Journal of Pharmacological Sciences 127 (2015) 439–445

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Contents lists available at ScienceDirect

Journal of Pharmacological Sciences

journal homepage: www.elsevier.com/locate/jphs

Full paper

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

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ARTICLE INFO

Article history:
Received 10 February 2015
Received in revised form
11 March 2015
Accepted 12 March 2015
Available online 20 March 2015

Keywords:
Anti-Alzheimer drugs
Antipsychotic drugs
Behavioral and psychological symptoms of dementia (BPSD)
Cholinesterase inhibitors
Extrapyramidal side effects

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.

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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Peer review under responsibility of Japanese Pharmacological Society.

http://dx.doi.org/10.1016/j.jphs.2015.03.004

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

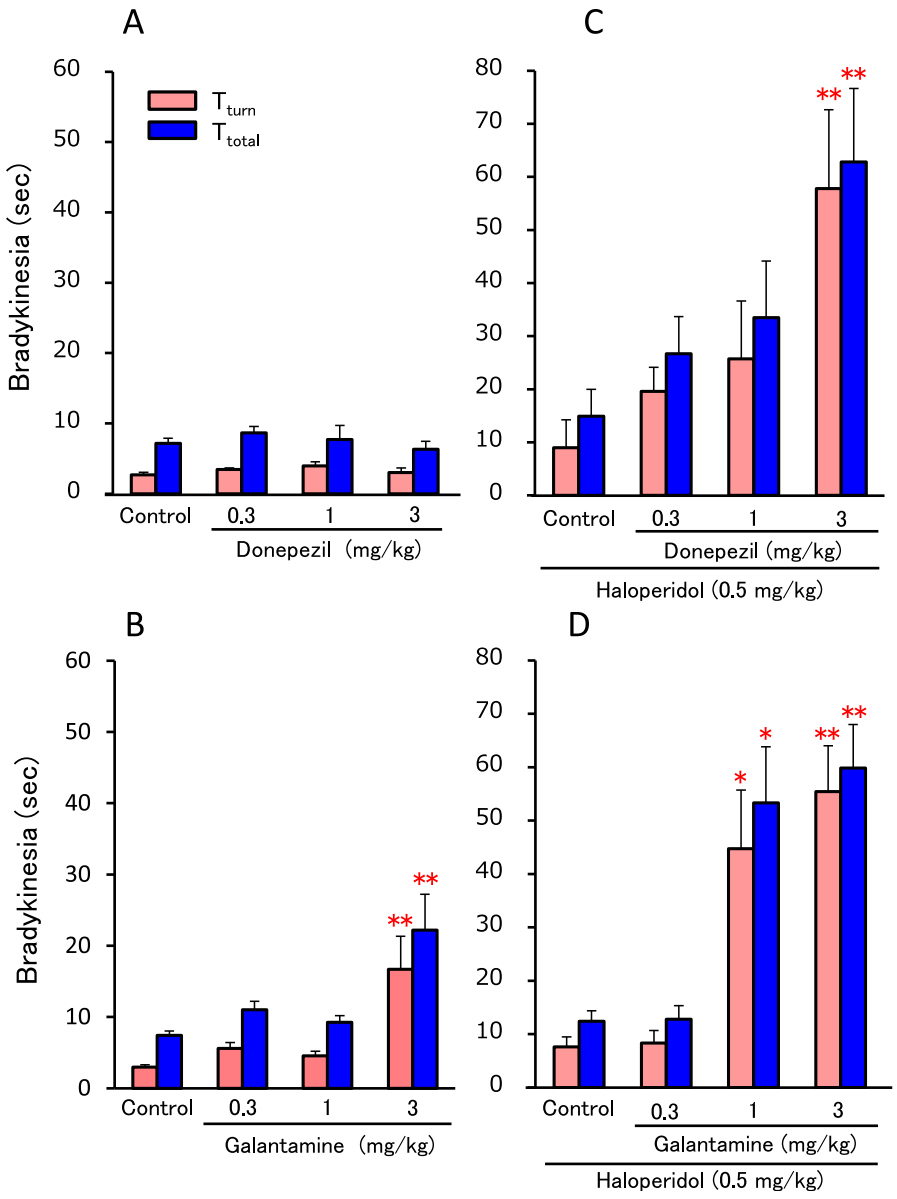

Fig. 1. Effects of cholinesterase inhibitors (ChEI) on haloperidol-induced bradykinesia. The pole test was performed 30 min after injections of the cholinesterase inhibitors (ChEIs) donepezil and galantamine. In the experiments with haloperidol, it was given simultaneously with ChEI. Each column represents the mean ± S.E.M. of 6–13 mice. $^{*}P < 0.05$, $^{**}P < 0.01$; Significantly different from the control value with vehicle (A and B) or haloperidol (C and D) alone.

by trihexyphenidyl (T_{turn}: F (9,10) = 22.9095, $P < 0.0001$, T_{total}: F (9,10) = 15.0222, $P = 0.0002$) (Fig. 2A), but was not affected by mecamylamine (Fig. 2B).

