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European Journal of Pharmacology 520 (2005) 86–90

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Antidepressant-like effect of coadministration of sulpiride and fluvoxamine in mice

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Received 9 May 2005; received in revised form 2 August 2005; accepted 8 August 2005
Available online 2 September 2005

Abstract

We have recently reported that coadministration of sulpiride, an antipsychotic drug, and fluvoxamine, a selective serotonin (5-HT) reuptake inhibitor, selectively increases in vivo dopamine release in the prefrontal cortex. This study examined the effects of coadministration of these drugs on duration of immobility in the tail suspension test using mice. Neither sulpiride (3 or 10 mg/kg) nor fluvoxamine (10 or 20 mg/kg) alone affected immobility time, whereas coadministration significantly reduced immobility time. WAY100635, a 5-HT_{1A} receptor antagonist, did not affect the effects of sulpiride and fluvoxamine coadministration, but reduced immobility time in combination with fluvoxamine (20 mg/kg). A high dose of fluvoxamine alone (60 mg/kg) also reduced immobility time. These results suggest that the antidepressant-like effects of fluvoxamine in combination with sulpiride or WAY100635 in the tail suspension test are mediated by the activation of dopamine or 5-HT systems, respectively.

Keywords: Tail suspension test; Sulpiride; Fluvoxamine; Antidepressant; WAY100635

1. Introduction

Enhancement of central serotonergic function underlies the therapeutic effects of selective serotonin (5-HT) reuptake inhibitors (SSRIs), which have become the most used class of antidepressant agents. However, many individuals experience depressive episodes that are resistant to SSRI treatment (Barbui and Hotopf, 2001; Ferrier, 1999; Nelson, 1999). Clinical studies show that atypical antipsychotics such as risperidone and olanzapine are effective when added to an SSRI in cases of depression where SSRI treatment alone is ineffective (treatment-resistant depression) (O'Connor and Silver, 1998; Ostroff and Nelson, 1999; Shelton et al., 2001). To clarify the neurochemical mechanisms underlying this clinical effect, Zhang et al. (2000) and Koch et al. (2004) examined the effects of combinations of atypical antipsychotics and SSRIs on monoamine levels in rat prefrontal cortex. The results demonstrated that a combination of olanzapine with fluoxetine produces robust, sustained increases in extracellular dopamine, noradrenaline and 5-HT levels in rat prefrontal cortex. This finding suggests that prefrontal monoamine neurotransmitters may contribute to the clinical effect of combination therapy using atypical antipsychotics and an SSRI.

We have recently examined the effects of coadministering the typical dopamine D_2 receptor antagonist sulpiride and the SSRI fluvoxamine on prefrontal monoamine release, to study the role of dopamine D_2 receptor blockade in the combination effect (Ago et al., 2005). Our study revealed that coadministration of sulpiride at 3–10 mg/kg and fluvoxamine at 10–20 mg/kg causes a selective increase in prefrontal dopamine release in rats. This finding suggests that the combination may have antidepressant effects, given previous reports that various

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0014-2999/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2005.08.011

drugs with antidepressant potential selectively increase extracellular dopamine levels in rat prefrontal cortex (Tanda et al., 1994, 1996). With respect to preclinical study on the antidepressant effects of atypical antipsychotics/SSRI combinations, Renard et al. (2001) reported that coadministration of sulpiride at 0.5–2.0 mg/kg and fluvoxamine at 4 mg/kg significantly reduced immobility time in the forced swimming test. The effect on immobility time was significant but small in these experiments, and sulpiride did not affect the anti-immobility effect of fluvoxamine at 32 mg/kg. Furthermore, the antidepressant-like effect of the combination has not been examined in animal tests other than the forced swimming test. The present study examined whether the combination of sulpiride with fluvoxamine exhibits antidepressant-like effects in the tail suspension test in mice. Since our previous study showed that the 5-HT_{1A} receptor antagonist, WAY100635, inhibited combination-induced increases in prefrontal dopamine release (Ago et al., 2005), the effects of WAY100635 on antidepressant-like effects of the combination were also examined to study the role of the prefrontal dopamine system in behavioral effects.

