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Involvement of dopamine D_1 receptors and α_1-adrenoceptors in the antidepressant-like effect of chlorpheniramine in the mouse tail suspension test

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Abstract

It has been reported that chlorpheniramine, a classical antihistamine, has antidepressant-like effects in animal models of depression. In this study, we examined the involvement of dopaminergic (dopamine D_1 and dopamine D_2 receptors), noradrenergic (α_1- and β-adrenoceptors) and serotonergic (5-HT_{1A} and 5-HT_2 receptors) receptors in the antidepressant-like effect of chlorpheniramine in the mouse tail suspension test. We also investigated the involvement of these monoamine receptors in the antidepressant-like effect of imipramine for comparison with the mechanisms of the effect of chlorpheniramine. Both imipramine and chlorpheniramine significantly reduced the duration of immobility in the tail suspension test without affecting spontaneous locomotor activity in mice. The anti-immobility effect of imipramine (30 mg/kg, i.p.) was significantly antagonized by the selective dopamine D_1 receptor antagonist SCH23390 but not by the other receptor antagonists. In contrast, the anti-immobility effect of chlorpheniramine was significantly inhibited by SCH23390 and the selective α_1-adrenoceptor antagonist prazosin, but not by the other receptor antagonists. In conclusion, these results suggest that chlorpheniramine exerts an antidepressant-like effect in the mouse tail suspension test that is mediated by at least the activation of dopamine D_1 receptors and α_1-adrenoceptors. In addition, the antidepressant-like effect of chlorpheniramine may be induced by several mechanisms that are different from those involved in the antidepressant-like effect of imipramine.
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Keywords: Imipramine; Chlorpheniramine; Tail suspension test; Antidepressant-like effect

1. Introduction

It has recently been discussed that old antihistamines may be useful as safe, non-cardiotoxic and well-tolerated antidepressants and/or anxiolytics (Hellbom, 2006). Charlton (2005) has proposed that many conditions which respond to selective serotonin reuptake inhibitors (SSRIs), including milder depression and many anxiety states, would also respond to old antihistamines such as chlorpheniramine because several SSRIs were synthesized by chemical modification of these antihistamines (Domino, 1999). In fact, it is well established that chlorpheniramine inhibits the reuptake of monoamines as well as tricyclic antidepressants and SSRIs (Lidbrink et al., 1971; Shishido et al., 1991; Tatsumi et al., 1997). Hellbom and Humble (2003) reported that chlorpheniramine ameliorates panic attacks, phobias and lowered mood in patients with hay fever. However, little information is available on the antidepressant and anxiolytic effects of chlorpheniramine. It has been suggested that the diverse effects of chlorpheniramine modulate mood and emotional behaviors (Onodera et al., 1994).

The forced swimming test and tail suspension test are used as screening methods for putative antidepressants (Porsolt et al., 1977; Steru et al., 1985). Rogoz et al. (1981) reported that chlorpheniramine exerted an antidepressant-like effect in the rat forced swimming test. They suggested that the action of chlorpheniramine was not a consequence of its antihistamine activity because mepyramine and clemastine, selective histamine H_1

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receptor antagonists, had no effect in that experiment. We also reported that chlorpheniramine exerted an antidepressant-like effect in the mouse tail suspension test, although the selective histamine H_1 receptor antagonists cetirizine and epinastine had no significant effect in non-diabetic control mice (Hirano et al., 2006). On the basis of these findings, it could be speculated that the monoamine accumulation produced by chlorpheniramine might exert an antidepressant-like effect in these behavioral despair tests.

