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ORIGINAL INVESTIGATION

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Combined treatment of quetiapine with haloperidol in animal models of antipsychotic effect and extrapyramidal side effects: comparison with risperidone and chlorpromazine

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Abstract *Rationale:* Quetiapine, an atypical neuroleptic, has beneficial antipsychotic effects in schizophrenic patients, but with a lower incidence of extrapyramidal symptoms (EPS) compared with typical antipsychotics. While typical antipsychotics are often switched to atypical agents when adverse effects become limiting, there is little preclinical information to support this strategy, both in terms of efficacy and side effects. *Objectives:* The antipsychotic effects and EPS during concomitant administration of quetiapine with haloperidol, a typical antipsychotic agent, were evaluated in mice and compared with chlorpromazine and risperidone. *Methods:* We first investigated the antipsychotic effects and EPS liability of quetiapine, risperidone, chlorpromazine, and haloperidol when administered alone to select optimal doses for subsequent combination studies. The second study was designed to evaluate the antipsychotic efficacy and EPS profile of concomitant administration of quetiapine, risperidone, or chlorpromazine with haloperidol. Antipsychotic effects were evaluated with the methamphetamine-induced hyperlocomotion test, and EPS liability was evaluated in a catalepsy-induction model. *Results:* Quetiapine, risperidone, chlorpromazine, and haloperidol dose-dependently reduced methamphetamine-induced hyperlocomotion, with ED_{50} values of 5.6, 0.020, 1.8, 0.035 mg/kg, respectively. In the catalepsy test, quetiapine only weakly induced catalepsy at the highest dose of 100 mg/kg, whereas risperidone, chlorpromazine, and haloperidol dose-dependently induced catalepsy with ED_{50} values of 0.25, 4.6, and 0.10 mg/kg, respectively. While the combination of quetiapine (6 mg/kg) and haloperidol (0.04 mg/kg) significantly reduced methamphetamine-induced hyperlocomotion in comparison with haloperidol alone, quetiapine (10, 32 mg/kg) plus haloperidol did not potentiate the cataleptogenic activity of haloperidol. In contrast, risperidone (0.1, 0.32 mg/kg) or chlorpromazine (3.2 mg/kg) significantly augmented catalepsy induced by haloperidol. Catalepsy induced by co-administration of quetiapine (10 mg/kg) and haloperidol (0.1 mg/kg) was significantly potentiated by WAY100635, a 5-HT_{1A} antagonist, and catalepsy induced by co-administration of risperidone (0.1 mg/kg) and haloperidol (0.1 mg/kg) was significantly antagonized by 8-OH-DPAT, a 5-HT_{1A} agonist. *Conclusion:* The present study demonstrated that the combined administration of quetiapine with haloperidol did not aggravate EPS, possibly because of its affinity for 5-HT_{1A} receptors. This finding may have the clinical implication that quetiapine could provide a successful regimen in switching from typical antipsychotic agents in the symptom management of schizophrenia, or even in adjunctive therapy with other antipsychotic agents.

Keywords Catalepsy · Locomotor hyperactivity · Quetiapine · Risperidone · Haloperidol · Chlorpromazine · Combination · Schizophrenia · Mice

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Introduction

Quetiapine, a dibenzothiazepine derivative with atypical antipsychotic properties, effectively treats positive symptoms in schizophrenic patients with similar efficacy to typical antipsychotics such as haloperidol (Arvanitis et al. 1997), as well as demonstrating efficacy in treating negative symptoms and cognitive impairment in these patients (Purdon et al. 2001; Velligan et al. 2002). In addition, quetiapine shows a lower incidence of extrapyramidal symptoms (EPS) (Meats 1997) and other adverse events such as increases in serum prolactin levels, compared with typical antipsychotics (Hamner et al. 1996; Arvanitis et al. 1997; Peuskens and Link 1997; Copolov et al. 2000). In experimental animals, quetiapine only weakly induces catalepsy in rats and dystonic liability in haloperidol-sensitized monkeys, and only transiently

elevates serum prolactin levels in rats (Migler et al. 1993; Saller and Salama 1993). Similarly, quetiapine alleviates negative symptoms in an animal model of schizophrenia (Guan et al. 2000). Quetiapine binds with higher affinity to α_1-adrenergic and α_2-adrenergic, histamine H_1, 5-HT_{1A}, and 5-HT_{2A} receptors than to dopamine D_2 receptors (Richelson and Souder 2000), which potentially contributes to its unique pharmacological actions.

