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Involvement of the sigma$_1$ receptor in inhibiting activity of fluvoxamine on marble-burying behavior: Comparison with paroxetine

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Abstract

In the present study, we examined the involvement of the sigma$_1$ receptor in the inhibitory effect of the selective serotonin reuptake inhibitor (SSRI) fluvoxamine, compared with that of paroxetine, on marble-burying behavior, which is an animal model of obsessive–compulsive disorder. Sigma$_1$ receptor agonists (+)-SKF 10047 and PRE-084 significantly inhibited marble-burying behavior. Sigma receptor antagonist BD 1047 and selective sigma$_1$ receptor antagonist BD 1063 significantly attenuated the inhibition of marble-burying behavior by fluvoxamine. In contrast, selective sigma$_2$ receptor antagonist SM-21 failed to affect the inhibition of marble-burying behavior by fluvoxamine. On the other hand, BD 1047 and BD 1063 had no effect on the inhibition of marble-burying behavior by paroxetine. These observations show that activation of the sigma$_1$ receptor is a necessary component in the inhibitory effect of fluvoxamine on marble-burying behavior, and that the mechanism of its action is clearly different from that of paroxetine.

Keywords: Serotonin reuptake inhibitor; Marble-burying behavior; Sigma$_1$ receptor; Fluvoxamine; obsessive–compulsive disorder

1. Introduction

Obsessive–compulsive disorder is a psychiatric condition with a lifetime prevalence of 1–3%, and is characterized by recurrent and persistent thoughts, impulses or images (obsessions), and/or repetitive, seemingly purposeful behaviors (compulsions) (e.g., doubting, checking and washing) (Rasmussen and Eisen, 1992; Sasson et al., 1997). Although classified as an anxiety disorder, patients with obsessive–compulsive disorder demonstrate a high incidence of comorbid depression (Sasson et al., 1997). Currently, the serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors (SRIs) and selective 5-HT reuptake inhibitors (SSRIs) are considered the first choice agents for pharmacological treatment of obsessive–compulsive disorder (Greist et al., 2003). However, up to 50% of patients with obsessive–compulsive disorder fail to respond in an SSRIs trial (Goodman et al., 1989).

Marble-burying behavior is considered to be a potential model of obsessive–compulsive disorder, on the basis of behavioral similarity (Ichimaru et al., 1995; Londei et al., 1998; Njung'e and Handley, 1991). Indeed, SSRIs such as fluvoxamine and paroxetine, which have been used to treat human obsessive–compulsive disorder symptoms, inhibit marble-burying behavior, without affecting locomotor activity (Harasawa et al., 2006; Hirano et al., 2005; Ichimaru et al., 1995; Shinomiya et al., 2005). On the other hand, the inhibition of marble-burying behavior by SSRI fluvoxamine is antagonized by NAN-190, a 5-HT$_{1A}$ receptor antagonist (Ichimaru et al., 1995). Moreover, we have previously reported that a 5-HT$_{1A}$/5-HT$_7$ receptor agonist (±)-8-Hydroxy-2-(di-n-propylamino)tetralin hydrobromide (8-OH-DPAT) inhibits marble-burying behavior, without affecting locomotor activity, and this inhibition is antagonized by WAY 100135, a 5-HT$_{1A}$ receptor antagonist (Matsushita et al., 2005). These findings suggest that the 5-HT$_{1A}$ receptor is involved in marble-burying behavior.

