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Involvement of the sigma$_1$ receptor in the antidepressant-like effects of fluvoxamine in the forced swimming test in comparison with the effects elicited by paroxetine

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ABSTRACT

We studied the involvement of the sigma$_1$ receptor in the antidepressant-like effects of the selective serotonin reuptake inhibitor (SSRI) fluvoxamine in DBA/2 mice using the forced swimming test. The effects of the selective sigma$_1$ receptor antagonist N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino) ethylamine (BD1047) at 1 mg/kg significantly antagonized the anti-immobility elicited by fluvoxamine (10 mg/kg). However, the anti-immobility effects elicited by another SSRI, paroxetine (5 m/kg), were not altered by BD1047. The selective sigma$_1$ receptor agonist 2*S*-(2α,6α,11*R**)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocin-8-ol ((+)SKF-10047) elicited dose-dependent anti-immobility effects in DBA/2 mice. BD1047 significantly blocked the anti-immobility effects induced by (+)SKF-10047 at 10 mg/kg. These results suggested that the sigma$_1$ receptor was associated with fluvoxamine-induced antidepressant-like effects but not with paroxetine-induced antidepressant-like effects.

1. Introduction

Sigma receptors are non-opioid, non-phencyclidine receptors located within neurons (Maurice et al., 2001). There are two types of sigma receptors: 1 and 2. Activation of sigma$_1$ receptors enhances influx of calcium ions (Ca^{2+}), leading to the modulation of several physiological functions (Hayashi et al., 2000; Maurice et al., 2001). Many sigma$_1$ receptors are present in the brain (Maurice et al., 2001). Studies have suggested that these receptors are linked to neurological disorders such as schizophrenia, anxiety or depression (Bermack and Debonnel, 2005; Lucas et al., 2008a,b; Maurice et al., 2001).

Fluvoxamine and paroxetine are selective serotonin reuptake inhibitors (SSRIs). They are used for therapy of major depression, anxiety and panic disorder (Figgitt and McClellan, 2000; Wagstaff et al., 2002). Fluvoxamine and paroxetine have a high affinity for the 5-hydroxytryptamine (5-HT; serotonin) transporter, and inhibit reuptake of 5-HT (Figgitt and McClellan, 2000; Wagstaff et al., 2002). Recent studies on the mechanism of action of fluvoxamine have focused on the involvement of the sigma$_1$ receptor because fluvoxamine shows high affinity for sigma$_1$ receptors but not for sigma$_2$ receptors (Narita et al., 1996). In contrast, paroxetine has low affinity for sigma$_1$ receptors (Narita et al., 1996). Hashimoto et al. reported that attenuation of cognitive deficits by fluvoxamine in mice is mediated by sigma$_1$ receptors, and that paroxetine has no such effect (Hashimoto et al., 2007).

The typical evaluation method for antidepressants is the forced swimming test as proposed by Porsolt et al. (1977). This test is used extensively in mice and rats. Many antidepressants (including tricyclic antidepressants and the atypical antidepressant mianserin) have been shown to shorten the immobility time (Porsolt et al., 1977; Sugimoto et al., 2002; Yamada and Sugimoto, 2002).

It has been reported that the sigma$_1$ receptor may have a role in depression because the sigma$_1$ receptor agonists (+)SKF-10047 and igmesine reduce the immobility time in the forced swimming test (Urani et al., 2001; Villard et al., 2011). Fluvoxamine acts as a sigma$_1$ receptor agonist, but whether the antidepressant effects of fluvoxamine are related to sigma$_1$ receptors is not known.

We reported that the baseline immobility time in the forced swimming test is quite different in various strains of mice (ICR, ddY, C57BL, DBA/2 and BALB/c) and that this phenomenon is associated with levels of binding to the 5-HT transporter and not

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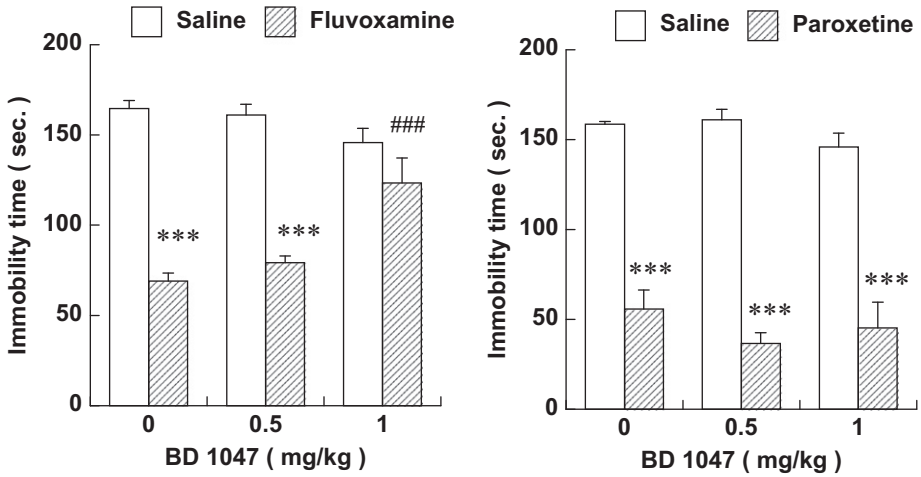