Most antipsychotic drugs induce frequent EPS in schizophrenic patients, and they often require concomitant medication with anti-Parkinson's agents. Furthermore, the presence of EPS is predictive of patients who will later exhibit tardive dyskinesia, an extremely serious side effect associated with long-term antipsychotic therapy (Casey 1999). Treatment with typical antipsychotics is often switched to atypical antipsychotics, such as quetiapine, when the typical agents produce intolerable adverse effects (Weiden et al. 1997; Kinon et al. 2000). In this regard, it is common clinical practice to switch to the new drug after first adding the atypical antipsychotic agent to prevent aggravation of psychotic symptoms. Recent clinical studies have suggested that switching to quetiapine is clinically beneficial for patients showing a poor response or intolerable side effects on their previous antipsychotic medications and does not exacerbate patients' symptoms (Cutler et al. 2002; Nayer et al. 2003). In spite of accumulating clinical demands for such a switching strategy, however, there is limited preclinical information to support this combination strategy of atypical and typical antipsychotic agents, both in terms of efficacy and side effects.

The present study was designed to investigate the influence of combined administration of quetiapine with haloperidol in animal models of schizophrenia (Weiss and Kilts 1995): its antipsychotic efficacy (using a methamphetamine-induced hyperlocomotion model) and side-effect profile (using a mouse catalepsy model). We also tested a second atypical antipsychotic agent, risperidone, and a typical antipsychotic agent, chlorpromazine, in the same experimental paradigms. Finally, we expanded our study to clarify the possible mechanism by which atypical antipsychotic agents interact with a typical agent to alter their propensity of inducing extrapyramidal side effects in the light of the possible involvement of 5-HT_{1A} receptors, one of the putative mechanisms contributing to the unique features of atypical antipsychotic drugs including quetiapine (Bantick et al. 2001).

Materials and methods

Animals

Adult male ddY mice were purchased from Japan SLC Co. Ltd (Hikisa, Shizuoka, Japan) at the age of 6 weeks old and were used at 7 weeks old. They were housed in groups of eight to nine in polycarbonate cages with clean paper tips as bedding, under controlled conditions of light (12 h light–dark cycle, light on at 7:00 a.m.) and temperature (23 ±1°C). Mice had free access to water and food throughout the experiment. All animal experimental procedures were performed under the guidelines of the Animal Experiment Committee of Fujisawa Pharmaceutical Co. Ltd.

Methamphetamine-induced hyperlocomotion

Mice were placed in the experimental chamber (L30×W36×H17 cm) 30 min after injection of methamphetamine (1 mg/kg, IP) and locomotor activity was immediately recorded for 30 min using ANIMEX AUTO (MK-110; Muromachi Kikai Co. Ltd, Tokyo, Japan).

Catalepsy

The mouse's forepaws were placed on a horizontal steel bar (diameter 0.3 cm), elevated 3 cm above the tabletop, and the duration of cataleptic time was recorded for up to 30 s. If the catalepsy time was 30 s in at least one trial out of two, it was regarded as the drug-induced catalepsy and scored as "+", otherwise it was scored as "–". The incidence of catalepsy was expressed as the percentage of mice scored as "+" in the total mouse group.

Drugs

Quetiapine was provided from AstraZeneca (Cheshire, UK). Risperidone was synthesized at Fujisawa Pharmaceutical Co. Ltd (Osaka, Japan). Chlorpromazine, WAY100635, and 8-OH-DPAT were purchased from Sigma-Aldrich Co. (St Louis, Mo., USA). Haloperidol and methamphetamine were purchased from Dainippon Pharmaceutical (Osaka, Japan). Quetiapine was suspended in 0.5% methylcellulose, and risperidone and haloperidol were dissolved in saline. Chlorpromazine, WAY100635, and 8-OH-DPAT were dissolved in distilled water. All drugs were freshly prepared and administered in a volume of 10 ml/kg. Quetiapine, risperidone, and chlorpromazine were administered orally 1 h before the measurement. Haloperidol, WAY100635, and 8-OH-DPAT were injected intraperitoneally 30 min before the measurement.

