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Interaction between anti-Alzheimer and antipsychotic drugs in modulating extrapyramidal motor disorders in mice

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ABSTRACT

Antipsychotics are often used in conjunction with anti-Alzheimer drugs to treat the behavioral and psychological symptoms of dementia (BPSD). Here, we examined the effects of cholinesterase inhibitors (ChEIs), donepezil and galantamine, on antipsychotic-induced extrapyramidal side effects (EPS) in mice. The effects of serotonergic agents on the EPS drug interaction were also evaluated. Donepezil (0.3–3 mg/kg) did not induce EPS signs by itself; however, it significantly potentiated bradykinesia induction with a low dose of haloperidol (0.5 mg/kg) in dose-dependent and synergistic manners. Galantamine (0.3–3 mg/kg) elicited mild bradykinesia at a high dose and dose-dependently augmented haloperidol-induced bradykinesia. The EPS potentiation by galantamine was blocked by trihexyphenidyl (a muscarinic antagonist), but not by mecamylamine (a nicotinic antagonist). In addition, the bradykinesia potentiation by galantamine was significantly reduced by (±)-8-hydroxy-2-(di-n-propylamino)-tetralin (a 5-HT_{1A} agonist), ritanserin (a 5-HT_2 antagonist), and SB-258585 (a 5-HT_6 antagonist). The present results give us a caution for the antipsychotics and ChEIs interaction in inducing EPS in the treatment of BPSD. In addition, second generation antipsychotics, which can stimulate 5-HT_{1A} receptors or antagonize 5-HT_2 and 5-HT_6 receptors, seem to be favorable as an adjunctive therapy for BPSD.

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1. Introduction

Alzheimer's disease is the most common neurodegenerative disorder that shows the cognitive deficits (e.g., disorientation, impairments in learning and memory functions) as the primary symptom (1). Besides cognitive deficits, patients with Alzheimer's disease often exhibit various behavioral and psycho-emotional abnormalities, known as the behavioral and psychological symptoms of dementia (BPSD), including psychosis (e.g., hallucinations and delusion), psychomotor excitement, and mood disturbances (e.g., anxiety, depression, and the loss of motivation) (2–4). BPSD, especially psychosis and psychomotor excitement, markedly impair the QOL of these patients and disrupt medical treatments and nursing care.

Since Alzheimer's disease accompanies the loss of central acetylcholine (ACh) neurons (1,5) that control cognitive functions, several cholinesterase inhibitors (ChEIs) such as donepezil, galantamine, and rivastigmine are widely used in the treatment of Alzheimer's disease. These agents can reverse the depletion of ACh level in Alzheimer's disease by inhibiting cholinesterase. In addition, anti-Alzheimer's drugs are often used in combination with antipsychotic agents which can ameliorate the BPSD (4,6,7), yielding greater efficacy over monotherapy (8). However, information on drug interactions between antipsychotic and anti-Alzheimer's drugs is still limited, especially in terms of the induction of side effects and safe combinations of these agents.

The most frequent side effects of antipsychotic drugs are extrapyramidal motor disorders such as bradykinesia, muscle rigidity, resting tremors, and akathisia (9–11). These extrapyramidal side effects (EPS) are primarily brought about by the blockade of striatal dopamine D_2 receptors. Thus, first generation (typical) antipsychotics show high liability to induce EPS. On the other hand, several second generation (atypical) antipsychotics with fewer EPS

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are now available, including risperidone, perospirone, olanzapine and quetiapine. These agents not only interact with D_2 receptors, but also with 5-HT receptors (e.g., 5-HT_2, 5-HT_{1A} and 5-HT_6 receptors) (10–13) which are implicated in the atypicality of the second generation antipsychotics (14–16). Furthermore, extrapyramidal motor symptoms are also known to be controlled by the ACh interneurons in the striatum (17).

In the present study, to evaluate the interaction between anti-Alzheimer and antipsychotic drugs in inducing EPS, we examined the effects of the ChEIs, donepezil and galantamine, on haloperidol-induced bradykinesia using the mouse pole test. In addition, we also investigated the effects of various serotonergic agents on the antipsychotics and ChEIs interactions to clarify the possibility that second generation antipsychotics can reduce this EPS drug interaction.

2. Materials and methods

2.1. Animals

Male ddY mice (25–35 g) (Japan SLC, Shizuoka, Japan) were used. Animals were housed in air-conditioned rooms under a 12-h light/dark cycle (light on: 8:00 a.m.) and allowed *ad libitum* access to food and water. The housing conditions and animal care methods complied with the Guide for the Care and Use of Laboratory Animals of the Ministry of Education, Science, Sports and Culture of Japan. The 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 reported previously (18). Briefly, mice were placed head-upward at the top of a wooden pole (8 mm in diameter and 45 cm in height), and the time for the animal to rotate downward completely (T_{turn}) and descend to the floor (T_{total}) was then measured with a cut-off time of 90 s. Animals typically received training (3–5 min/session/day) for pole-descending behavior for 3–4 days, and only mice that showed T_{turn} <8 s and T_{total} <18 s in the pre-test trial (generally performed 2 h before the test trial) were used.