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Sigma receptors consist of two subtypes, sigma$_1$ and sigma$_2$ receptors (Bowen et al., 1989). The sigma$_1$ receptor, localized intracellularly within neurons, is a 223-amino acid protein, which has been cloned in several animal species and humans (Hanner et al., 1996; Kekuda et al., 1996; Pan et al., 1998; Seth et al., 1997, 1998). The sigma$_1$ receptor mediates a potent modulation of several neurotransmitter systems by affecting intracellular second messengers systems, particularly Ca^{2+} mobilization (Hayashi et al., 2000; Hayashi and Su, 2001). On the other hand, the sigma$_2$ receptor is enriched in lipid rafts, which affect Ca^{2+} signaling through sphingolipid products, and is related to cellular growth and apoptosis (Crawford and Bowen, 2002; Gebreselassie and Bowen, 2004). SSRIs possess high-to-moderate affinity for sigma$_1$ receptors but not sigma$_2$ receptors (Narita et al., 1996; Sanchez and Meier, 1997). Among the SSRIs, fluvoxamine has the highest affinity for sigma$_1$ receptors, whereas paroxetine has weak affinity for sigma$_1$ receptors. Interestingly, sigma$_1$ receptor stimulation demonstrates antidepressant- and anxiolytic-like properties in mice (Bermack and Debonnel, 2005; Kamei et al., 1996). Furthermore, neurosteroids dehydroepiandrosterone sulfate and pregnenolone sulfate behave as sigma$_1$ receptor agonists, and show beneficial effects in memory processes, stress and depression, through the sigma$_1$ receptor (Maurice et al., 1999, 2001; Reddy et al., 1998; Urani et al., 2001). These findings suggest that this receptor may in some way play a role in the mechanism of action of fluvoxamine. However, whether the sigma$_1$ receptor is involved in the inhibition of marble-burying behavior by fluvoxamine remains unconfirmed. Therefore, we investigated the involvement of the sigma$_1$ receptor in the inhibitory effect of fluvoxamine on marble-burying behavior, compared with the effect of paroxetine.

2. Materials and methods

2.1. Animals

Five-week-old male ICR mice (Nihon SLC, Shizuoka, Japan) were used in each experiment. For at least 7 days before the behavioral tests, the mice were housed in a room under controlled temperature (23±2 °C), 60±10% relative humidity, and a cycle of 12 h light and 12 h dark, with the period of light starting at 07:00 h. The animals had free access to food (CE-2, Crea Japan, Tokyo, Japan) and water in their home cages. All procedures regarding animal care and use were performed in compliance with the regulations established by the Experimental Animal Care and Use Committee of Fukuoka University.

2.2. Drugs

N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)ethylamine dihydrobromide (BD 1047), 1-[2-(3,4-dichlorophenyl)ethyl]-4-methylpiperazine dihydrochloride (BD 1063), (±)-tropanyl-2-(4-chorophenoxy)-butanoate maleate (SM-21) and 2S-(2α,6α,11R)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride [(+)-SKF 10047] were purchased from Tocris Cookson, (MO, USA). 2-(4-morpholinethyl)-1-phenylcyclohexanecarboxylate hydrochloride (PRE-084) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Fluvoxamine maleate and paroxetine hydrochloride hemihydrate were generous gifts from Solvay Pharmaceutical (Tokyo, Japan) and GlaxoSmithKline (West Sussex, UK), respectively. Fluvoxamine and paroxetine were dissolved in distilled water, and were administered orally 60 min before the test. BD 1047, BD 1063, SM-21, (+)-SKF 10047 and PRE-084 were dissolved in saline, and were administered intraperitoneally (i.p.) 30 min before the test.

2.3. Marble-burying behavior test

The marble-burying behavior test was performed as described previously (Matsushita et al., 2005). All experiments were conducted between 10:00 and 17:00 h. The mice were placed individually in clear plastic boxes (30×30×28 cm), containing 25 glass marbles (1.5 cm in diameter) evenly spaced on sawdust 5 cm deep, without food and water. At the same time, the locomotor activity of mice was measured using an automated activity counter (NS-AS01; Neuroscience, Tokyo, Japan) placed 15 cm above the same plastic boxes. The activity was measured with the illumination of a 100 W bulb. The results of marble-burying behavior were expressed as the number of marbles buried to at least two-thirds of the depth, within 30 min. The observer did not know which agent was being tested.