3.2. *Effects of serotonergic drugs on galantamine-enhanced induction of bradykinesia*

Since the induction of EPS is reportedly reduced by activation of 5-HT_{1A} receptors or blockade of 5-HT_2, 5-HT_3, and 5-HT_6 receptors (14–16,21), we next investigated the effects of serotonergic agents (i.e., (±)-8-OH-DPAT, ritanserin, ondansetron, and SB-258585) on the galantamine (1 mg/kg, i.p.)-enhanced induction of bradykinesia. As shown in Fig. 3A, the 5-HT_{1A} agonist (±)-8-OH-DPAT (0.1–1 mg/kg, i.p.) markedly attenuated galantamine and haloperidol-induced bradykinesia in a dose-dependent manner (T_{turn}: $X^2 = 19.1601$, df = 3, $P = 0.0003$, T_{total}: $X^2 = 19.5649$, df = 3, $P = 0.0002$). In particular, 0.3 and 1 mg/kg of (±)-8-OH-DPAT reduced T_{turn} and T_{total} values almost to control levels (T_{turn}: 5.4 ± 1.29 and T_{total}: 11.7 ± 1.66 at 0.3 mg/kg, T_{turn}: 6.2 ± 2.55 and T_{total}: 14.0 ± 2.79 at 1 mg/kg). The ameliorative actions of (±)-8-OH-DPAT (1 mg/kg, i.p.) on the galantamine-enhanced bradykinesia were completely antagonized by (s)-WAY-100135 (3 mg/kg, s.c.) (T_{turn}: $X^2 = 18.2919$, df = 2, $P = 0.0001$, T_{total}: $X^2 = 18.0477$, df = 2, $P = 0.0001$) (Fig. 3B). In addition, the 5-HT_2 antagonist ritanserin (0.3–3 mg/kg, i.p.) and 5-HT_6 antagonist SB-258585 (1–10 mg/kg, i.p.) significantly reversed galantamine-potentiated bradykinesia (T_{turn}: $X^2 = 13.3976$, df = 3, $P = 0.0039$ and T_{total}: $X^2 = 13.6573$, df = 3, $P = 0.0034$ for ritanserin; T_{turn}: $X^2 = 14.6323$, df = 3, $P = 0.0022$, T_{total}: $X^2 = 13.2154$, df = 3, $P = 0.0042$ for SB258585) (Fig. 4A and C). However, the 5-HT_3 antagonist ondansetron (0.1–1 mg/kg, i.p.) failed to significantly affect T_{turn} and T_{total} values at any dose examined (Fig. 4B).