Several lines of evidence indicate that serotonergic, dopaminergic, and noradrenergic neurotransmissions are involved in the expression of an antidepressant-like effect in the behavioral despair models of depression (Elhwuegi, 2004). In the mouse tail suspension test, it has been reported that acute treatment with antagonists of dopamine D_2/D_3 receptors (Ferrari and Giuliani, 1997) and α_1-adrenoceptors (Stone and Quartermain, 1999) significantly increase the duration of immobility. These observations indicate the possibility that the function of dopamine D_2/D_3 receptors and α_1-adrenoceptors might be needed for the antidepressant-like effect. Furthermore, Mayorga et al. (2001) reported that the antidepressant-like effects of SSRIs were not exerted in 5-HT_{1A} receptor mutant mice. We previously reported that the antidepressant-like effect of fluoxetine was antagonized by pretreatment with either a selective 5-HT_{1A} or 5-HT_2 receptor antagonist (Miyata et al., 2004). These observations suggest that the antidepressant-like effects of SSRIs are induced by the activation of 5-HT_{1A} and 5-HT_2 receptors. Therefore, it seems likely that the antidepressant-like effect in the mouse tail suspension test is mediated, at least in part, by the activation of dopamine D_2/D_3 receptors, α_1-adrenoceptors, 5-HT_{1A} and 5-HT_2 receptors. In the rat forced swimming test, another behavioral despair test, the activation of dopamine D_1 and D_2 receptors (Borsini et al., 1988; D'Aquila et al., 1994), α_1- and β-adrenoceptors (Kitada et al., 1983; Parale et al., 1987) and 5-HT_{1A} and 5-HT_{2C} receptors exerts an antidepressant-like effect (Wieland and Lucki, 1990; Cryan and Lucki, 2000). Based on these findings, we hypothesized that the antidepressant-like effect of chlorpheniramine in the mouse tail suspension test might be mediated by the activation of several monoamine receptors.

The purpose of this study was to clarify the involvement of serotonergic (5-HT_{1A} and 5-HT_2), dopaminergic (dopamine D_1 and dopamine D_2) and noradrenergic (α_1 and β) receptors in the expression of the antidepressant-like effect of chlorpheniramine in the mouse tail suspension test. We also investigated the involvement of these monoamine receptors in the antidepressant-like effect of imipramine for comparison with the mechanisms of the effect of chlorpheniramine.

2. Materials and methods

2.1. Animals

Male ICR mice (Tokyo Laboratory Animals Science Co., Ltd., Tokyo), 5 weeks of age, were used. They were housed 10 per cage and had free access to food and water. The animal room was maintained at 24±1 °C and 55±5% humidity with a 12-h light–dark cycle (light on at 8:00, light off at 20:00). Mice were adapted for at least 1 week before testing. All behavioral observations were performed between 11:00 and 17:00 each day. The animals were used only once. This study was carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the Committee on the Care and Use of Laboratory Animals of Hoshi University, which is accredited by the Ministry of Education, Science, Sports and Culture.

2.2. Drugs

The drugs used in this study were imipramine hydrochloride, (±)-chlorpheniramine maleate, the selective 5-HT_{1A} receptor antagonist *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]-ethyl-*N*-2-pyridinylcyclohexanecarboxamide (WAY-100635), the selective 5-HT_2 receptor antagonist 6-methyl-1-(1-methylethyl)-ergoline-8β-carboxylic acid 2-hydroxy-1-methylpropyl ester (LY53,857), the α_1-adrenoceptor antagonist prazosin, the β-adrenoceptor antagonist propranolol, the selective dopamine D_1 receptor antagonist R-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3benzazepine-HCl (SCH23390) and the selective dopamine D_2 receptor antagonist raclopride. All drugs were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Imipramine, chlorpheniramine, WAY-100635, LY53,857 and raclopride were dissolved in saline. Prazosin was dissolved in distilled water. Propranolol was dissolved in a small volume of dimethyl sulfoxide (DMSO) and then diluted with saline. SCH23390 was dissolved in a small volume of distilled water and then diluted with saline. All drug doses were calculated as the salt weight. All drugs were administered in a volume of 0.1 ml/10 g of body weight. Imipramine and chlorpheniramine were injected i.p. 30 min before testing. All antagonists were injected s.c. 60 min before testing. The dose ranges of imipramine and chlorpheniramine were based on those used in previous reports showing that these drugs exerted antidepressant-like effects in the tail suspension test (Steru et al., 1985; Hirano et al., 2006). The dose ranges of antagonists were based on our pilot study.

2.3. Tail suspension test

The procedure was according to our previous report (Kamei et al., 2003). The tail suspension apparatus consisted of a white translucent plastic box (30×30×30 cm) with a hook in the middle of the ceiling from which was suspended by the tail, using adhesive Scotch tape affixed to the hook. The hook was connected to a strain gauge (TAIL SUSPENSION AMP, Neuroscience Inc., Tokyo, Japan) that picked up all movements of the mouse and transmitted them to a central processing unit, which calculated the total duration of immobility and the strength of movements during the 10 min of the test. Each mouse was suspended individually. The movements of the mice were digitized and processed by a Super Scope II (GWI; Somerville, MA, USA). A threshold level was set to exclude movement caused by respiration. The duration of immobility was defined as the total amount of time that the animal showed no movement.