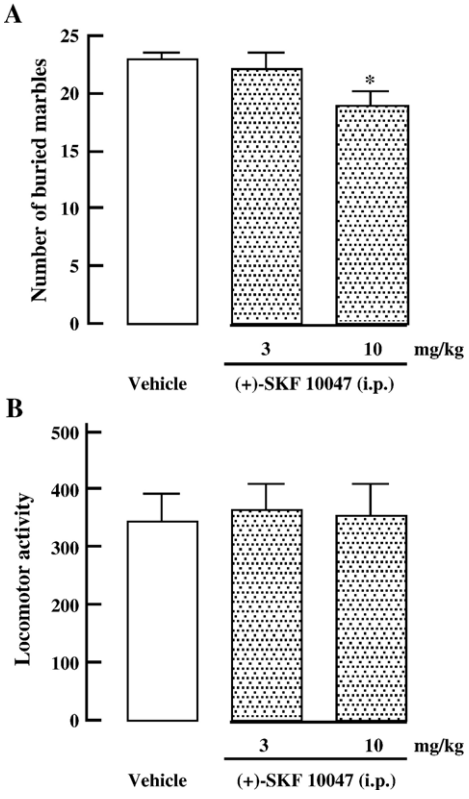

Fig. 1. Effect of (+)-SKF 10047 on marble-burying behavior in mice. (A) Marble-burying behavior, (B) locomotor activity. Values are expressed as the mean±SEM (n=9–10). *P<0.05 compared to the vehicle-treated group (Student–Newman–Keuls post-hoc test).

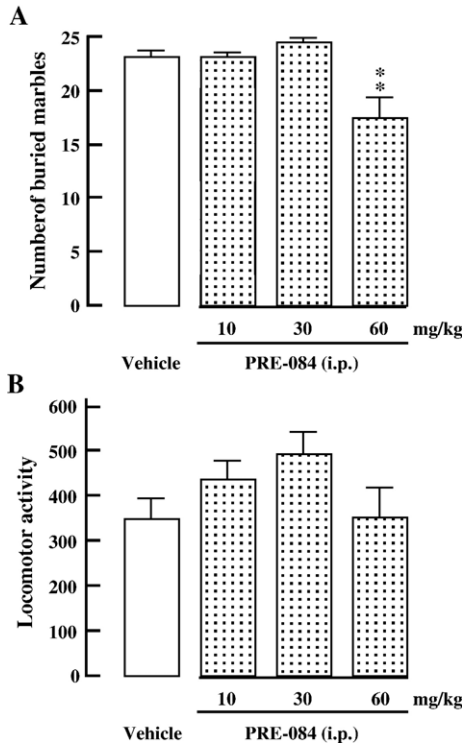

Fig. 2. Effect of PRE-084 on marble-burying behavior in mice. (A) Marble-burying behavior, (B) locomotor activity. Values are expressed as the mean± SEM (n=8–10). **P<0.01 compared to the vehicle-treated group (Student–Newman–Keuls post-hoc test).

2.4. Statistical analysis

The results obtained in the marble-burying behavior test were analyzed using one-way analysis of variance (ANOVA), followed by the Student–Newman–Keuls post-hoc test to determine whether there were differences between the groups. A probability level of $P<0.05$ was accepted as statistically significant. Values are expressed as the mean±SEM.

3. Results

To examine whether sigma receptor agonists exhibited inhibitory effect on obsessive–compulsive disorder, their effects were examined using the animal model of obsessive–compulsive disorder. The sigma$_1$ receptor agonist (+)-SKF 10047, at a dose of 10 mg/kg, significantly reduced the number of buried marbles, without affecting locomotor activity [number of buried marbles: $F(2,26)=4.000$, $P<0.05$ by one-way ANOVA; $P<0.05$ by the Student–Newman–Keuls post-hoc test; locomotor activity: $F(2,26)=0.047$, $P>0.1$ by one-way ANOVA, Fig. 1]. Similarly, PRE-084, at a dose of 60 mg/kg, the sigma$_1$ receptor agonist, significantly reduced the number of buried marbles without affecting locomotor activity [number of buried marbles: $F(3,30)=8.687$, $P<0.001$ by one-way ANOVA; $P<0.01$ by the Student–Newman–Keuls post-hoc test; locomotor activity: $F(3,30)=1.849$, $P>0.1$ by one-way ANOVA, Fig. 2].