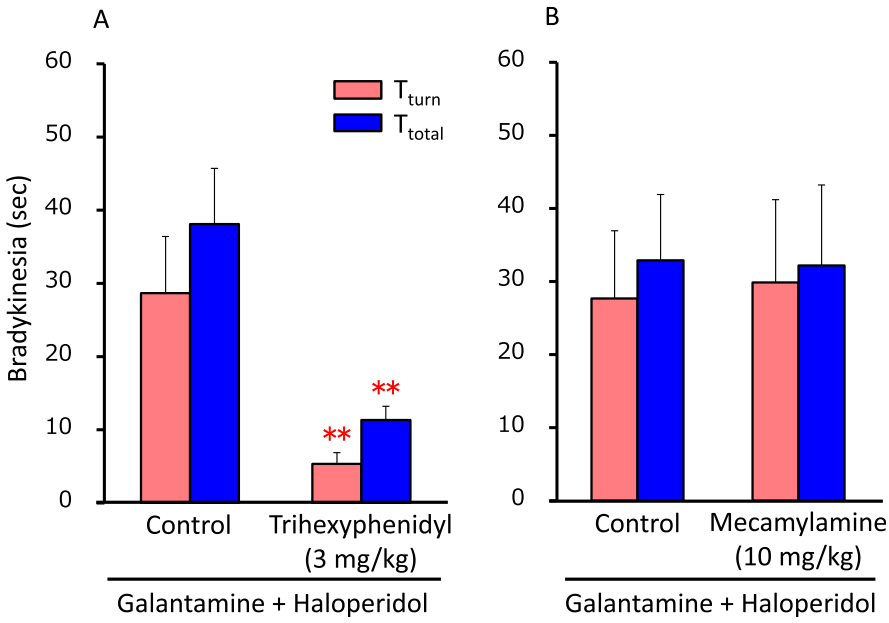

Fig. 2. Effects of anti-cholinergic agents on the galantamine-enhanced induction of bradykinesia. The pole test was performed 30 min after a simultaneous injection of galantamine (1 mg/kg, i.p.) and haloperidol (0.5 mg/kg, i.p.). The anti-cholinergic agents, trihexyphenidyl and mecamylamine, were given 15 min before the galantamine injection. Each column represents the mean ± S.E.M. of 10–11 mice. $^{**}P < 0.01$; Significantly different from the control value with the injection of haloperidol and galantamine.

4. Discussion

Drug-induced EPS (e.g. bradykinesia, muscle rigidity, tremors, dystonia, and akathisia) disrupt the movements and motor functions of patients, which seriously impairs their QOL and daily life activity. Specifically, antipsychotics frequently induce EPS by blocking striatal D_2 receptors (14,17). In addition, ChEIs that elevate brain ACh levels by inhibiting cholinesterases also have the potential to evoke EPS or worsen drug-induced EPS. In the present study, we examined the effects of the ChEIs, donepezil and galantamine, using doses that reportedly ameliorated cognitive deficits in animals (19,20). Although these agents by themselves were generally tolerable in inducing EPS, a high dose of galantamine caused mild bradykinesia. In addition, donepezil and galantamine both markedly potentiated the induction of bradykinesia when combined with a low dose of haloperidol. The potentiation of haloperidol-induced bradykinesia by ChEIs appeared to occur in a synergistic manner. These results give us a caution for the antipsychotics (D_2 antagonists) and ChEIs interaction in inducing EPS in the treatment of BPSD, even if the monotherapy with ChEIs rarely evokes EPS. Antipsychotic-induced EPS are usually treatable with muscarinic antagonists (e.g., trihexyphenidyl and biperiden)

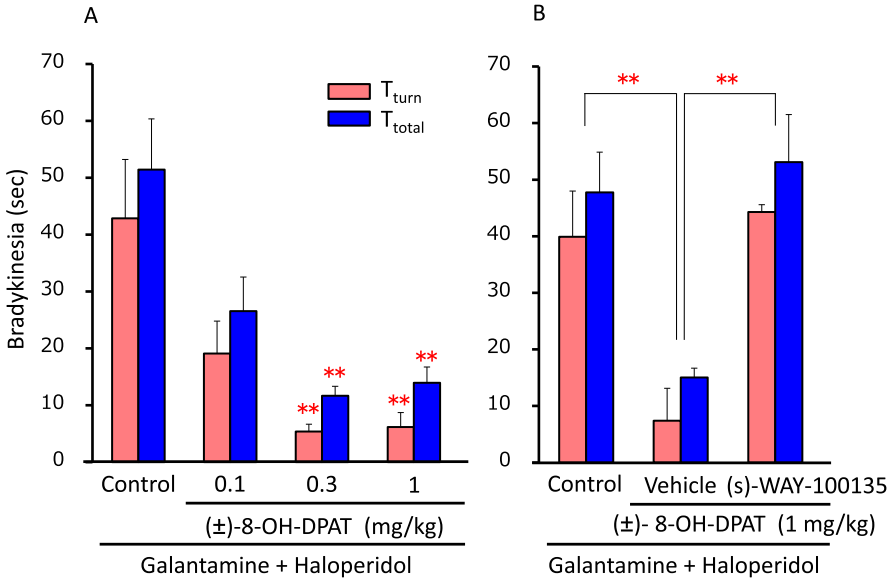

Fig. 3. Effects of the 5-HT_{1A} agonist (±)-8-OH-DPAT on the galantamine-enhanced induction of bradykinesia and its reversal by (S)-WAY-100135. The pole test was performed 30 min after the simultaneous injection of galantamine (1 mg/kg, i.p.) and haloperidol (0.5 mg/kg, i.p.). (±)-8-OH-DPAT was given 15 min before the haloperidol and galantamine injections and (s)-WAY-100135 was given 15 min before the (±)-8-OH-DPAT injection. Each column represents the mean ± S.E.M. of 10–13 mice. $^{**}P < 0.01$; Significantly different from the control value with the galantamine and haloperidol injections.

