Effect of YM992, a Novel Antidepressant With Selective Serotonin Re-uptake Inhibitory and 5-HT$_{2A}$ Receptor Antagonistic Activity, on a Marble-Burying Behavior Test as an Obsessive-Compulsive Disorder Model

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ABSTRACT—YM992 ((S)-2-[[7-fluoroindan-4-yl]oxy]methyl)morpholine) monohydrochloride is a novel antidepressant with selective serotonin (5-hydroxytryptamine, 5-HT) re-uptake inhibition and 5-HT$_{2A}$ receptor antagonistic activity. The effects of YM992 and two selective 5-HT re-uptake inhibitors (SSRIs) were studied in a marble-burying behavior test as a model of an obsessive-compulsive disorder (OCD) in mice at doses of 5, 10 and 15 mg/kg, i.p. YM992 and fluoxetine significantly inhibited marble-burying behavior at a dose of 15 mg/kg (i.p.) without affecting spontaneous locomotor activities. Citalopram also significantly inhibited the behavior at doses of 5, 10 and 15 mg/kg (i.p.) without affecting spontaneous locomotor activities. These results suggest that YM992, as well as SSRIs, may exhibit anti-OCD activity in addition to an antidepressive effect in clinical use.

Keywords: YM992, Obsessive-compulsive disorder, Marble-burying behavior test

Obsessive-compulsive disorder (OCD) is characterized by repeated, persistent and dysphoric thoughts (obsessions), which are ego-dystonic, repetitive, seemingly purposeful behaviors (compulsions) (1). At present, the most efficacious pharmacological treatments for OCD are antidepressants with serotonin (5-hydroxytryptamine, 5-HT) re-uptake inhibition (2). One tricyclic antidepressant (TCA), clomipramine, and four selective 5-HT re-uptake inhibitors (SSRIs), fluvoxamine, fluoxetine, paroxetine and sertraline, are approved by the Food and Drug Administration (FDA) for use in patients with OCD (3). YM992 ((S)-2-[[7-fluoroindan-4-yl]oxy]methyl)morpholine) monohydrochloride is a novel compound with selective 5-HT re-uptake inhibition and 5-HT$_{2A}$ receptor antagonistic activity (4). The pharmacological profile of YM992 is different from that of TCAs and SSRIs, and it shows high efficacy in various tests, some of which predict the antidepressant activity of drugs (5).

In the present study, we examined the anti-anxiety activity, especially the anti-OCD activity, of YM992 in comparison with effects of SSRIs using a marble-burying behavior test. The marble-burying behavior test is suggested to be a useful model for evaluating anti-OCD drugs (6).

YM992 monohydrochloride was synthesized in our laboratory. Citalopram hydrobromide (H. Lundbeck & Co. A/S, Copenhagen, Denmark) and fluoxetine hydrochloride (Eli Lilly & Co., Indianapolis, IN, USA) were obtained commercially. All compounds were dissolved in saline. YM992 monohydrochloride, citalopram hydrobromide and fluoxetine hydrochloride were used as YM992, citalopram and fluoxetine, respectively. The doses of all drugs were expressed in terms of the free base.

Male ICR mice (SLC, Shizuoka) weighing 28 – 40 g were used. The marble-burying behavior test was based on the method of Njung’e et al. (7). Drugs were dosed intraperitoneally (i.p.) 20 min before the test. The mice were placed individually in plastic cages (21 × 38 × 14 cm) containing 20 clean glass marbles (10 mm in diameter) evenly spaced on 5 cm deep sawdust (β-chip) without food or water. The results of marble-burying behavior were expressed as the number of marbles at least two-thirds buried in this paradigm within 20 min.

The locomotor activity of mice measured by using a SUPER-MEX sensor (Muromachi Kikai Co., Ltd., Tokyo).
Twenty minutes after i.p. injection, the mice were placed individually in plastic cages (21 × 38 × 14 cm) bedded with 5-cm-deep sawdust (β-chip). The results of locomotor activity were expressed as total counts of locomotor activities for 20 min.