Fluvoxamine at a dose of 30 mg/kg significantly reduced the number of buried marbles, without affecting locomotor activity [$F(4,48)=11.019$, $P<0.0001$ by one-way ANOVA; $P<0.01$ by the Student–Newman–Keuls post-hoc test, Fig. 3]. Similarly, paroxetine at a dose of 3 mg/kg significantly reduced the number of buried marbles, without affecting locomotor activity [$F(4,41)=3.549$, $P<0.05$ by one-way ANOVA; $P<0.05$ by the Student–Newman–Keuls post-hoc test, Fig. 4]. The effect of the sigma receptor antagonist BD 1047 on the inhibition of marble-burying behavior by fluvoxamine or paroxetine was examined. BD 1047 attenuated the inhibition of marble-burying behavior by fluvoxamine at a dose of 3 mg/kg ($P<0.05$ by the Student–Newman–Keuls post-hoc test, Fig. 3A). No change in locomotor activity during the marble-burying behavior was observed at this time [$F(4,48)=0.406$, $P>0.05$ by one-way ANOVA, Fig. 3B]. In addition, BD 1047 alone at the same dose had no effect on the number of buried marbles and locomotor activity ($P>0.05$ by the Student–Newman–Keuls post-hoc test, Fig. 3). On the other hand, BD 1047 had no effect on the inhibition of marble-burying behavior by paroxetine in the 1–10 mg/kg dose range ($P>0.05$ by the Student–Newman–Keuls post-hoc test, Fig. 4A). Moreover, the drug did not affect the locomotor activity in paroxetine-treated mice [$F(4,41)=0.907$, $P>0.1$ by one-way ANOVA, Fig. 4B].

The effect of the selective sigma$_1$ receptor antagonist BD 1063 on the inhibition of marble-burying behavior by fluvoxamine or paroxetine was then examined. BD 1063 attenuated

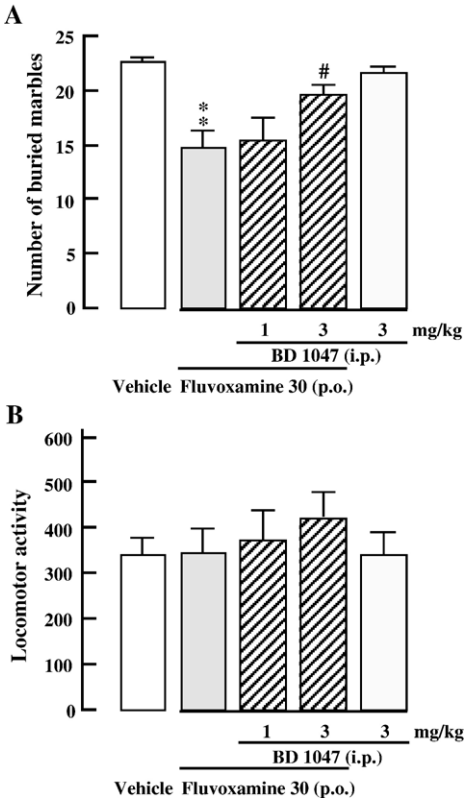

Fig. 3. Effect of BD 1047 on inhibition of marble-burying behavior by fluvoxamine in mice. (A) Marble-burying behavior, (B) locomotor activity. Values are expressed as the mean±SEM (n=8–14). **P<0.01 compared to the vehicle-treated group, $^{\#}P$<0.05 compared to the group treated with fluvoxamine alone (Student–Newman–Keuls post-hoc test).

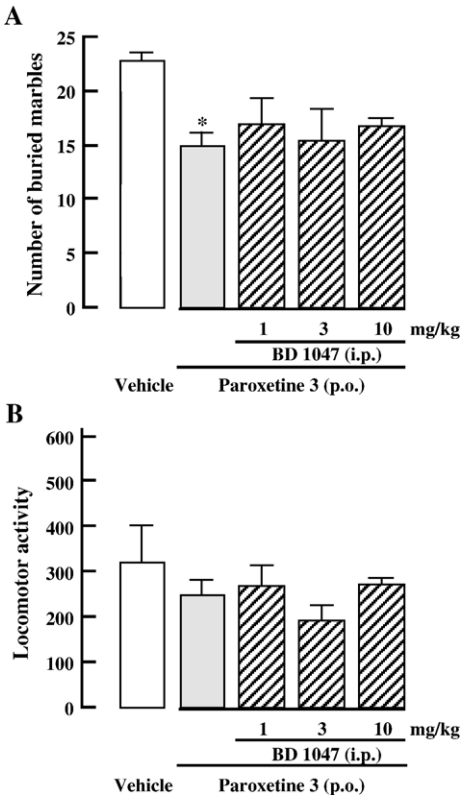

Fig. 4. Effect of BD 1047 on inhibition of marble-burying behavior by paroxetine in mice. (A) Marble-burying behavior, (B) locomotor activity. Values are expressed as the mean ± SEM (n = 8–13). *P < 0.05 compared to the vehicle-treated group (Student–Newman–Keuls post-hoc test).