2. Materials and methods

2.1. Animals and drugs

Male ddY mice (3-weeks-old) were housed in groups of 5–6/cage (24×17×12 cm) under controlled environmental conditions (22±1 °C; 12/12 h light/dark cycle, lights on at 08:00 h; food and water ad libitum) for ≥1 week before being used in the experiment. All procedures involving animals and animal care were conducted in accordance with the Guiding Principles for the Care and Use of Laboratory Animals as approved by the Japanese Pharmacological Society. The following drugs were used: fluvoxamine (Solvay Seiyaku, Kawagoe, Japan); sulpiride (Fujisawa Pharmaceutical, Osaka, Japan); *N*-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-*N*-(2-pyridinyl)cyclohexanecarboxamide (WAY100635) (Mitsubishi Pharma, Yokohama, Japan). All other chemicals used were of the highest commercially available purity. Fluvoxamine and WAY100635 were dissolved in saline (0.9% NaCl solution). Sulpiride was dissolved in 0.1 M HCl and was adjusted to pH 6–7 using 0.1 M NaOH. Drugs were injected intraperitoneally at 10 ml/kg.

2.2. Tail suspension test

The tail suspension apparatus was made of a white plastic box (30×30×30 cm) with a hook in the center of the ceiling from mice were suspended by the tail, using adhesive tape. The hook was connected to a strain gauge that picked up all movements of the mouse and transmitted them to a central processing unit (Load Cell converter) (Neuroscience Inc., Osaka, Japan). Each mouse was suspended individually. Total duration of immobility during the 6-min test was automatically calculated using MicroAct for Tail-Suspension ver. 1.03 software (Neuroscience Inc., Japan). The following threshold criteria were used: threshold (% standard deviation of total amplitude of vibrations), 70.00%; maximum frequency, 30.00 Hz; minimum frequency, 1.00 Hz; minimum duration, 1.00 s; and event gap, 0.30 s. Immobility time was defined as the total duration during which mouse movements were below the threshold.

2.3. Measurement of spontaneous locomotor activity

Locomotor activity of each mouse was measured using a digital counter system with an infrared sensor (Supermex®, Muromachi Kikai, Tokyo, Japan). The mouse was placed in a clear plastic cage (24×17×12 cm) 30 min after administration of the drugs, and locomotor activity was recorded for 6 min.

2.4. Statistics

Data were analyzed using one-way analysis of variance (ANOVA) followed by the Dunnett's test and two-way ANOVA followed by the Tukey–Kramer test. Statistical analyses were performed using Stat View 5.0 software (SAS Institute Inc., Cary, NC, USA) for an Apple Macintosh computer. Values of $P<0.05$ were considered statistically significant.

3. Results

Fig. 1 shows the effects of sulpiride and fluvoxamine, alone and in combination, on duration of immobility in the tail suspension test in mice. Sulpiride at 3 and 10 mg/kg alone did not affect the immobility time of mice ($F(2,46)=0.737$, *n.s.*). Fluvoxamine at 10 and 20 mg/kg

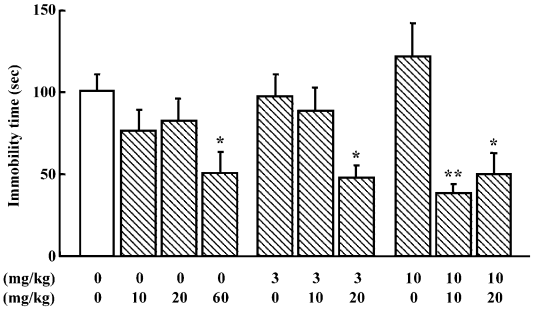

Fig. 1. Effects of sulpiride and fluvoxamine, alone and in combination, on immobility time of mice in the tail suspension test. Sulpiride at 3 and 10 mg/kg and fluvoxamine at 10, 20 and 60 mg/kg were administered intraperitoneally 30 min before the experiment. Results represent means±S.E.M. of 12–22 mice.*$P<0.05$, **$P<0.01$, compared with vehicle/saline-treated group.