All animal procedures were approved by the ethical committee of Yamanouchi Pharmaceutical Co., Ltd.

The results of the marble-burying behavior test were analyzed by the Steel test. The results of the locomotor activity were analyzed by the Dunnett multiple comparison test.

YM992 and fluoxetine inhibited marble-burying behavior in a dose-dependent manner, and the effect was statistically significant at a dose of 15 mg/kg (i.p.) (Fig. 1: A and B). At this dose, no significant changes were observed in spontaneous locomotor activities (Fig. 2: A and B). Citalopram also inhibited marble-burying behavior in a dose-dependent manner, and the effect was statistically significant at doses of 5, 10 and 15 mg/kg (i.p.) (Fig. 1C). It did not significantly affect spontaneous locomotor activities (Fig. 2C).

OCD is a disorder characterized by recurrent and persistent thoughts, impulses or images (obsessions), and/or repetitive behaviors or mental acts (compulsions) causing a significant impairment of functioning (1). Although OCD is classified as an anxiety disorder, practical anxiolytic agents are generally ineffective in reducing OCD symptoms. In clinical reports, SSRIs and clomipramine are effective in reducing OCD symptoms. Clomipramine is a monoamine re-uptake inhibitor that inhibits both noradrenaline (NE) and 5-HT, but it is one of the most potent inhibitors of 5-HT re-uptake as compared with other monoamine reuptake inhibitors (8). With clomipramine treatment, the decrease in obsessional symptoms correlates with the decrease in the concentration of the 5-HT metabolite 5-hydroxyindole acetic acid (5-HIAA) in cerebrospinal fluid (CSF), implicating the inhibition of 5-HT re-uptake in the anti-OCD effect (9). It is therefore proposed that a dysfunction of the 5-HTergic system may be involved in OCD, although the pathological details of OCD are still unknown.

The marble-burying behavior test has been described as an OCD model (6). SSRIs, which have been found to be effective against human OCD symptoms, inhibit marble-burying behavior (7). Moreover, since burying-behavior is not habituating, it is suggested that it is compulsive (6).

In this study, YM992 as well as fluoxetine and citalopram significantly inhibited marble-burying behavior without affecting spontaneous locomotor activities. These effects were therefore not attributable to non-specific sedative effects. The results of fluoxetine and citalopram were consistent with previous studies (10, 11). Their order of potency was correlated with their 5-HT re-uptake inhibition activities in the l-5-HTP potentiation study (5).
YM992 exhibits 5-HT re-uptake inhibition and 5-HT<sub>2A</sub>-receptor antagonistic activity (4, 5). This property would contribute to efficacy of YM992 in various tests for evaluating antidepressant activity (5). Several reports suggested that 5-HT<sub>2A</sub> receptor antagonistic activity also contributes to the anti-OCD effects. Some drugs with 5-HT<sub>2A</sub> receptor antagonistic activity potentiated the effect of zimeldine, which is one of SSRIs, on the marble-burying behavior test (7). (±)-1-(2,5-Dimethoxy-4-iodophenyl)2-amino-propane (DOI), a 5-HT<sub>2A/2C</sub> agonist, was reported to disrupt in rats prepulse inhibition (PPI), which is also deficient in OCD patients, via 5-HT<sub>2A</sub> receptors (12). Furthermore, the co-administration of risperidone, which exhibits 5-HT<sub>2A</sub> and dopamine 2 (D<sub>2</sub>) receptor antagonistic activities, with SSRIs is reported to be effective in SSRI-refractory OCD patients (13). Taken together, YM992 would be expected to exert more favorable effect in OCD patients compared to SSRIs, but nevertheless, the effect of YM992 in the marble-burying behavior test is equipotent to other SSRIs in this study. Consequently further investigation will be needed.

In conclusion, YM992 significantly inhibits marble-burying behavior, which is a model for evaluating clinical potential in the treatment of OCD. The underlying mechanisms of OCD are still unknown, but this result suggests that YM992 may exhibit anti-OCD activity in addition to an antidepressive effect in clinical use.

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