the inhibition of marble-burying behavior by fluvoxamine at a dose of 1 mg/kg [$F(4,53) = 11.217$, $P < 0.0001$ by one-way ANOVA; $P < 0.05$ by the Student–Newman–Keuls post-hoc test, Fig. 5A]. No change in locomotor activity during the marble-burying behavior was observed at this time [$F(4,53) = 2.233$, $P > 0.05$ by one-way ANOVA, Fig. 5B]. In addition, BD 1063 alone at this effective dose had no effect on the number of buried marbles and locomotor activity ($P > 0.05$ by the Student–Newman–Keuls post-hoc test, Fig. 5). However, a higher dose (3 mg/kg) of BD 1063 alone significantly increased the locomotor activity (data not shown). Therefore, the higher dose was not used in this study. On the other hand, BD 1063 had no effect on the inhibition of marble-burying behavior by paroxetine [$F(3,41) = 9,251$, $P < 0.0001$ by one-way ANOVA; $P > 0.05$ by the Student–Newman–Keuls post-hoc test, Fig. 6A]. Moreover, the drug failed to affect the locomotor activity in paroxetine-treated mice [$F(3,41) = 0.059$, $P > 0.1$ by one-way ANOVA, Fig. 6B].

The effect of the selective sigma$_2$ receptor antagonist SM-21 on the inhibition of marble-burying behavior by fluvoxamine was also examined. SM-21 failed to affect the inhibition of marble-burying behavior by fluvoxamine in the 0.3–10 mg/kg dose range [$F(4,49) = 8.163$, $P < 0.0001$ by one-way ANOVA; $P > 0.05$ by the Student–Newman–Keuls post-hoc test, Fig. 7A]. In addition, high dose (10 mg/kg) SM-21 significantly increased locomotor activity in fluvoxamine-treated mice [$F(4,49) = 3.332$, $P < 0.05$ by one-way ANOVA; $P < 0.05$ by the Student–Newman–Keuls post-hoc test, Fig. 7B].

4. Discussion

The present pharmacological study showed that activation of the sigma$_1$ receptor is a necessary component of the inhibitory effect of fluvoxamine on marble-burying behavior. First, SSRIs fluvoxamine and paroxetine inhibited marble-burying behavior, without affecting locomotor activity. The present findings are consistent with those of previous studies (Harasawa et al., 2006; Hirano et al., 2005; Ichimaru et al., 1995; Shinomiya et al., 2005). Second, the sigma receptor antagonist BD 1047 and selective sigma$_1$ receptor antagonist BD 1063 significantly attenuated the inhibition of marble-burying behavior by fluvoxamine, without affecting locomotor activity. In contrast, selective sigma$_2$ receptor antagonist SM-21 did not affect the inhibition of marble-burying behavior by fluvoxamine. Therefore, sigma$_1$ receptor agonistic activity may be involved in the inhibition of marble-burying behavior by fluvoxamine. On the other hand, we found that BD 1047 and BD 1063 had no effect on the inhibition of marble-burying behavior by paroxetine. These findings indicate that the effect of paroxetine is not due to sigma$_1$ receptor-mediated mechanisms. Indeed, fluvoxamine has the highest affinity for the sigma$_1$ receptors, whereas