2.4. Spontaneous locomotor activity

Spontaneous locomotor activity of mice was measured by a digital counter with an infrared sensor (NS-AS01, Neuroscience Inc., Tokyo, Japan). The apparatus detects the movement of animals, based on released infrared rays associated with their temperature, and records a digital count. A mouse was placed individually in a transparent plastic cage (27×17×13 cm), a transparent plastic ceiling was installed, and an infrared sensor was placed at the center of the ceiling. Mice were placed in the measurement cage and recording was started. Total activity counts were automatically recorded for 10 min, consistent with the measurement period in the tail suspension test.

2.5. Statistics

Data are expressed as the means with S.E.M. Significant differences were determined by one-way or two-way analysis of variance (ANOVA) for factorial comparisons and the Dunnett test for multiple comparisons. Significance was considered to be $P<0.05$.

3. Results

3.1. Anti-immobility effects of imipramine and chlorpheniramine in the mouse tail suspension test

As shown in Fig. 1, imipramine (3–30 mg/kg, i.p.) and chlorpheniramine (1–10 mg/kg, i.p.) significantly decreased the duration of immobility in mice (Fig. 1). Neither imipramine (30 mg/kg, i.p.) nor chlorpheniramine (10 mg/kg, i.p.) affected the spontaneous locomotor activity of mice (Table 1).

3.2. Effects of monoamine receptor antagonists on the anti-immobility effect of imipramine and chlorpheniramine

The effects of monoamine receptor antagonists on the anti-immobility effects of imipramine and chlorpheniramine are shown in Fig. 2. Prazosin (0.01 and 0.1 mg/kg, s.c.) dose dependently and significantly increased the duration of immobility of saline (i.p.)-treated mice. The other antagonists when given in combination with saline had no significant effect on the duration of immobility.

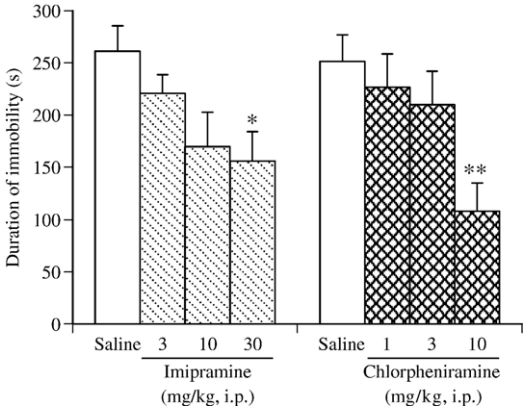

Fig. 1. Effects of imipramine and chlorpheniramine on the duration of immobility in the mouse tail suspension test. Each column represents the mean±S.E.M. for 9–10 mice. One-way ANOVA revealed that the duration of immobility was significantly affected by imipramine [$F(3, 39)=3.3534$, $P<0.05$] and chlorpheniramine [$F(3, 38)=4.7591$, $P<0.01$]. *$P<0.05$ and **$P<0.05$ vs. respective saline-treated groups (Dunnett test).

Table 1
Effects of imipramine and chlorpheniramine on the spontaneous locomotor activity of mice

Drugs	Locomotor activity (counts/10 min)
Saline (i.p.)	342.2±22.6
Imipramine (30 mg/kg, i.p.)	331.4±34.3
Chlorpheniramine (10 mg/kg, i.p.)	383.6±19.1

Data represent the mean locomotor activity counts±S.E.M. for 10 mice. There was no difference between groups (Dunnett test).

