*) is a 5-HT_2- and not a 5-HT_{1C}-mediated phenomenon. Pharmacol. Biochem. Behav. 48, 383–396.

Hatanaka, K., Nomura, T., Hidaia, K., Takeuchi, H., Yatsugi, S., Fujii, M., Yamaguchi, T., 1996. Biochemical profile of YM992, a novel selective serotonin re-uptake inhibition with 5-HT_{2A} receptor antagonistic activity. Psychopharmacology 35, 1621–1626.

Hayakawa, H., Yokota, N., Shimizu, M., Yamawaki, S., 1993. Repeated treatment with electroconvulsive shock increase numbers of serotonin$_{1A}$ receptors in the rat hippocampus. Biog. Amines 9, 295–306.

Honda, K., Nakagawa, C., Inagaki, O., Shibasaki, M., Takenaka, T., Takeda, M., 1986. Adrenoceptor blocking and cardiovascular effects of the optical isomers of amosulalol (YM-09538), a combined α-and β-adrenoceptor blocking agent, and the corresponding deoxy derivative (YM-11133) in rats. Jpn. J. Pharmacol. 41, 459–466.

Hrdina, P.D., Vu, T.B., 1993. Chronic fluoxetine treatment upregulates 5-HT uptake sites and 5-HT_2 receptors in rat brain: an autoradiographic study. Synapse 14, 324–331.

Janscar, S.M., Leonard, B.E., 1981. The effects of antidepressant drugs on conditioned taste of aversion learning of the olfactory bulbectomized rat. Neuropharmacology 20, 1341–1345.

Jesberger, J.A., Richardson, J.S., 1986. Effects of antidepressant drugs on the behavior of olfactory bulbectomized and sham-operated rats. Behav. Neurosci. 100, 256–274.

Johnson, A.M., 1991. The comparative pharmacological properties of selective serotonin re-uptake inhibitors in animals. In: Feighner, J.P., Boyer, W.F. (Eds.), Selective Serotonin Re-uptake Inhibitors. John Wiley&Sons, Chichester, pp. 37–70.

Lakoski, J.M., Aghajanian, G.K., 1985. Effects of ketanserin on neuronal responses to serotonin in the prefrontal cortex, lateral geniculate and dorsal raphe nucleus. Neuropharmacology 24, 265–273.

Leonard, B.E., 1995. Mechanisms of action of antidepressants. CNS Drugs 4, 1–12.

Lesch, K.P., Mayer, S., Disselkamp-Tietze, J., Hoh, A., Wiesmann, M., Osterheider, M., Schulte, H.M., 1990. 5-HT_{1A} receptor responsivity in unipolar depression: evaluation of ipsapirone-induced ACTH and cortisol secretion in patients and controls. Biol. Psychiatry 28, 620–628.

Lucki, I., Nobler, M.S., Frazer, A., 1984. Differential actions of serotonin antagonists on two behavioral models of serotonin receptor activation in the rat. J. Pharmacol. Exp. Ther. 228, 133–139.

Mann, J.J., Arango, V., Underwood, D., 1990. Serotonin and suicidal behavior. Ann. NY Acad. Sci. 600, 476–484.

Neckers, L.M., Zarrow, M.X., Myers, M.M., Denenberg, V.H., 1975. Influence of olfactory bulbectomy and the serotonergic system upon intermale aggression and maternal behavior in the mouse. Pharmacol. Biochem. Behav. 3, 545–550.

Riblet, L.A., Gatewood, C.F., Mayol, R.F., 1979. Comparative effects of trazodone and tricyclic antidepressants on uptake of selected neurotransmitters by isolate rat brain synaptosomes. Psychopharmacology 63, 99–101.

Steru, L., Chermat, R., Thierry, B., Simon, P., 1985. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology 85, 367–370.

Weiss, S., Sebben, M., Kemp, D.E., Bockaert, J., 1986. Serotonin 5-HT_1 receptors mediate inhibition of cyclic AMP production in neurons. Eur. J. Pharmacol. 120, 230–277.

Welner, S.A., De Montigny, C., Desroches, J., Desjardins, P., Suranyl-Cadotte, B.E., 1989. Autoradiographic quantification of serotonin$_{1A}$ receptors in rat brain following antidepressant drug treatment. Synapse 4, 347–352.