Data analysis

In methamphetamine-induced hyperlocomotion, the data are expressed as mean±SEM. Statistical analysis for the changes in locomotor activity between groups was made using Student's *t*-test (for vehicle-treated normal versus methamphetamine control) and one-way ANOVA followed by Dunnett's multiple comparisons (for multiple drug-treated groups). ED_{50} value was calculated from linear regression analysis. Statistically significant changes in the incidence of catalepsy were calculated using Chi-square test (for comparison of two groups) and Dunnett's

multiple comparison test (for multiple groups). The ED_{50} value was calculated using linear regression analysis.

Results

Effect of quetiapine, risperidone, chlorpromazine, or haloperidol alone

In the first study, we investigated the antipsychotic effects and EPS liability of quetiapine, risperidone, chlorpromazine, or haloperidol alone in an attempt to compare the spectrum of each drug and to provide rationale for choosing optimal doses for subsequent combination studies.

Methamphetamine-induced hyperlocomotion Methamphetamine treatment (0.1, 0.32, 1, 3.2 mg/kg, IP) dose-dependently increased locomotor activity (data not shown). Hyperlocomotion induced by methamphetamine (1 mg/kg) was dose-dependently reduced by single injections of quetiapine, risperidone, chlorpromazine, or haloperidol, with ED_{50} values of 5.6, 0.020, 1.8, 0.035 mg/kg, respectively (Table 1).

Catalepsy Risperidone, chlorpromazine, and haloperidol dose-dependently induced catalepsy at low doses (Table 1), whereas quetiapine only minimally induced catalepsy at only the highest dose (100 mg/kg). ED_{50} values of quetiapine, risperidone, chlorpromazine, and haloperidol were 95, 0.25, 4.6, and 0.10 mg/kg, respectively (Table 1). The therapeutic index of each compound was calculated using ED_{50} values for inhibiting methamphetamine-induced hyperlocomotion versus those of eliciting catalepsy: quetiapine and risperidone showed wider therapeutic windows than did chlorpromazine and haloperidol (Table 1).

Table 1 Inhibitory effect of quetiapine, risperidone, chlorpromazine, or haloperidol alone on methamphetamine-induced hyperlocomotion and on the incidence of catalepsy in mice. Each value of the methamphetamine-induced hyperlocomotion test represents the average counts of locomotor activity (±SEM) measured for 30 min using Animex system (n=8). Methamphetamine (*MAP*; 1 mg/kg) was intraperitoneally administered 30 min before the measurement. In both experiments, quetiapine, risperidone, and chlorpromazine were orally administered 1 h before measurement, and haloperidol was intraperitoneally administered 30 min before measurement. Therapeutic index of each compound was calculated using the ED_{50} values of inhibition on methamphetamine-induced hyperlocomotion (A) and catalepsy (B)

Antipsychotic agents	Methamphetamine-induced hyperlocomotion			Catalepsy			Therapeutic index (B)/(A)
	Dose (mg/kg)	Locomotor activity (counts/30 min)	ED_{50} (A) (mg/kg)	Dose (mg/kg)	Incidence of catalepsy (%)	ED_{50} (B) (mg/kg)	
Quetiapine	Vehicle	960±117	5.6			95	17
	MAP alone	2404±185		Vehicle	0		
	MAP+1	2459±170		10	0		
	MAP+3.2	2254±178		32	0		
	MAP+10	1080±317**		100	57.14$^{\#\#}$		
	MAP+32	703±288**					
Risperidone	Vehicle	801±165	0.020			0.25	13
	MAP alone	2417±240		Vehicle	0		
	MAP+0.0032	2051±177		0.1	28.57		
	MAP+0.01	1681±170*		0.32	50.00$^{\#}$		
	MAP+0.032	1721±212		1	85.71$^{\#\#}$		
	MAP+0.1	1134±172**					
Chlorpromazine	Vehicle	895±76	1.8			4.6	2.6
	MAP alone	2345±242		Vehicle	0		
	MAP+0.1	2290±175		1	7.14		
	MAP+0.32	2135±306		3.2	35.71		
	MAP+1	1986±142		10	78.57$^{\#\#}$		
	MAP+3.2	1325±220**					
Haloperidol	Vehicle	840±102	0.035			0.10	2.9
	MAP alone	2130±234		Vehicle	0		
	MAP+0.01	1781±192		0.032	7.14		
	MAP+0.032	1552±118*		0.1	50.00$^{\#}$		
	MAP+0.1	1192±130**		0.32	92.86$^{\#\#}$		
	MAP+0.32	308±53**					

