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5-HT_{1A} agonist alleviates serotonergic potentiation of extrapyramidal disorders via postsynaptic mechanisms

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ABSTRACT

We previously demonstrated that 5-HT stimulants, including selective serotonin reuptake inhibitors (SSRIs), potentiated antipsychotic-induced extrapyramidal symptoms (EPS) by stimulating 5-$HT_{2A/2C}$, 5-HT_3 and 5-HT_6 receptors. Here, we studied the effects of the 5-HT_{1A} agonist (±)-8-hydroxy-2-(di-n-propylamino) tetralin ((±)-8-OH-DPAT) on the fluoxetine enhancement of EPS (i.e., bradykinesia and catalepsy) to determine if the 5-HT_{1A} agonist can counteract the serotonergic potentiation of EPS. Fluoxetine did not induce EPS signs by itself, but significantly potentiated haloperidol-induced bradykinesia in mice. (±)-8-OH-DPAT (0.1–1 mg/kg, i.p.) significantly attenuated the fluoxetine enhancement of haloperidol-induced bradykinesia in a dose-dependent manner. A selective 5-HT_{1A} antagonist (s)-WAY-100135 completely reversed the anti-EPS action of (±)-8-OH-DPAT. Microinjection studies using rats revealed that local application of (±)-8-OH-DPAT into the dorsolateral striatum or the motor cortex significantly diminished fluoxetine-enhanced catalepsy. In contrast, (±)-8-OH-DPAT injected into the medial raphe nucleus failed to affect EPS induction. The present results illustrate that 5-HT_{1A} agonist can alleviate the SSRI enhancement of EPS by activating postsynaptic 5-HT_{1A} receptors in the striatum and cerebral cortex.

1. Introduction

The serotonergic system is implicated in controlling various physiological processes such as psycho-emotional, sensori-motor, cognitive and autonomic functions (Barnes and Sharp, 1999; Baumgarten and Grozdanovic, 1995; Roth, 1994). It is now known that, among 5-HT receptor subtypes, 5-HT_{1A}, 5-$HT_{2A/2C}$, 5-HT_3 and 5-HT_6 receptors play a crucial role in modulating extrapyramidal motor disorders, including antipsychotic-induced extrapyramidal symptoms (EPS) (Meltzer, 1991; Meltzer et al., 2003; Ohno, 2011; Ohno et al., 2013; Shimizu and Ohno, 2013; Shimizu et al., 2013). Numerous studies have shown that the blockade of 5-$HT_{2A/2C}$ receptors attenuates antipsychotic-induced EPS (e.g., catalepsy and bradykinesia) (Kapur and Remington, 2001; Meltzer, 1991; Meltzer et al., 2003). Based on this evidence, a series of second-generation antipsychotics (SGAs) (e.g., risperidone and olanzapine), which commonly exhibit higher affinity to 5-$HT_{2A/2C}$ receptors than to D_2 receptors, have been developed over the past two decades. In addition, stimulation of 5-HT_{1A} receptors has been shown to improve antipsychotic-induced EPS and motor disabilities in animal models of Parkinson's disease (Ishibashi and Ohno, 2004; Neal-Beliveau et al., 1993; Ohno et al., 2008a, 2008b, 2009; Prinssen et al., 2002; Shimizu et al., 2010; Wadenberg et al., 1999). Moreover, we recently demonstrated that blockade of 5-HT_3 and 5-HT_6 receptors also attenuated EPS induction while 5-HT_4, 5-HT_5 or 5-HT_7 receptors have only limited roles in modifying EPS (Ohno et al., 2011). It is therefore conceivable that stimulation of 5-HT_{1A} receptors or inhibition of 5-$HT_{2A/2C}$, 5-HT_3 and 5-HT_6 receptors reduces extrapyramidal motor disorders associated with the deficit of nigro-striatal dopaminergic neurotransmission.