Fig. 1. Effects of BD1047 on fluvoxamine- and paroxetine-induced anti-immobility in DBA/2 mice. Results are the mean ± S.E.M. ($N=5$). Fluvoxamine (10 mg/kg) and paroxetine (5 mg/kg) were given via the intraperitoneal (i.p.) route. BD1047 was injected i.p. 30 min before fluvoxamine or paroxetine. $^{***}P<0.001$ vs. saline of the respective group. $^{\#\#\#}P<0.001$ vs. saline + fluvoxamine-treated groups.

with those of binding to the noradrenaline transporter (Sugimoto et al., 2008). Furthermore, we found that there were variations in responses to fluvoxamine and paroxetine in different strains of mice. DBA/2 mice were the most sensitive to fluvoxamine and paroxetine because these SSRIs shortened the immobility time (Sugimoto et al., 2008, 2011).

In the present study, using DBA/2 mice, we examined the involvement of the sigma$_1$ receptor in the antidepressant-like effects of fluvoxamine in the forced swimming test and compared the effects with those elicited by paroxetine.

2. Materials and methods

Experiments were undertaken in accordance with the Guiding Principles for Care and Use of Laboratory Animals as approved by The Japanese Pharmacological Society. The study protocol was approved by the Ethics Committee of the Yokohama College of Pharmacy (Yokohama, Japan).

2.1. Animals

Male DBA/2Cr mice (age, 6–7 weeks) were purchased from SLC Japan Inc. (Shizuoka, Japan). Mice were housed in groups of 5 under a controlled 12–12-h light–dark cycle (light from 7 am to 7 p.m.) with a room temperature of 23 ± 1 °C and humidity of 55 ± 5%. Mice had free access to food and water. Each mouse was used only once.

2.2. Forced swimming test

The forced swimming test was carried out according to the methods described by Porsolt et al. (1977) and our previous reports (Sugimoto et al., 2008; Yamada and Sugimoto, 2002). Each mouse was placed in a 25-cm glass cylinder (diameter, 10 cm) containing 10 cm of water at 23 ± 1 °C. Immobility was recorded during a 6-min swimming test. Mice were judged to be immobile if they floated, their hindlimbs were immobile, and if only small movements of the forepaws were made to keep the head above the water level.

2.3. Drugs and treatment

Fluvoxamine maleate and paroxetine maleate were obtained from Sigma-Aldrich (St. Louis, MO, USA). 2*S*-(2α,6α,11*R**)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride ((+)SKF-10047) and N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino) ethylamine dihydrobromide (BD1047) were purchased from Tocris Bioscience (Bristol, UK). All drugs were dissolved in physiological (0.9%) saline. All drugs were injected via the intraperitoneal (i.p.) route. Mice in the control group received saline. BD1047 was administered 30 min before fluvoxamine, paroxetine or (+)SKF-10047. Thirty minutes after treatment with fluvoxamine, paroxetine, and (+)SKF-10047, the forced swimming test was carried out. The doses of (+)SKF-10047 and BD1047 chosen were those that had been shown to stimulate or block the respective receptors (Egashira et al., 2007; Ago et al., 2011).

2.4. Measurement of locomotor activity

The locomotor activity of mice was measured using a digital counter with an infrared sensor (NS-AS01, Neuroscience Inc., Tokyo, Japan) following the method described in previous reports (Sugimoto et al., 2008, 2011). An infrared sensor was set over an open-top clear polycarbonate cage (22.5 × 33.8 × 14.0 cm) into which each mouse was placed. Locomotor activity was determined over 10 min. The apparatus was used to detect and record a digital count of the horizontal movements of animals.

2.5. Statistical analysis

Results are means ± S.E.M. of 5–6 mice in behavioral studies. Effects of (+)SKF-10047 on the immobility time in each mouse strain were analyzed by one-way ANOVA followed by Dunnett's multiple comparison *post-hoc* test. The influences of BD1047 on the anti-immobility effects of fluvoxamine, paroxetine and (+)SKF-10047 were analyzed by two-way ANOVA followed by Tukey's multiple comparison *post-hoc* test.