*P<0.05, **P<0.01, statistically significant compared with methamphetamine-alone group of each experiment (by ANOVA followed by Dunnett's multiple comparisons). Each value in catalepsy test represents the incidence of catalepsy (n=14). $^{\#}P$<0.05, $^{\#\#}P$<0.01, statistically significant compared with each vehicle-treated group (by Dunnett's multiple comparison test)

Effect of combined administration of quetiapine, risperidone or chlorpromazine with haloperidol

The second study was designed to determine the antipsychotic efficacy and side-effect profile of concomitant administration of quetiapine, risperidone, or chlorpromazine with haloperidol.

Methamphetamine-induced hyperlocomotion Doses of quetiapine, risperidone, chlorpromazine, and haloperidol were administered at their ED_{50} values for inhibiting methamphetamine-induced hyperlocomotion when used alone (Table 1): 6 mg/kg for quetiapine, 0.02 mg/kg for risperidone, 2 mg/kg for chlorpromazine, and 0.04 mg/kg for haloperidol. Both the combination of quetiapine and haloperidol and the combination of chlorpromazine and haloperidol significantly reduced methamphetamine-induced hyperlocomotion compared with haloperidol alone (Fig. 1). Risperidone plus haloperidol similarly protected methamphetamine-induced hyperlocomotion compared with the risperidone-alone group (Fig. 1).

Catalepsy Quetiapine (10 and 32 mg/kg) plus haloperidol (0.032, 0.1, and 0.32 mg/kg) did not enhance the cataleptogenic effects of haloperidol (Fig. 2). Furthermore, the combination of quetiapine (100 mg/kg) and haloperidol did not affect the incidence of catalepsy compared with haloperidol alone. In contrast, the combination of risperidone (0.1 mg/kg) and haloperidol (0.1 mg/kg) markedly augmented haloperidol-induced catalepsy (Fig. 3). Risperidone (0.32 mg/kg) also enhanced the catalepsy induced by combination with haloperidol (0.032 and 0.1 mg/kg). Similarly, the combination of chlorpromazine (3.2 mg/kg) and haloperidol (0.1 mg/kg) showed greater cataleptic effects than haloperidol alone (Fig. 4).

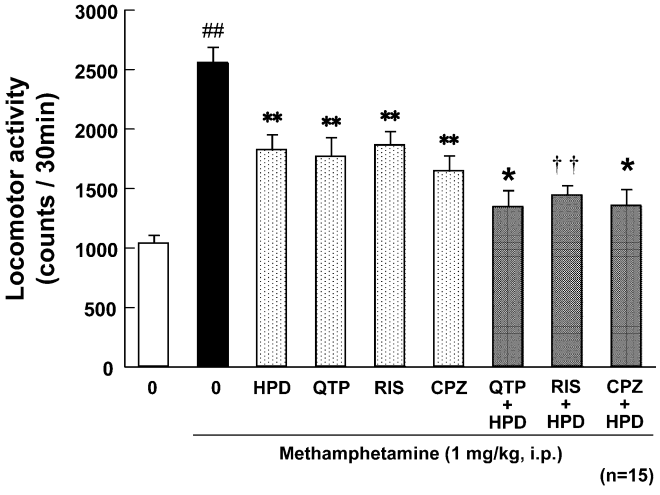

Fig. 1 Effects of concomitant administration of quetiapine (*QTP*), risperidone (*RIS*) or chlorpromazine (*CPZ*), and haloperidol (*HPD*) on methamphetamine-induced hyperlocomotion in mice. Each column represents the average counts of locomotor activity±SEM measured for 30 min using the Animex system. Dosage of each drug used was based on the ED_{50} value for each compound determined in the first study (Table 1); quetiapine 6 mg/kg, risperidone 0.02 mg/kg, chlorpromazine 2 mg/kg, haloperidol 0.04 mg/kg. Methamphetamine (1 mg/kg) was intraperitoneally administered 30 min before measurement. Quetiapine, risperidone, and chlorpromazine were orally administered 1 h before measurement, and haloperidol was intraperitoneally administered 30 min before the measurement. Number of animals was 15 for each treatment group. $^{\#\#}P<0.01$, statistically significant compared with vehicle-treated group (by Student's *t*-test). $^{**}P<0.01$, statistically significant compared with methamphetamine-alone group (by ANOVA followed by Dunnett's multiple comparison test). $^{*}P<0.05$ statistically significant compared with haloperidol alone group (by ANOVA followed by Dunnett's multiple comparison test). $^{\ddagger}P<0.01$, statistically significant compared risperidone-alone group (by Student's *t*-test)