Table 1
Effects of sulpiride, fluvoxamine and WAY100635, alone and in combination, on spontaneous locomotor activity of mice. Drugs were administered intraperitoneally 30 min before the experiment. Results represent means±S.E.M. of 10–14 mice

Treatment (mg/kg)	Total activity (counts/6 min)
Vehicle	1320±80
Sulpiride (3)	1091±94
Sulpiride (10)	984±88
WAY100635 (0.1)	1178±101
Saline	1339±85
Fluvoxamine (10)	1385±117
Fluvoxamine (20)	1384±122
Fluvoxamine (60)	950±145 [a]
Sulpiride (3)+fluvoxamine (10)	1024±82
Sulpiride (3)+fluvoxamine (20)	1214±94
Sulpiride (10)+fluvoxamine (10)	1170±56
Sulpiride (10)+fluvoxamine (20)	1037±79
WAY100635 (0.1)+sulpiride (10)+fluvoxamine (20)	991±64
WAY100635 (0.1)+fluvoxamine (20)	1222±74

[a] $P<0.05$, compared with saline-treated group.

alone also did not affect the immobility time of mice ($F(2,46)=1.295$, *n.s.*). Fluvoxamine alone at a higher dose (60 mg/kg) caused a significant decrease in immobility time of mice ($F(3,58)=3.121$; $P=0.0332$), but also significantly decreased spontaneous locomotor activity ($F(13,161)=2.595$, $P=0.0029$) (Table 1). However, co-administration of sulpiride at 3 mg/kg and fluvoxamine at 20 mg/kg or sulpiride at 10 mg/kg and fluvoxamine at 10–20 mg/kg significantly reduced immobility time. Two-way ANOVA revealed a significant interaction between sulpiride and fluvoxamine treatment ($F(4,120)=3.051$, $P=0.0198$). Locomotor activity was unaffected by any of sulpiride at 3 and 10 mg/kg, fluvoxamine at 10 and 20 mg/kg or any combinations thereof (Table 1).

Fig. 2 shows the effect of WAY100635 on combination-induced decreases in immobility time in the tail suspension test. Two-way ANOVA revealed a significant main effect of sulpiride plus fluvoxamine ($F(1,59)=14.242$, $P=0.0004$),

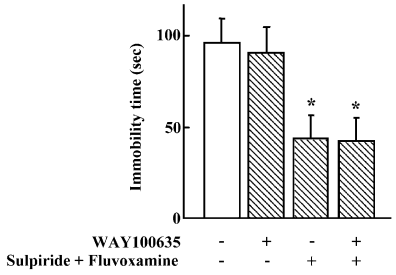

Fig. 2. Effects of WAY100635 on sulpiride/fluvoxamine combination-induced decreases in immobility time in mouse tail suspension test. WAY100635 at 0.1 mg/kg, sulpiride at 10 mg/kg and fluvoxamine at 20 mg/kg were administered intraperitoneally 30 min before the experiment. Results represent means±S.E.M. of 15 mice. *$P<0.05$, compared with saline-treated group.

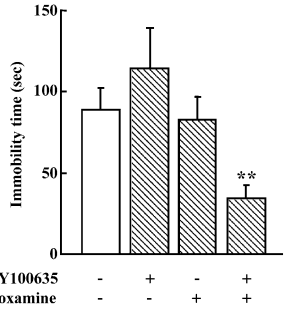

Fig. 3. Effects of WAY100635 and fluvoxamine, alone and in combination, on immobility time of mice in the tail suspension test. WAY100635 at 0.1 mg/kg and fluvoxamine at 20 mg/kg were administered intraperitoneally 30 min before the experiment. Results represent means±S.E.M. of 10–11 mice. **$P<0.01$, compared with saline-treated group.

but not of WAY100635 treatment ($F(1,59)=0.048$, *n.s*). WAY100635 did not affect combination-induced decreases in immobility time of mice ($F(1,59)=0.025$, *n.s*).