Antipsychotic drugs are sometimes used in combination with antidepressants in the treatment of schizophrenia and mood disorders (e.g., bipolar disorder and psychotic depression). We have previously shown that antipsychotic-induced EPS was significantly potentiated by various antidepressants, including selective serotonin reuptake inhibitors (SSRIs) (Tatara et al., 2012). In addition, EPS enhancement by SSRIs (e.g., fluoxetine) was reversed by 5-$HT_{2A/2C}$, 5-HT_3 or 5-HT_6 antagonists (Tatara et al., 2012), suggesting that SSRIs potentiate EPS induction by stimulating 5-$HT_{2A/2C}$, 5-HT_3 and 5-HT_6 receptors. These findings highlighted the drug interaction between antipsychotics and antidepressants with regard to EPS induction in the clinical setting. On the other hand, 5-HT_{1A} agonists are known to be effective for the treatment of depression and anxiety (Akimova et al., 2009; Blier and Ward, 2003; Feighner and Boyer, 1989; Fuller, 1991; Ohno, 2011; Pucadyil et al., 2005). In addition, recent studies have shown that

Abbreviations: dlST, dorsolateral striatum; MC, motor cortex; MRN, medial raphe nucleus; EPS, extrapyramidal symptoms; (±)-8-OH-DPAT, (±)-8-hydroxy-2-(di-n-propylamino) tetralin; SGA, second generation antipsychotic; SSRI, selective serotonin reuptake inhibitor.

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5-HT_{1A} agonists provide benefits in the treatment of schizophrenia (e.g., attenuation of antipsychotic-induced EPS and improvement of cognitive deficits) and depression (e.g., augmentation and/or acceleration of the antidepressants' actions) (Appelberg et al., 2001; Meltzer and Sumiyoshi, 2008; Newman-Tancredi, 2010; Ohno et al., 2012; Papakostas et al., 2004; Sato et al., 2009; Shimizu and Ohno, 2013; Sumiyoshi et al., 2008). Thus, 5-HT_{1A} agonists are expected to be useful as adjunctive drugs in the treatment of schizophrenia and mood disorders; however, information on the interaction between 5-HT_{1A} agonists and antidepressants (e.g., SSRIs) in modulating antipsychotic-induced EPS is very limited.

To address these issues, we studied the effects of the 5-HT_{1A} agonist (±)-8-hydroxy-2-(di-n-propylamino) tetralin ((±)-8-OH-DPAT) on the fluoxetine enhancement of haloperidol-induced EPS (i.e., bradykinesia and catalepsy) to determine if the 5-HT_{1A} agonist can counteract the SSRI enhancement of EPS.

2. Materials and methods

2.1. Animals

Male ddY mice (25–35 g) or SD rats (200–250 g) (Japan SLC, Shizuoka, Japan) were used. The animals were kept in air-conditioned rooms under a 12-h light/dark cycle, and allowed ad libitum access to food and water. All animal procedures were carried out in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institute of Health, USA, and experimental protocols of this study were approved by the Experimental Animal Research Committee at Osaka University of Pharmaceutical Sciences.

2.2. Evaluation of bradykinesia

The pole test was performed as described previously (Ohno et al., 2008a). Briefly, mice were placed head-upward at the top of a wooden pole (8 mm in diameter and 45 cm in height), and then the time for the animal to rotate downward completely (T_{turn}) and to descend to the floor (T_{total}) was measured with a maximum limit of 90 s. Animals usually received training (3–5 min/session/day) in pole-descending behavior for 3 or 4 days, and only mice that showed T_{turn} <8 s and T_{total} <18 s in the pre-test trial (usually performed 2 h before the test trial) were used. Bradykinesia was evaluated as the prolongation of T_{turn} or T_{total}.

Based on our previous dose–response results for haloperidol-induced bradykinesia (Ohno et al., 2008a), the dose of haloperidol was set at 0.5 mg/kg (i.p.), which induces weak bradykinesia. Namely, mice were first given fluoxetine and 30 min later, injected with haloperidol. The pole test was performed 30 min after haloperidol injection. (±)-8-OH-DPAT or vehicle was administered simultaneously with fluoxetine 30 min before the haloperidol injection. In the experiment with (S)-WAY-100135, it was administered 15 min before the (±)-8-OH-DPAT injection.