Involvement of 5-HT_{1A} receptors in catalepsy produced by combining either quetiapine or risperidone with haloperidol

We next wanted to clarify the role of 5-HT_{1A} receptors in the mechanism by which risperidone, but not quetiapine, augmented haloperidol-induced catalepsy. WAY100635, a 5-HT_{1A} antagonist, was investigated for its effects on the catalepsy observed following co-administration of quetiapine and haloperidol. In accordance with our previous results (see Fig. 2), co-administration of quetiapine (10 mg/kg) and haloperidol (0.1 mg/kg) significantly induced catalepsy, but this was exactly comparable with that produced by haloperidol alone and quetiapine did not enhance the catalepsy by haloperidol. Co-administration of WAY100635 (0.1 and 1 mg/kg) with quetiapine and haloperidol dose-dependently enhanced the catalepsy, with statistical significance at 1 mg/kg (Fig. 5). WAY100635 had no effects on the catalepsy induced by haloperidol alone at the doses used here (Fig. 5), and did not produce any cataleptic behaviors when administered alone (data not shown).

We finally evaluated the effect of 8-OH-DPAT, a 5-HT_{1A} agonist, on catalepsy enhanced by co-administration of risperidone and haloperidol. As with the previous experiment (Fig. 3), catalepsy induced by haloperidol

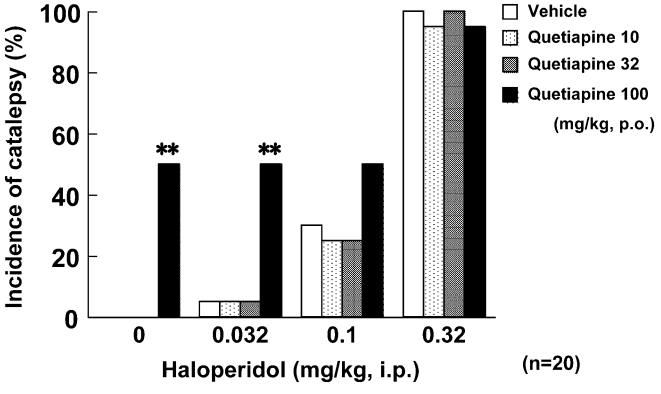

Fig. 2 Effect of quetiapine on haloperidol-induced catalepsy in mice. Each column represents the incidence of catalepsy. Quetiapine (10, 32, 100 mg/kg) was orally administered 1 h before measurement, and haloperidol (0.032, 0.1, 0.32 mg/kg) was intraperitoneally administered 30 min before measurement. Number of animals was 20 for each treatment group. $^{**}P<0.01$, statistically significant compared with quetiapine 0 mg/kg treated group in each haloperidol treated group (by Dunnett's multiple comparison test)

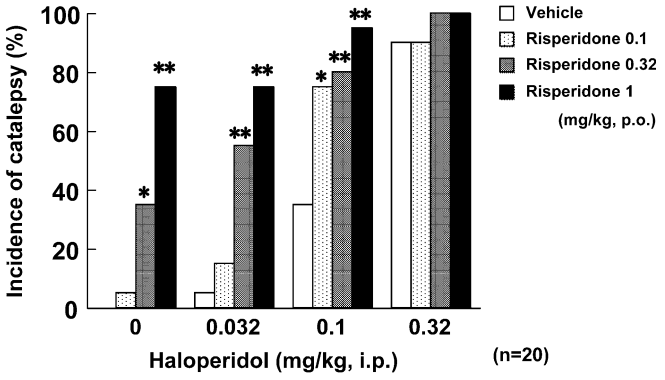

Fig. 3 Effect of risperidone on haloperidol-induced catalepsy in mice. Each column represents the incidence of catalepsy. Risperidone (0.1, 0.32, 1 mg/kg) was orally administered 1 h before measurement, and haloperidol (0.032, 0.1, 0.32 mg/kg) was intraperitoneally administered 30 min before the measurement. Number of animals was 20 for each treatment group. *P<0.05, **P<0.01, statistically significant compared with risperidone 0 mg/kg treated group in each haloperidol treated group (by Dunnett's multiple comparison test)

