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The antipsychotic trifluoperazine reduces marble-burying behavior in mice via D_2 and 5-HT_{2A} receptors: Implications for obsessive–compulsive disorder

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ABSTRACT

Trifluoperazine, a typical antipsychotic drug, not only antagonizes dopamine D_2 receptors but also enhances serotonin 5-HT_2 receptor-mediated behavior. Moreover, trifluoperazine suppresses human purinergic receptor P2X7 responses and calmodulin. However, the effect of trifluoperazine on marble-burying behavior, which has been considered an animal model of obsessive–compulsive disorder (OCD), has not been studied. Here, we examined the effect of trifluoperazine on marble-burying behavior in mice. Oral administration of paroxetine, a selective serotonin reuptake inhibitor, significantly reduced marble-burying behavior without affecting total locomotor activity. Similar results were obtained for trifluoperazine (3 mg/kg). The D_2 receptor agonist, quinpirole (0.03 mg/kg, intraperitoneal [i.p.]), and 5-HT_{2A} receptor antagonist, ketanserin (0.3 mg/kg, i.p.), significantly counteracted this reduction of marble-burying behavior by trifluoperazine. These results show that trifluoperazine reduces marble-burying behavior via D_2 and 5-HT_{2A} receptors, and may be a useful drug for the treatment of OCD.

1. Introduction

Obsessive–compulsive disorder (OCD) is a psychiatric condition with a lifetime prevalence of 1–3%, which is characterized by recurrent and persistent thoughts, impulses or mental images (obsessions), and/or repetitive, seemingly purposeful behaviors (compulsions) (for example, doubting, checking, and washing). OCD is classified as "Obsessive–compulsive and related disorders" (DSM-5) (American Psychiatric Association, 2013). Serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors (SRIs), especially selective 5-HT reuptake inhibitors (SSRIs), are first-line agents for the pharmacological treatment of OCD (Greist et al., 2003). However, up to 50% of patients with OCD failed to respond in a SSRI trial (Goodman et al., 1989). Therefore, many studies have assessed the effectiveness of antipsychotic augmentation for refractory OCD (Dold et al., 2013).

To date, there have been many attempts to develop animal models of OCD. Among them, marble-burying behavior is a pharmacological model for study of OCD (Ichimaru et al., 1995). It is reduced by SSRIs such as fluvoxamine and paroxetine, which have been used to treat the symptoms of human OCD (Egashira et al., 2007, 2012; Hirano et al., 2005; Ichimaru et al., 1995). This behavior reflects repetitive and compulsive behaviors rather than novelty-induced anxiety (Londei et al., 1998; Thomas et al., 2009). More recently, it has been proposed as assessment of compulsive-like behaviors characteristic of OCD (Mitra et al., 2017a, 2017b). In addition, some atypical antipsychotic drugs reduce marble-burying behavior without affecting locomotor activity (Egashira et al., 2008b; Matsushita et al., 2005).

Trifluoperazine, a typical antipsychotic drug, not only antagonizes dopamine D_2 receptors but also enhances 5-HT_2 receptor-mediated behavior (Kim et al., 1999). Trifluoperazine was also reported to be superior to a placebo for treatment of generalized anxiety disorder in a randomized, double-blind, placebo-controlled trial (Gao et al., 2006). Moreover, trifluoperazine is as effective as paroxetine in suppressing human purinergic receptor P2X7 responses, which link inflammation to depressive disorders (Dao-Ung et al., 2015). Trifluoperazine strongly inhibits calmodulin (Prozialeck and Weiss, 1982). We previously reported that oral administration of trifluoperazine reduced both mechanical allodynia and increased Ca^{2+}/calmodulin dependent protein

Abbreviations: DOI, (±)-2,5-dimethoxy-4-iodoamphetamine; 5-HT, serotonin; OCD, obsessive–compulsive disorder; 8-OH-DPAT, 8-hydroxy-2-(dipropylamino)tetralin; SERT, serotonin transporter; SRIs, serotonin reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TFP, trifluoperazine