The present study examined if fluvoxamine combined with WAY100635 exhibits antidepressant-like effects in the mouse tail suspension test (Fig. 3). Co-administration of WAY100635 at 0.1 mg/kg and fluvoxamine at 20 mg/kg significantly reduced immobility time. Two-way ANOVA revealed significant interactions between WAY100635 and fluvoxamine treatment ($F(1,42)=5.669$, $P=0.0222$). The combination of WAY100635 with fluvoxamine did not affect locomotor activity of mice (Table 1).

4. Discussion

Previous neurochemical studies have shown that the atypical antipsychotic olanzapine in combination with an SSRI produces robust, sustained increases in extracellular levels of dopamine in rat prefrontal cortex (Zhang et al., 2000; Koch et al., 2004). This effect may explain the clinical effectiveness of combination therapy for treatment-resistant depression, given the significance of dopaminergic neurons in depression (Willner, 1997). We have recently shown that the combination of sulpiride with fluvoxamine also markedly increases prefrontal dopamine release (Ago et al., 2005). The present results show that co-administration of sulpiride and fluvoxamine exerts an antidepressant-like effect in the mouse tail suspension test. Sulpiride at 3 mg/kg with fluvoxamine at 20 mg/kg and sulpiride at 10 mg/kg with fluvoxamine at 10 or 20 mg/kg significantly reduced immobility time in mice. These drugs, given alone or combination, did not affect locomotor activity of mice, suggesting that the anti-immobility effect of the combination is not a false positive response. These findings thus suggest that the enhanced dopamine system in the prefrontal cortex plays a role in the antidepressant-like effects of the sulpiride/fluvoxamine combination.

Our previous study also showed that sulpiride at 3 mg/kg with fluvoxamine at 10 mg/kg significantly increased prefrontal dopamine release, although the effects were less

than those from sulpiride at 10 mg/kg with fluvoxamine at 10 mg/kg (Ago et al., 2005). In contrast, the present study showed that the combination of sulpiride at 3 mg/kg with fluvoxamine at 10 mg/kg did not affect immobility time in the tail suspension test. The lack of an antidepressant-like effect for sulpiride at 3 mg/kg plus fluvoxamine at 10 mg/kg may be due to reduced enhancement of the prefrontal dopamine system. Alternatively, the apparent discrepancy may be due to species differences in sensitivity of the prefrontal dopamine system to sulpiride and fluvoxamine. This point will be clarified by future experiments using microdialysis in mice.

Our recent study showed that the 5-HT_{1A} receptor antagonist WAY100635 blocks combination-induced increases in prefrontal dopamine release (Ago et al., 2005). Furthermore, we found that 5-HT_{1A} receptor activation increases prefrontal dopamine release in rats and mice (Sakaue et al., 2000; Ago et al., 2003). These findings suggest that the effects of the sulpiride/fluvoxamine combination are mediated by activation of 5-HT_{1A} receptors, consistent with previous findings that the 5-HT_{1A} receptor agonist 8-hydroxy-2-(dipropylamino)tetralin potentiates sulpiride-induced dopamine release in the prefrontal cortex (Ichikawa and Meltzer, 1999). We then examined the role of 5-HT_{1A} receptors in the antidepressant-like effects of the sulpiride/fluvoxamine combination. The present study showed that WAY100635 did not affect combination-induced antidepressant-like effects. This behavioral result appears in sharp contrast with the neurochemical observation that WAY100635 antagonizes combination-induced increases in prefrontal dopamine release (Ago et al., 2005). However, the possibility cannot be excluded that the antidepressant-like effects of sulpiride/fluvoxamine combination are mediated by an enhanced dopamine system, since 5-HT_{1A} receptor antagonists enhance the effects of SSRIs on the 5-HT system, which also plays a role in depression.