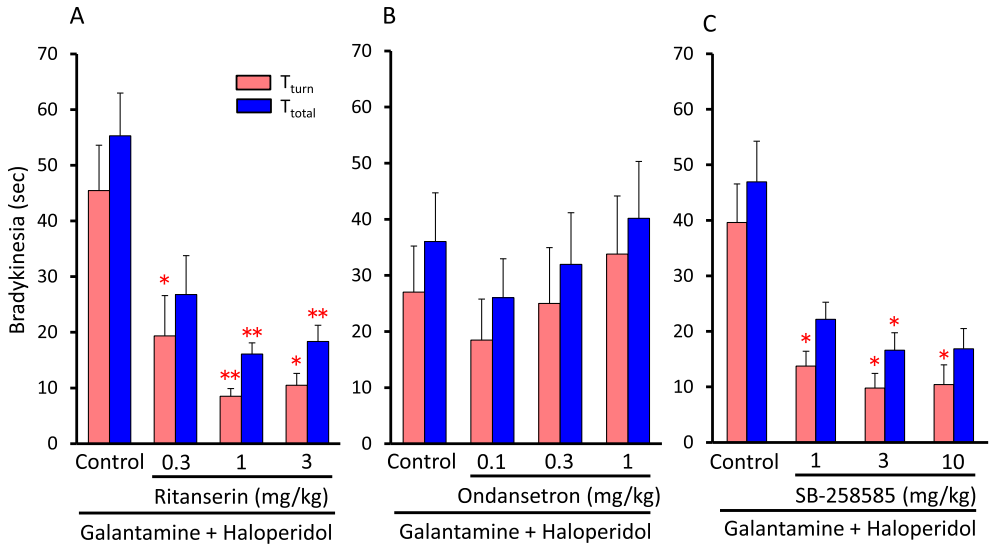

Fig. 4. Effects of 5-HT antagonists on the galantamine-enhanced induction of bradykinesia. The pole test was performed 30 min after the simultaneous injection of galantamine (1 mg/kg, i.p.) and haloperidol (0.5 mg/kg, i.p.). 5-HT antagonists were given 15 min before the galantamine and haloperidol injections. Each column represents the mean ± S.E.M. of 8–17 mice. $^{*}P < 0.05$, $^{**}P < 0.01$; Significantly different from the control value with the galantamine and haloperidol injections.

(14,23); however, the usage of these agents should be avoided in patients with Alzheimer's disease because they impair cognitive functions and/or counteract the therapeutic actions of ChEIs. Therefore, information on the safety control of EPS is particularly important in the treatment of Alzheimer's disease.

Although the precise mechanisms underlying the synergistic potentiation of EPS by ChEIs remain unclear, they appear to involve the D_2 receptor-mediated regulation of cholinergic interneurons in the striatum (Fig. 5). Dopamine derived from the substantia nigra negatively regulates the firing of striatal cholinergic interneurons and the blockade of D_2 receptors is known to facilitate the firing of cholinergic interneurons and enhance the ACh release (24,25). Therefore, ChEIs may augment the induction of EPS more potently in the presence of haloperidol (D_2 antagonist) than with their single administration (Fig. 5).

In this study, galantamine induced and augmented EPS more potently than donepezil. Galantamine has been shown to have an allosteric stimulatory effects on nicotinic ACh receptors (26,27), which may account for higher EPS liability of this agent. However, the potentiation of bradykinesia induction by galantamine was completely antagonized by trihexyphenidyl, but unaffected by macamylamine. These results strongly suggest that EPS liability by