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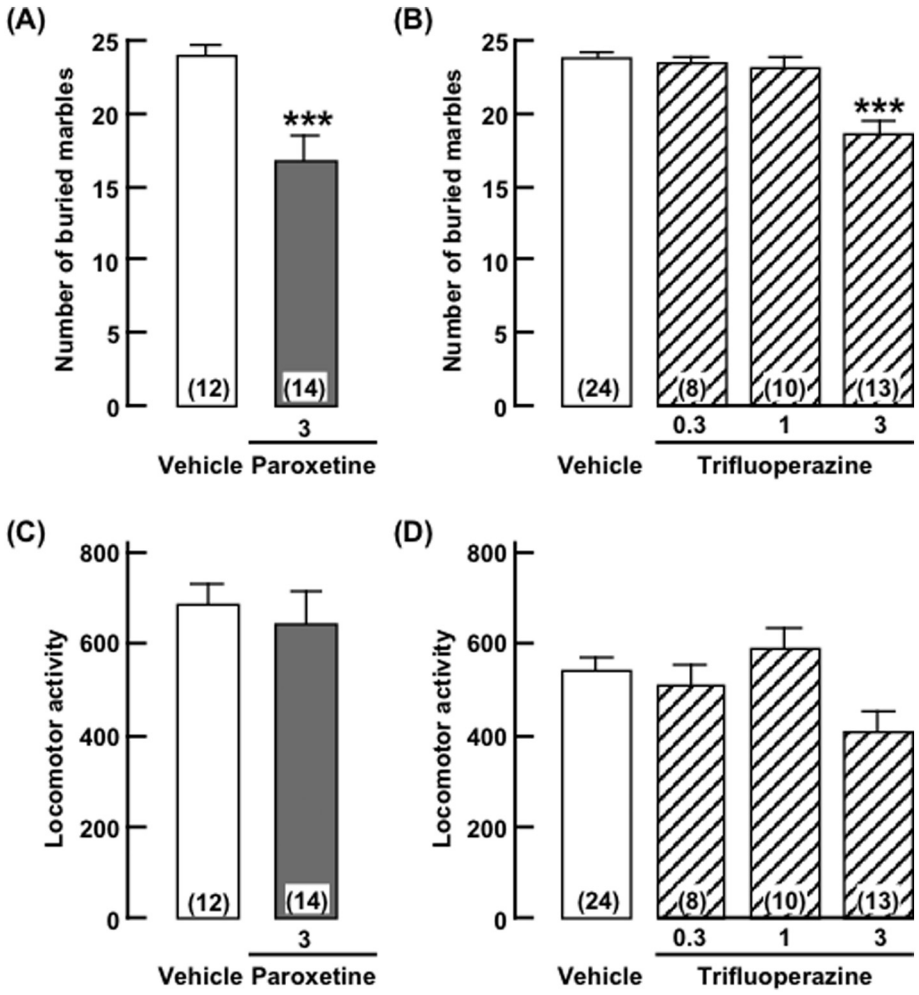

Fig. 1. Effect of paroxetine (A, C) and trifluoperazine (B, D) on marble-burying behavior in mice. Data are presented as number of buried marbles (A, B) and total locomotor activity (C, D). Paroxetine (3 mg/kg) and trifluoperazine (0.3, 1, and 3 mg/kg) were administered orally 60 min or 30 min before the test, respectively. Values are expressed as mean ± SEM. ***$P < 0.001$ compared with the vehicle-treated group (Mann–Whitney U test or Scheffe's test). The number of mice is shown at the bottom of each column.

kinase II (CaMKII) phosphorylation induced by oxaliplatin, a platinum-based chemotherapeutic agent (Shirahama et al., 2012). Treatment of cancer cells with trifluoperazine reduces angiogenesis and prevents cancer cell invasion through D_2 receptors to modulate the β-catenin pathway (Pulkoski-Gross et al., 2015). Most recently, trifluoperazine has been reported to inhibit glioblastoma invasion by binding to calmodulin and disinhibiting calcium release channel inositol 1,4,5-trisphosphate receptor subtype 3 (Kang et al., 2017). Calcium signaling seems to be related in the marble-burying behavior. We previously reported that calcium channel antagonists reduced marble-burying behavior (Egashira et al., 2008a). We also found that a calcium chelator EDTA/AM reduced marble-burying behavior (unpublished data). Recently, calcium signaling pathway has been reported to be associated with the clinical response to SSRIs and SSRIs with antipsychotics in patients with OCD (Umehara et al., 2016). Thus, trifluoperazine has not only antipsychotic effect but also various pharmacological effects. However, the effect of trifluoperazine on marble-burying behavior has not been studied. Therefore, we investigated the effect of trifluoperazine on marble-burying behavior in mice.

2. Materials and methods

2.1. Animals

Male ICR mice, 5-week-old, were obtained from Japan SLC Inc. (Hamamatsu, Japan). Mice were used at age 6–12 weeks in each experiment. The mice were housed in groups of four per cage. The total number of mice used was 224. For at least 7 days before the behavioral tests, the mice were housed in a room under controlled temperature (23 ± 2 °C), relative humidity (60 ± 2%), and ambient lighting (12 h light–dark cycle, with the light period starting at 07:00 h) conditions. The animals had free access to food (CE-2; Clea Japan, Tokyo, Japan) and water in their home cages. All animal care and use procedures were performed in compliance with the regulations established by the Experimental Animal Care and Use Committee of Fukuoka University, which are in accordance with the universal principles of laboratory animal care.

2.2. Drugs

Trifluoperazine dihydrochloride, quinpirole hydrochloride, and ketanserin tartrate were purchased from Sigma-Aldrich (St. Louis, MO, USA). Paroxetine hydrochloride was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Trifluoperazine and paroxetine were dissolved in distilled water. Quinpirole and ketanserin were dissolved in saline. The doses, administration route, and administration schedules of these drugs were based on previous reports (Egashira et al., 2008b, 2012; Nilsson et al., 2006) and preliminary data. All drugs were administered at a volume of 0.1 mL/10 g of body weight. Doses are in terms of the base.

2.3. Marble-burying test

The marble-burying behavioral test was performed as described previously (Matsushita et al., 2005). All experiments were performed between 10:00 and 17:00 h. Mice were placed individually, without