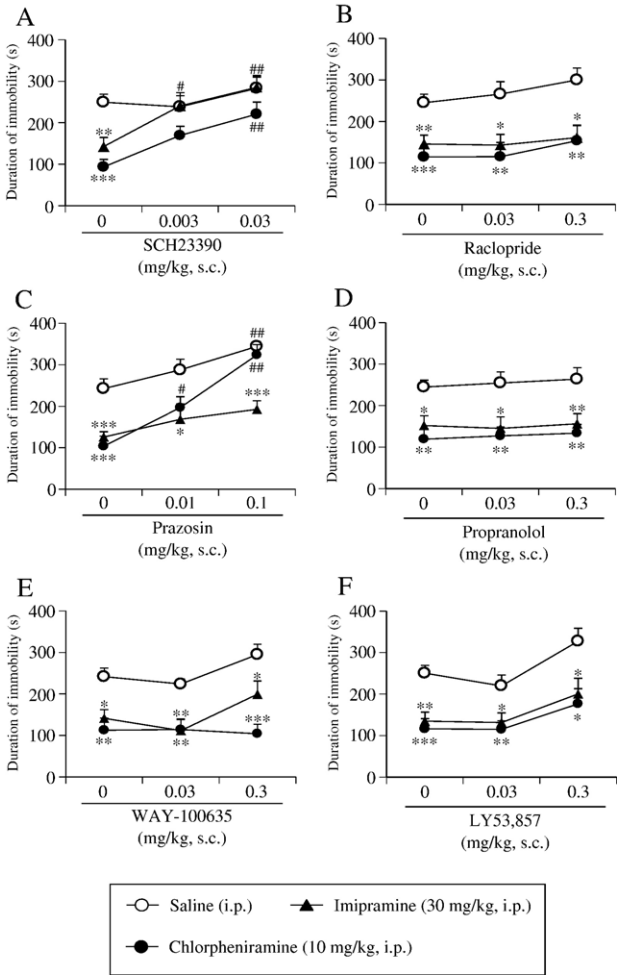

Fig. 2. Effects of SCH23390 (A), raclopride (B), prazosin (C), propranolol (D), WAY-100635 (E) and LY53,857 (F) on the anti-immobility effects of imipramine and chlorpheniramine. Each symbol represents the mean±S.E.M. for 7–10 mice. *$P<0.05$, *$P<0.01$ and ***$P<0.001$ vs. respective antagonist-saline-treated groups (Dunnett test). #$P<0.05$ and ##$P<0.01$ significant difference from the corresponding imipramine-saline-treated or chlorpheniramine-saline-treated groups (Dunnett test). The two-way ANOVA revealed that SCH23390 [$F(2, 76)=11.674$, $P<0.001$], prazosin [$F(2, 76)=21.240$, $P<0.001$] and LY53,857 [$F(2, 73)=7.234$, $P<0.01$] significantly affected the duration of immobility. A significant interaction effect was detected for prazosin×antidepressants [$F(2, 76)=2.792$, $P<0.05$].

Table 2
Effects of monoamine receptor antagonists on the spontaneous locomotor activity of imipramine- and chlorpheniramine-treated mice

Drugs	Locomotor activity (counts/10 min)		
	Saline (i.p.)	Imipramine (30 mg/kg, i.p.)	Chlorpheniramine (10 mg/kg, i.p.)
Saline (s.c.)	359.4±16.1	295.0±64.5	381.0±28.5
SCH23390 (0.03 mg/kg, s.c.)	247.5±61.1	175.8±19.2	238±33.9
Raclopride (0.3 mg/kg, s.c.)	358.4±47.6	212.3±39.9	327.6±39.9
Prazosin (0.1 mg/kg, s.c.)	378.6±27.3	246.2±42.9[a]	402.4±29.1
Propranolol (0.3 mg/kg, s.c.)	323.2±21.2	210.4±43.8	331.0±64.0
WAY-100635 (0.3 mg/kg, s.c.)	347.3±70.7	306.2±45.5	392.0±40.3
LY53,857 (0.3 mg/kg, s.c.)	381.2±42.6	301.0±62.5	415.8±23.2

Data represent the mean locomotor activity counts±S.E.M. for 5 – 6 mice. Each drug was administered at the maximal doses for the tail suspension test. Dunnett test revealed a significant decrease ([a]$P<0.05$) in the prazosin–imipramine-treated group compared to the prazosin–saline-treated group. The two-way ANOVA revealed that spontaneous locomotor activity was significantly affected by monoamine receptor antagonists [$F(6, 92)=3.749$, $P<0.05$] and antidepressants [$F(2, 92)=11.420$, $P<0.001$], but not by their interaction [$F(12, 92)=0.251$, $P=0.995$].

Pretreatment with SCH23390 (0.003 and 0.03 mg/kg, s.c.) dose dependently and significantly increased the duration of immobility of imipramine-treated mice to the same levels observed in saline-treated mice (Fig. 2A). The other antagonists had no significant effect on the duration of immobility in imipramine-treated mice (Fig. 2B–F).