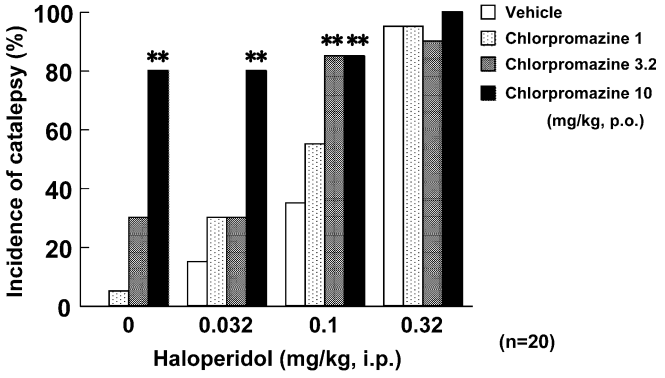

Fig. 4 Effect of chlorpromazine on haloperidol-induced catalepsy in mice. Each column represents the incidence of catalepsy. Chlorpromazine (1, 3.2, 10 mg/kg) was orally administered 1 h before measurement, and haloperidol (0.032, 0.1, 0.32 mg/kg) was intraperitoneally administered 30 min before measurement. Number of animals was 20 for each treatment group. **P<0.01, statistically significant compared with chlorpromazine 0 mg/kg treated group in each haloperidol treated group (by Dunnett's multiple comparison test)

(0.1 mg/kg) was significantly aggravated by risperidone (0.1 mg/kg). The enhanced catalepsy induced by co-administration of risperidone and haloperidol was significantly antagonized dose-dependently by 8-OH-DPAT (0.001 and 0.01 mg/kg; Fig. 6). 8-OH-DPAT had no significant effects on haloperidol-induced catalepsy (Fig. 6), and 8-OH-DPAT alone had no effect in this catalepsy model (data not shown).

Discussion

In the present study, quetiapine was evaluated for its ability to potentiate the antipsychotic effects and EPS of haloperidol, and it was compared with two other antipsychotic agents, risperidone, and chlorpromazine. In the first study, which evaluated the antipsychotic effects and EPS liability of each drug when treated alone, most agents significantly inhibited methamphetamine-induced hypermotility, a model of antipsychotic efficacy, and induced catalepsy, a predictive measure of EPS (Weiss and Kilts 1995), at similar doses. However, in the case of quetiapine, the dose that produced antipsychotic effects (10 mg/kg) was much lower than the dose required to weakly induce

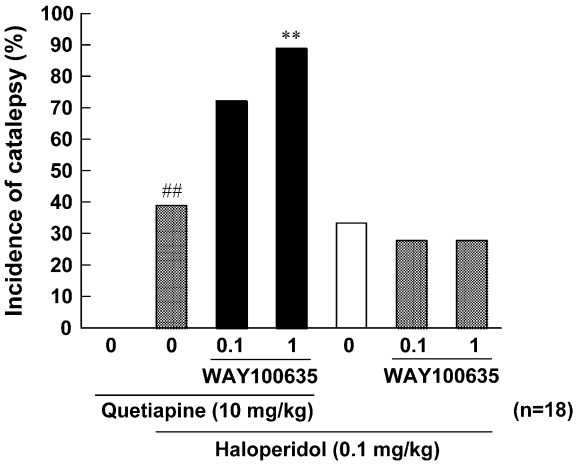

Fig. 5 Effect of treatment with WAY100635 on catalepsy induced by co-administration of quetiapine and haloperidol in mice. Each column represents the incidence of catalepsy. Quetiapine (10 mg/kg) was orally administered 1 h before measurement, and haloperidol (0.1 mg/kg) and WAY100635 (0.1, 1 mg/kg) was intraperitoneally administered 30 min before the measurement. Number of animals was 18 for each treatment group. ##P<0.01, statistically significant compared with quetiapine-alone group (by Chi-square test). **P<0.01, statistically significant compared with quetiapine plus haloperidol treated group (by Dunnett's multiple comparison test)