WAY100635-induced inhibition of presynaptic 5-HT_{1A} autoreceptors is known to enhance SSRI-induced 5-HT release (Ago et al., 2005; Dawson and Nguyen, 1998; Hjorth et al., 1997; Romero et al., 1996). The neurochemical observations support the augmentation therapy of SSRIs combined with 5-HT_{1A} receptor blockade (Artigas et al., 2001; Blier and Bergeron, 1998). Furthermore, some behavioral studies show that SSRI/5-HT_{1A} receptor antagonist combinations increase 5-HT function (Bristow et al., 2000; Gobert et al., 2000; Grignaschi et al., 1998; Millan and Perrin-Monneyron, 1997; Trillat et al., 1998). However, conflicting accounts have been reported about the effect of SSRIs with 5-HT_{1A} receptor blockade on the antidepressant-like effect. Cousins and Seiden (2000) reported that relatively low doses of WAY100635 enhance the antidepressant-like profile of fluoxetine in the differential reinforcement of low rates 72-s schedule in rats. Similar findings were shown in an experiment using duloxetine, a 5-HT and noradrenaline reuptake inhibitor, with the antidepressant-like effect of duloxetine enhanced by WAY100635 in the forced swim test in rats (Millan et al., 1998). In contrast, Moser and Sanger (1999) reported that 5-HT_{1A} receptor antagonists do not potentiate the antidepressant-like effect of fluoxetine in the forced swim test in rats. In addition, no potentiation by 5-HT_{1A} receptor antagonists is observed in the effect of SSRIs on ethanol and food intake (Ciccocioppo et al., 1997). Furthermore, Da-Rocha et al. (1997) reported that when combined with fluoxetine, but not with fluvoxamine, WAY100135 significantly reduced immobility time in the forced swim test. The present study demonstrated that WAY100635 in combination with fluvoxamine exerts an antidepressant-like effect in the tail suspension test. Furthermore, the present study shows that fluvoxamine at higher doses exerts antidepressant-like effects. These findings, taken together with the previous finding that 5-HT_{1A} receptor blockade reduces the combination-induced dopamine release in the prefrontal cortex, but it also potentiates the 5-HT release (Ago et al., 2005), suggest that the antidepressant-like effects of combined sulpiride/fluvoxamine in the presence of WAY100635 are due to enhancement of the 5-HT system.

In general, drug metabolism plays a key role in changes to the pharmacological effects induced by the combined administration of two drugs. Although we did not determine cerebral concentrations of fluvoxamine after treatment in the presence and absence of sulpiride, our previous study showed that sulpiride did not affect fluvoxamine-induced increases in 5-HT and noradrenaline levels in rat prefrontal cortex, and fluvoxamine did not increase sulpiride-induced increases in striatal dopamine levels (Ago et al., 2005). In view of these observations, the effect of combined sulpiride/fluvoxamine on immobility time is unlikely to be attributable to pharmacokinetic interactions.

In conclusion, this study shows that co-administration of sulpride and fluvoxamine exhibits an antidepressant-like effect in the tail suspension test. This effect may be mediated not only by an enhanced dopamine system, but also an enhanced 5-HT system. Sulpiride exerts antidepressant activity at doses 4–5 times lower than usual neuroleptic values (Benkert and Holsboer, 1984; Maier and Benkert, 1994; Vergoni et al., 1995), and the effect is considered to be mediated by enhanced dopaminergic activity (Serra et al., 1990). The present results imply that fluvoxamine may be clinically useful as an agent augmenting the antidepressant effects of sulpiride, as with atypical antipsychotics. We also demonstrated that co-administration of fluvoxamine and WAY100635 results in antidepressant-like effects in the tail suspension test. These findings suggest that interactions between the dopamine and 5-HT systems play a key role in the antidepressant-like effects of atypical antipsychotic/SSRI combinations.

Acknowledgements

This work was supported in part by a grant from the Ministry of Education, Science, Sports and Culture of Japan.

We acknowledge the donation of WAY100635 (Mitsubishi Pharma, Yokohama), fluvoxamine (Solvay Seiyaku, Saitama) and sulpiride (Fujisawa Pharmaceutical, Osaka).

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