2.3. Microinjection study of (±)-8-OH-DPAT

Microinjection of (±)-8-OH-DPAT into the dorsolateral striatum (dlST; +1.0 mm anterior from the bregma, ±1.0 mm lateral from the midline, 3.5 mm inferior to the brain surface), motor cortex (MC; +1.8 mm anterior from the bregma, ±3.0 mm lateral from the midline, 2 mm inferior to the brain surface) or the medial raphe nucleus (MRN; −7.8 mm posterior from the bregma, 0 mm lateral from the midline, 8.5 mm inferior to the brain surface) (Paxinos and Watson, 2007) was performed using rats, as published previously (Ohno et al., 2011; Shimizu et al., 2010). Briefly, male SD rats were anesthetized with pentobarbital (40 mg/kg, i.p.) and fixed in a stereotaxic instrument (SR-6; Narishige, Tokyo, Japan). Small holes were made in the skull and stainless steel-guide cannulae were inserted into a position 1 mm above the dlST, MC or MRN injection sites and fixed to the skull using dental cement. After a recovery period of about 1 week, animals with chronically-implanted guide cannulae were subjected to the microinjection experiments.

On the day of the experiment, injection cannulae filled with the drug solution were inserted into the dlST, MC or MRN through the guide cannulae. Under freely-moving conditions, the animals were first given fluoxetine (10 mg/kg, i.p.) and, 15 min later, (±)-8-OH-DPAT (5-HT_{1A} agonist) at 5 μg/1 μL/site was slowly injected into the dlST, MC or MRN at a flow rate of 0.25 μL/min for 4 min using a microinfusion pump (KDS220; Kd Scientific Inc., USA). The control animals were given the same volume of vehicle alone. Then, haloperidol (0.5 mg/kg, i.p.) was given to the animals 15 min after the (±)-8-OH-DPAT microinjection. For the evaluation of EPS signs, the catalepsy test was performed 30 min after the haloperidol injection and the time taken for animals to show a cataleptic posture was measured for up to 300 s. When the same animals were treated with a different drug (or vehicle) solution, the microinjection study was performed after a drug withdrawal period of at least 4 days.

After the experiments, the animals were deeply anesthetized with pentobarbital (80 mg/kg, i.p.) and the brain was removed from the skull. Coronal sections (100 μm thickness) were prepared from each brain using a microslicer (DSK, Kyoto, Japan) and the position of each injection site was checked.

2.4. Drugs

Haloperidol and (±)-8-OH-DPAT ((±)-8-hydroxy-2-(di-n-propylamino)-tetralin hydrobromide) were purchased from Sigma-Aldrich (St. Louis, MO), (S)-WAY-100135 was from Tocris (Bristol, UK), and fluoxetine hydrochloride was from LKT Laboratories Inc (St. Paul, MN). All drugs were first dissolved in 1% lactate solution and diluted with physiological saline. The above drugs were injected intraperitoneally or subcutaneously in a volume of 1 mL/kg into rats or 5 mL/kg into mice.

2.5. Statistical analysis

Data are expressed as the mean ± S.E.M. Statistical significance of differences among multiple groups was determined by the non-parametric Kruskal–Wallis test followed by the Steel–Dwass multiple comparison test. Comparisons between two groups were performed using Mann–Whitney's *U*-test.

3. Results

3.1. Effects of fluoxetine on haloperidol-induced bradykinesia in mice

In the mouse pole test, control animals placed head-upward at the top of the pole easily rotated downward within 5 s (T_{turn}: 4.2 ± 0.39 s, $N = 8$) and descended to the floor within 10 s (T_{total}: 9.2 ± 0.49 s, $N = 8$). Treatment of mice with fluoxetine alone did not affect the pole-descending behavior of mice even at a high dose (20 mg/kg, i.p.); however, fluoxetine (5–20 mg/kg, i.p.) markedly enhanced haloperidol-induced bradykinesia in a dose-dependent manner (Fig. 1). Haloperidol at 0.5 mg/kg (i.p.) induced mild bradykinesia and slightly increased the T_{turn} and T_{total} values to 8.2 ± 1.80 and 15.4 ± 2.13 s ($p = 0.0473$), respectively. These values with haloperidol were significantly (T_{turn}: $p = 0.0421$, T_{total}: $p = 0.0011$) increased about 3 times by 20 mg/kg of fluoxetine (Fig. 1). Since fluoxetine or haloperidol exerted no or only marginal action in inducing EPS by itself, these agents seemed to interact in a synergistic manner to enhance bradykinesia (Fig. 1).