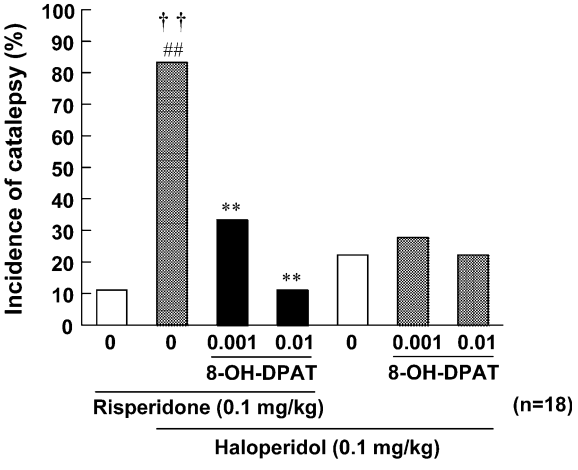

Fig. 6 Effect of 8-OH-DPAT on co-administration of risperidone and haloperidol on catalepsy in mice. Each column represents the incidence of catalepsy. Risperidone (0.1 mg/kg) was orally administered 1 h before measurement, and haloperidol (0.1 mg/kg) and 8-OH-DPAT (0.001, 0.01 mg/kg) was intraperitoneally administered 30 min before measurement. Number of animals was 18 for each treatment group. ##P<0.01, statistically significant compared with risperidone-alone group (by Chi-square test). ‡P<0.01, statistically significant compared with haloperidol alone group (by Chi-square test). **P<0.01, statistically significant compared with risperidone plus haloperidol treated group (by Dunnett's multiple comparison test)

catalepsy (100 mg/kg). Based on the ratio between ED_{50} values for inhibiting methamphetamine-induced hyperlocomotor activity and ED_{50} values for producing catalepsy, quetiapine and risperidone behaved as atypical antipsychotic agents with higher therapeutic indices compared with those of typical antipsychotic drugs such as chlorpromazine and haloperidol. The results are in accordance with previous observations by others in animal models (Migler et al. 1993) and also in clinical studies showing that atypical antipsychotic agents show wider margins in comparison with typical antipsychotic agents (Jibson and Tandon 1998). Therefore, these results suggest that these mice models used here mirror the clinical observations in terms of their sensitivity in distinguishing the profile of atypical from typical antipsychotic agents.

Quetiapine, risperidone, and chlorpromazine were evaluated for their antipsychotic effects in combination with haloperidol in a methamphetamine-induced hyperlocomotion model. The combination of quetiapine and haloperidol significantly inhibited methamphetamine-induced hyperlocomotion compared with haloperidol alone, and both risperidone and chlorpromazine similarly enhanced haloperidol-induced inhibition of methamphetamine-induced hyperlocomotion. This enhancement of haloperidol activity putatively occurred via a common mechanism, since the inhibitory activity of these drugs were additive (not synergistic) and there were no meaningful differences in the magnitude of the protection by any of three drugs combined with haloperidol. Alternatively, a ceiling effect of inhibition in the drug combinations might mask further changes even if quetiapine, risperidone, and chlorpromazine interacted with haloperidol through different modes of action.

The most important finding in the present study is that quetiapine did not enhance haloperidol-induced catalepsy, suggesting that quetiapine and haloperidol differentially modulate the neuronal systems responsible for expression of antipsychotic activity and EPS. In contrast, risperidone and chlorpromazine significantly enhanced haloperidol-induced catalepsy, even with a suboptimal dose of haloperidol (0.1 mg/kg). Although quetiapine and risperidone are both classified as atypicals, it is conceivable that these compounds have different modes of actions. The lack of catalepsy potentiation by the combination of quetiapine with haloperidol might be consistent with recent clinical observation that patients with schizophrenia who switched from typical agents to quetiapine experienced improvements in symptoms as well as a reduction in EPS (Cutler et al. 2002; Nayer et al. 2003), and also supports the further clinical use of such combination (at least quetiapine plus haloperidol) in schizophrenic patients.