The pole test was performed 30 min after the injection of anti-Alzheimer drugs (i.e., donepezil and galantamine). The test doses of donepezil and galantamine were set to those that reportedly improved cognitive deficits in rodents (19,20). In the combination studies, haloperidol or vehicle was administered simultaneously with the anti-Alzheimer drugs. The dose of halopeidol was set at 0.5 mg/kg (i.p.), which induced weak bradykinesia, based on the dose–response of haloperidol-induced bradykinesia (Supplemental Fig. 1). The cholinergic antagonists, trihexyphenidyl and mecamylamine, were administered 15 min before the combined treatment with galantamine (1 mg/kg, i.p.) and haloperidol (0.5 mg/kg, i.p.).

In the experiments to examine the effects of serotonergic agents, the 5-HT_{1A} agonist (±)-8-hydroxy-2-(di-n-propylamino)-tetralin ((±)-8-OH-DPAT, 0.1–1 mg/kg, i.p.), 5-HT_2 antagonist ritanserin (0.3–3 mg/kg, i.p.), 5-HT_3 antagonist ondansetron (0.1–1 mg/kg, i.p.), and 5-HT_6 antagonist SB-258585 (1–10 mg/kg, i.p.) were administered 15 min before the combined injection of galantamine (1 mg/kg, i.p.) and haloperidol (0.5 mg/kg, i.p.). The 5-HT_{1A} antagonist (S)-WAY-100135 was given 15 min before the (±)-8-OH-DPAT injection. The doses of serotonergic agents were set to those that reversed the serotonergic (i.e., treatment of 5-hydroxytryptophan or selective 5-HT reuptake inhibitors) potentiation of EPS (21,22).

2.3. Drugs

Haloperidol, donepezil hydrochloride, trihexyphenidyl hydrochloride, mecamylamine hydrochloride, (±)-8-OH-DPAT hydrobromide, ritanserin, ondansetron hydrochloride dihydrate, and SB-258585 dihydrochloride were purchased from Sigma–Aldrich (St. Louis, MO). Galantamine hydrobromide and (S)-WAY-100135 dihydrochloride were from Tocris (Bristol, UK). Haloperidol, donepezil, mecamylamine, (±)-8-OH-DPAT, (S)-WAY-100135, and ritanserin were first dissolved in 1% lactate solution and diluted with physiological saline. Other agents were dissolved in physiological saline. All drugs were injected intraperitoneally or subcutaneously in a volume of 5 mL/kg into mice.

2.4. Statistical analysis

Data are expressed as the mean ± S.E.M. The significance of differences in T_{turn} and T_{total} values was determined by a one-way ANOVA followed by a Tukey *post hoc* multiple comparisons test (for multiple comparisons) or the Student's *t*-test (for two group comparisons). When animals showed the upper limit of the observation time (90 s), comparisons were made by a non-parametric Kruskal–Wallis test followed by the Steel-Dwass *post hoc* test (for multiple comparisons) or Mann–Whitney's U test (for two group comparisons). A P value of less than 0.05 was considered significant.

3. Results

3.1. Effects of donepezil and galantamine on haloperidol-induced bradykinesia

Control animals placed head-upward at the top of the pole normally rotated downward within 3 s and descended to the floor within 11 s (Supplemental Fig. 1).

We examined the direct effects of the ChEIs, donepezil and galantamine, on the induction of bradykinesia. Donepezil did not significantly affect the pole-descending behavior of mice at doses up to 3 mg/kg (i.p.) (Fig. 1A). Galantamine did not induce bradykinesia at 0.3–1 mg/kg (i.p.), but significantly increased the pole-descending time of mice at 3 mg/kg (T_{turn}: F (3,35) = 8.0288, P = 0.0003, T_{total}: F (3,35) = 7.3261, P = 0.0006) (Fig. 1B). When co-administered with a low dose of haloperidol (0.5 mg/kg, i.p.), which weakly induced bradykinesia by itself (Supplemental Fig. 1), donepezil (3 mg/kg, i.p.) and galantamine (1–3 mg/kg, i.p.) both markedly potentiated bradykinesia induction (T_{turn}: X^2 = 13.9944, df = 3, P = 0.0029 and T_{total}: X^2 = 15.0129, df = 3, P = 0.0018 for donepezil; T_{turn}: X^2 = 22.2239, df = 3, P = 0.0001, T_{total}: X^2 = 24.7285, df = 3, P < 0.0001 for galantamine) (Fig. 1C and D). The T_{total} value with donepezil (3 mg/kg, i.p.) or haloperidol (0.5 mg/kg, i.p.) alone was 6.3 ± 0.89 or 14.9 ± 3.70 s, respectively (Fig. 1A and C). However, these values increased to 62.8 ± 8.69 s with the combined treatment using the same dose of donepezil and haloperidol (Fig. 1C). Similarly, the T_{total} values with galantamine (9.3 ± 0.92 and 22.2 ± 5.05 s at 1 and 3 mg/kg, i.p., respectively) and haloperidol (0.5 mg/kg, 12.4 ± 1.96 s) increased to 53.3 ± 10.51 and 59.8 ± 8.17 s, respectively, with their combination (Fig. 1B and D). These results indicate that the potentiation of bradykinesia induction by the interaction of haloperidol and ChEIs occurred in a synergistic manner.

We then examined the effects of trihexyphenidyl (a muscarinic antagonist) and mecamylamine (a nicotinic antagonist) on galantamine-enhanced bradykinesia to determine the subtype of ACh receptors involved in the potentiation of EPS. As shown in Fig. 1D, the induction of bradykinesia with galantamine (1 mg/kg, i.p.) and haloperidol (0.5 mg/kg, i.p.) was completely antagonized

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