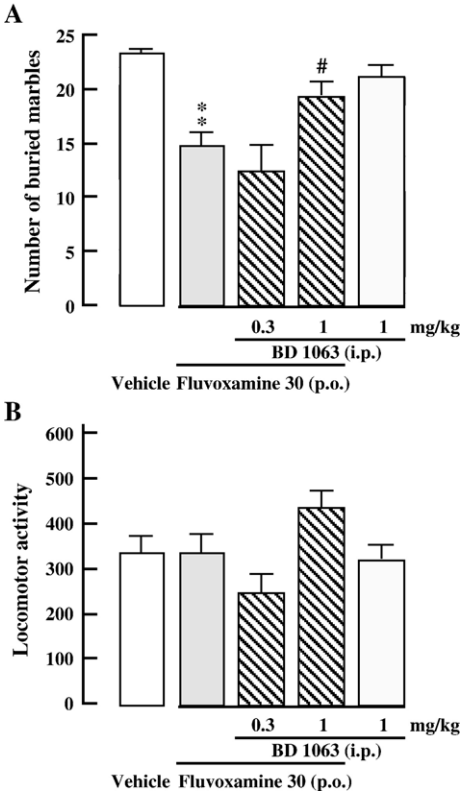

Fig. 5. Effect of BD 1063 on inhibition of marble-burying behavior by fluvoxamine in mice. (A) Marble-burying behavior, (B) locomotor activity. Values are expressed as the mean ± SEM (n = 8–14). **P < 0.01 compared to the vehicle-treated group, $^{\#}P$ < 0.05 compared to the group treated with fluvoxamine alone (Student–Newman–Keuls post-hoc test).

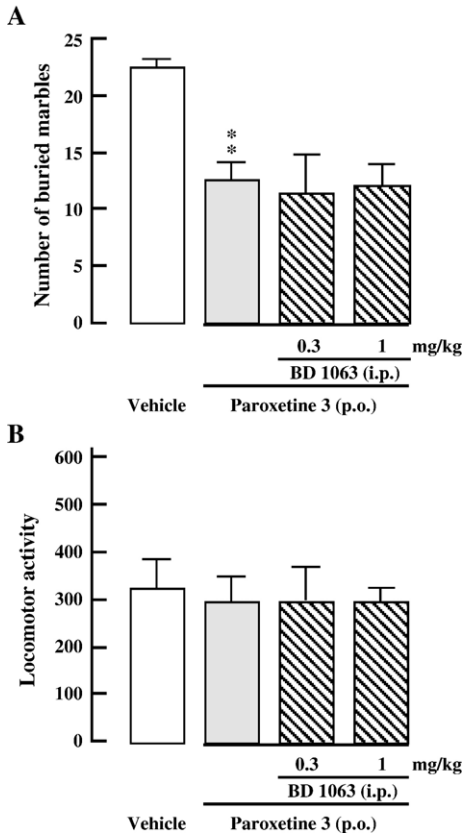

Fig. 6. Effect of BD 1063 on inhibition of marble-burying behavior by paroxetine in mice. (A) Marble-burying behavior, (B) locomotor activity. Values are expressed as the mean±SEM (n=8–16). **P<0.01 compared to the vehicle-treated group (Student–Newman–Keuls post-hoc test).

paroxetine has only weak affinity (Narita et al., 1996; Sanchez and Meier, 1997). It has also been reported that fluvoxamine, but not paroxetine, improves the phencyclidine-induced cognitive deficits in mice, and its effect is due to the agonistic activity of fluvoxamine at the sigma$_1$ receptors (Hashimoto et al., 2007). Thus, the mechanism of inhibitory effect of fluvoxamine is clearly different from that of paroxetine.

SSRIs, such as fluvoxamine and paroxetine, exert their effects by inhibiting the uptake of 5-HT from the synaptic cleft (Bosker et al., 1995; Gartside et al., 1995). The pharmacological potencies of SSRIs in the attenuation of marble-burying behavior correlate significantly with their brain 5-HT transporter (SERT) binding activities, and the *in vivo* SERT-binding potency of paroxetine is stronger than that of fluvoxamine (Hirano et al., 2005). Therefore, fluvoxamine may inhibit marble-burying behavior through not only inhibition of SERT but also the activation of sigma$_1$ receptors, whereas paroxetine may inhibit this behavior through mainly inhibition of SERT.