Atypical antipsychotic agents have binding affinities for many neurotransmitter receptors in the brain. Quetiapine reportedly has a low affinity for D_2 receptors but instead has higher affinity for the 5-HT_{2A} and 5-HT_{1A} than D_2 receptors (Richelson and Souder 2000). On the other hand, risperidone has higher affinity for 5-HT_{2A} than D_2 receptors, with low affinity for 5-HT_{1A} receptors (Richelson and Souder 2000). It is also reported that quetiapine exhibits a partial agonist activity at the 5-HT_{1A} receptor (Newman-Tancredi et al. 1998; Ichikawa et al. 2002). In contrast, risperidone is known to behave as a 5-HT_{1A} antagonist at higher dosages (Newman-Tancredi et al. 1998). In the present study, we demonstrated that catalepsy induced by co-administration of quetiapine and haloperidol was dose-dependently enhanced by low doses of WAY100635, a 5-HT_{1A} antagonist that did not alter haloperidol-induced catalepsy. This finding suggests that the 5-HT_{1A} agonistic property of quetiapine contributes to its low liability for inducing EPS, and that a normally hidden propensity masked by 5-HT_{1A} receptor agonism was reversed by WAY100635, consequently resulting in an apparent increase in EPS. In contrast, the fact that the enhanced catalepsy following co-administration of risperidone and haloperidol could be significantly inhibited by low dosages of 5-HT_{1A} agonist 8-OH-DPAT that failed to affect haloperidol-induced catalepsy, indicates that risperidone's property as a 5-HT_{1A} receptor antagonist could partly contribute to a high incidence of EPS after concomitant administration with haloperidol.

The present study clearly highlights the difference in the action of quetiapine and risperidone, but the study does not per se clarify how this phenomenon is observed in combination with haloperidol, peculiar for quetiapine among diverse atypical antipsychotics. Biochemical and behavioral pharmacological tests in animals have proven that quetiapine resembles clozapine, another atypical antipsychotic agent, in the profiles sharing partial agonist activity at the 5-HT_{1A} receptor (Meltzer et al. 1975; Casey 1989; Meltzer 1992). However, Ahlqvist et al. (2003) recently demonstrated that clozapine but not quetiapine or olanzapine blocked the catalepsy induced by dopamine antagonists, suggesting that clozapine has anticataleptic activity differing from quetiapine, possibly via other mechanisms rather than 5-HT_{1A} receptor agonism. As their finding is not fully compatible with our study that focused on the possible potentiation of catalepsy, it would be fascinating to evaluate combination effects using other diverse antipsychotic drugs in our experimental paradigms.

Serotonergic drugs are known to modulate EPS associated with antipsychotics through the interaction between serotonin and dopamine in the substantia nigra and the striatum (Kapur and Remington 1996). The serotonergic pathway from the dorsal raphe (Fibiger and Miller 1977; Olpe and Koella 1977) projects directly to the substantia nigra, and inhibits the firing of the nigral dopaminergic neurons (Nedergaard et al. 1988). The raphe-nigral neurons arise as collateral of the raphe-striatal neurons, thus providing a neural basis for coordinated modulation of midbrain and terminal dopaminergic functions (Kooy and Hattori 1980). Therefore, inhibition of serotonin function (for instance; activation of somatodendritic 5-HT_{1A} receptors in the nigra, or blockade of terminal 5-HT_{2A} receptors in the striatum) is expected to disinhibit the dopamine system and decrease blockade of D_2 receptors in the striatum, therefore inhibiting EPS (Kapur and Remington 1996). Thus, the 5-HT_{1A} partial agonist activity of quetiapine might prevent enhancement of catalepsy when co-administrated with haloperidol. 5-HT_{1A} partial agonists not only inhibit antipsychotic-induced EPS but also improve cognitive symptoms in schizophrenic patients and exert antidepressant and anxi-

olytic effects in humans (Millan 2000). Furthermore, biochemical studies using post-mortem schizophrenic brain have identified a reproducible elevation in 5-HT_{1A} receptor density in the frontal cortex (Burnet et al. 1997). Therefore, it is tempting to speculate that the 5-HT_{1A} partial agonist activity of quetiapine is involved, in part, in its therapeutic efficacy.

In conclusion, the present study provides compelling evidence that combined administration of quetiapine and haloperidol does not exacerbate EPS but still enhances the antipsychotic efficacy in animal models, suggesting that quetiapine could contribute to a successful regimen for switching from symptomatic management using typical antipsychotic agents, or adjunctive therapy with other antipsychotic agents.

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