Pretreatment with SCH23390 (0.003 and 0.03 mg/kg, s.c.) dose dependently and significantly increased the duration of immobility of chlorpheniramine-treated mice (Fig. 2A). However, SCH23390 did not completely antagonize the anti-immobility effect of chlorpheniramine. Pretreatment with prazosin (0.01 and 0.1 mg/kg, s.c.) dose dependently and significantly increased the duration of immobility of chlorpheniramine-treated mice to the same levels observed in saline-treated mice (Fig. 2C). The other antagonists had no significant effect on the duration of immobility in chlorpheniramine-treated mice (Fig. 2B, D–F).

3.3. Effects of monoamine receptor antagonists on the spontaneous locomotor activity of imipramine- and chlorpheniramine-treated mice

Combination treatment with prazosin and imipramine significantly decreased the locomotor activity compared with the effect of treatment with the prazosin-saline combination (Dunnett test, $P<0.05$). The other combinations did not significantly affect the spontaneous locomotor activity (Table 2).

4. Discussion

It has been reported that imipramine increases extracellular dopamine levels in the prefrontal cortex, hypothalamus, and limbic system, mediated by the inhibition of monoamine transporters (Matos et al., 1990; Rossetti et al., 1993; Jordan et al., 1994; Dazzi et al., 2001). In this study, we showed that the antidepressant-like effect of imipramine was significantly antagonized by the blockade of dopamine D_1 receptors. This antagonistic property was independent of the locomotor suppression. However, in the rat forced swimming test, dopamine D_2 receptor activation plays a crucial role in mediating the antidepressant-like effect of the tricyclic antidepressant desipramine (Borsini et al., 1988). It is possible that this discrepancy may be due to methodological differences. However, the other animal models of depression reveal that the activation of dopamine D_1 receptors is involved in the antidepressant-like effect of tricyclic antidepressants (Sampson et al., 1991; Gambarana et al., 1995). On the basis of these reports, it is likely that the antidepressant-like effect of imipramine is mediated through the dopaminergic system, and that dopamine D_1 receptor activation is crucial for the antidepressant-like effect of imipramine in the mouse tail suspension test.

The antidepressant-like effect of chlorpheniramine was significantly antagonized by the inhibition of dopamine D_1 receptors and α_1-adrenoceptors. These antagonistic properties were independent of the locomotor suppression. The other monoamine receptor antagonists did not block the effect of chlorpheniramine. It has been reported that chlorpheniramine inhibits monoamine uptake and leads to the accumulation of monoamines in the synaptic cleft (Lidbrink et al., 1971; Shishido et al., 1991; Dringenberg et al., 1998; Suzuki et al., 1999; Fujisaki et al., 2002). Therefore, the antidepressant-like effect of chlorpheniramine may be mediated by the activation of dopamine D_1 receptors and α_1-adrenoceptors as a consequence of the accumulation of monoamines. We previously reported that 5-HT_{1A} and 5-HT_2 receptor blockade significantly inhibited the antidepressant-like effect of fluoxetine (Miyata et al., 2004). However, this study revealed that 5-HT_{1A} and 5-HT_2 receptor antagonists did not inhibit the antidepressant-like effects of imipramine and chlorpheniramine. This result indicates that catecholaminergic neurotransmission may be essential for the antidepressant-like effect of chlorpheniramine in the mouse tail suspension test.

The primary differences between imipramine and chlorpheniramine are their affinities at several binding sites. For example, it has been reported that imipramine has high affinity at α_1-adrenoceptors and acts as an antagonist (Richelson and Nelson, 1984). In contrast, chlorpheniramine has little or no effect on α_1-adrenoceptors (Laduron et al., 1982). Therefore, the difference in the effect of prazosin on the antidepressant-like effects of chlorpheniramine and imipramine may result from their different affinities at α_1-adrenoceptors. We also observed that the antidepressant-like effect of chlorpheniramine was more potent than that of imipramine because chlorpheniramine was effective at an approximately 3-fold lower dose. This result may be consistent with a previous report showing that the binding affinity of chlorpheniramine at dopamine transporters was more potent than that of imipramine (Tatsumi et al., 1997).

In conclusion, these results suggest that chlorpheniramine exerts an antidepressant-like effect in the mouse tail suspension test mediated by the activation of dopamine D_1 and α_1-adrenoceptors. In addition, the mechanism of the antidepressant-like

effect of chlorpheniramine is mediated though pathways different from those of imipramine and fluoxetine. Thus, chlorpheniramine may be a new useful antidepressant.

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