We found that the sigma$_1$ receptor agonists (+)-SKF 10047 and PRE-084 significantly inhibited marble-burying behavior, without affecting locomotor activity. These findings suggest that activation of the sigma$_1$ receptor exhibits inhibitory effect on obsessive–compulsive disorder. The sigma$_1$ receptor is a unique intraneuronal protein, mediating an effective and wide-range neuromodulatory action in the brain. In particular, a recent hypothesis suggests that it acts a sensor/modulator of intracellular Ca^{2+} mobilization and homeostasis on the endoplasmic reticulum membrane, because activation of the receptor by agonists such as PRE-084 enhanced binding of inositol 1,4,5-triphosphate ($InsP_3$) to its receptor, and Ca^{2+} mobilization from $InsP_3$ receptor-sensitive pools (Hayashi et al., 2000; Hayashi and Su, 2001). Consequently, the sigma$_1$ receptor has been involved in learning and memory processes, the response to stress, depression, neuroprotection and pharmacodependence (Maurice et al., 1999, 2001). Furthermore, neurosteroids dehydroepiandrosterone sulfate and pregnenolone sulfate behave as sigma$_1$ receptor agonists, and produce antidepressant-like effects through the sigma$_1$ receptor (Reddy et al., 1998). The data presented in this paper show that the sigma$_1$ receptor is a new pharmacological target for obsessive–compulsive disorder.

Interestingly, sigma$_1$ receptor agonists such as (+)-pentazocine increase the firing activity of 5-HT neurons of the dorsal raphe nucleus (Bermack and Debonnel, 2001). Sigma$_1$ receptor agonist OPC-14523, similarly to other sigma receptor agonists, induces a significant increase in the firing activity of 5-HT neurons of the dorsal raphe nucleus (Bermack et al., 2004). This increase in firing activity is blocked by the coadministration of sigma$_1$ receptor antagonist *N,N*-dipropyl-2-(4-methoxy-3-(2-phenylethoxy)phenyl)ethylamine (NE-100), suggesting that it is mediated by sigma$_1$ receptors. In addition, OPC-14523 induces a decrease in the responsiveness of the 5-HT_{1A} autoreceptor (Bermack et al., 2004). Furthermore, recent electrophysiological

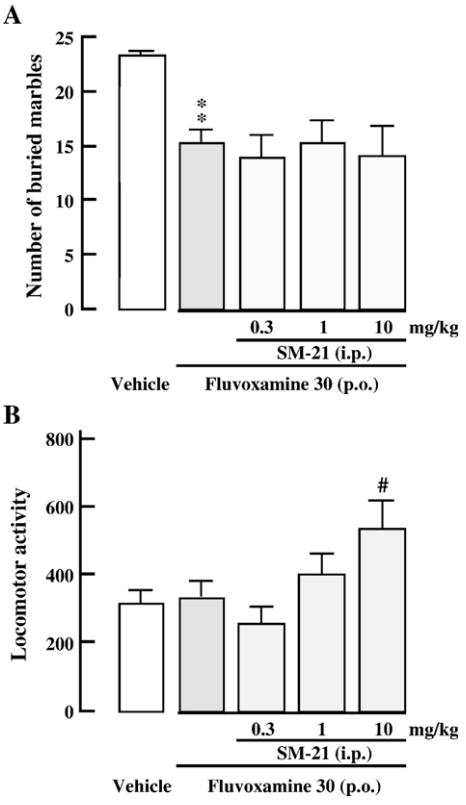

Fig. 7. Effect of SM-21 on inhibition of marble-burying behavior by fluvoxamine in mice. (A) Marble-burying behavior, (B) locomotor activity. Values are expressed as the mean±SEM (n=8–15). **P<0.01 compared to the vehicle-treated group (Student–Newman–Keuls post-hoc test).

studies in the rat have shown that neurosteroids such as dehydroepiandrosterone sulfate increase the firing activity of 5-HT neurons in the dorsal raphe nucleus, and at least some of these effects are mediated through activation of sigma receptors, since they are reversed by NE-100 (Robichaud et al., 2002). These findings suggest a clear modulation of 5-HT neurotransmission by sigma$_1$ receptors.

In conclusion, the study presented here demonstrates for the first time that activation of the sigma$_1$ receptor is a necessary component in the inhibitory effect of fluvoxamine on marble-burying behavior, and that the mechanism of its action is clearly different from that of paroxetine.

Acknowledgments

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