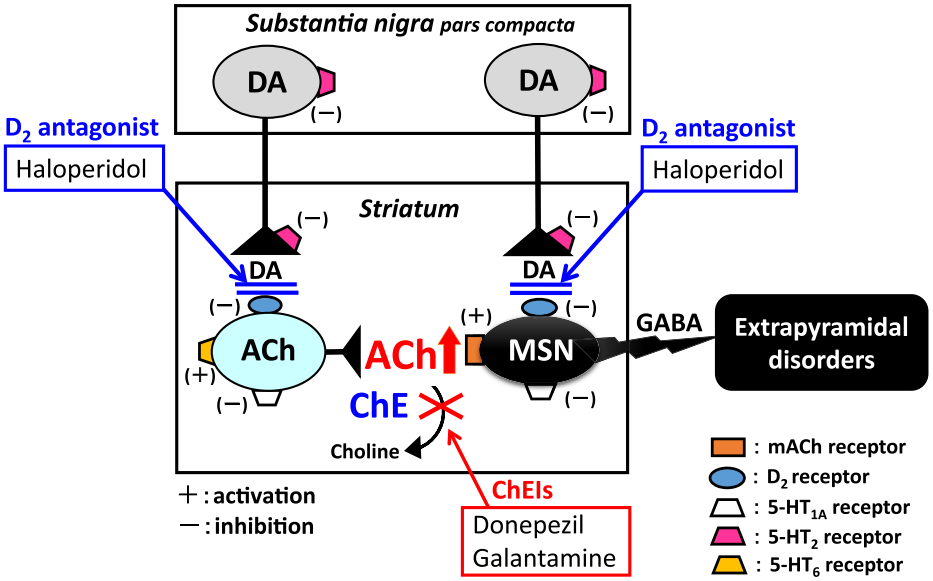

Fig. 5. A schematic diagram illustrating the striatal interaction between anti-Alzheimer and antipsychotic drugs in induction of extrapyramidal side effects. Striatal medial spiny neurons (MSNs) and acetylcholinergic interneurons receive dopaminergic inhibitory inputs from the substantia nigra pars compacta. Antipsychotics activate these striatal neurons and induce extrapyramidal side effects (EPS) by blocking D_2 receptors. Anti-Alzheimer drugs, donepezil and galantamine, increase the striatal acetylcholine (ACh) level by inhibiting cholinesterase (ChE), which leads to induction and/or worsening EPS. Particularly, ChE inhibitors (ChEIs) markedly potentiated haloperidol (D_2 antagonist)-associated EPS induction in a synergistic manner. Since the blockade of D_2 receptors on cholinergic interneurons facilitates their firing and enhance the ACh release, ChEIs seem to augment EPS more potently in the presence of haloperidol. In addition, stimulation of 5-HT_{1A} receptors (located on striatal neurons) or blockade of 5-HT_2 (located on dopaminergic neurons and nerve terminals) and 5-HT_6 receptors (located on acetylcholinergic interneurons) significantly reduced EPS synergistically enhanced by haloperidol and ChEIs. DA: dopamine.

galantamine is mediated solely by muscarinic receptors and nicotinic receptors are not involved. Alternatively, galantamine is known to act as a dual inhibitor of both ACh and butylylcholine esterases, whereas donepezil is a relatively specific inhibitor for ACh esterase (28,29). Thus, the prominent action of galantamine may result from its dual inhibitory actions on cholinesterases. In addition, since donepezil, but not galantamine, reportedly has an antagonistic effect in muscarinic receptors (30), this may also explain why the EPS potentiation with galantamine is stronger than that with donepezil.

Extrapyramidal motor disorders are now known to be modulated by multiple 5-HT receptors (11,16). The present results showed that the galantamine-enhanced induction of bradykinesia was markedly reduced by (±)-8-OH-DPAT. Although (±)-8-OH-DPAT also binds to 5-HT_7 receptors (31,32), the amelioration of bradykinesia by (±)-8-OH-DPAT was completely antagonized by the selective 5-HT_{1A} antagonist (s)-WAY-100135, indicating that activation of 5-HT_{1A} receptors can reduce the bradykinesia potentiation by ChEIs. We previously demonstrated that the anti-EPS actions of 5-HT_{1A} agonists were resistant to the presynaptic inactivation of 5-HT neurons by *p*-chlorophenylalanine (a tryptophan hydroxylase inhibitor), and local microinjections of (±)-8-OH-DPAT into the cerebral cortex (i.e., motor area) or the striatum inhibited EPS induction (18,33). Taken together, these findings indicate that 5-HT_{1A} agonist ameliorates the potentiation of EPS by ChEIs via their actions on postsynaptic 5-HT_{1A} receptors, probably in the cerebral cortex and/or striatum (Fig. 5).

In this study, ritanserin (a 5-HT_2 antagonist) and SB-258585 (a 5-HT_6 antagonist) reversed the galantamine-enhanced induction of bradykinesia, indicating that the blockade of 5-HT_2 and 5-HT_6 receptors counteracts the potentiation of EPS by ChEIs. Our results are consistent with the facts that blockade of 5-HT_2 receptors reverses the D_2 antagonistic actions of antipsychotics (e.g., increases in ACh release, dopamine turnover, and Fos expression) in the striatum by relieving the 5-HT_2 receptor-mediated inhibition of dopamine neuron firing in the substantia nigra and of dopamine release in the striatum (8,10,16,23,34–37) (Fig. 5). In addition, since 5-HT_6 receptors are expressed in striatal cholinergic interneurons and mediate 5-HT-induced excitation of ACh neurons (38), 5-HT_6 antagonists appear to alleviate ChEIs-enhanced EPS by inhibiting the activity of ACh neurons in the striatum (Fig. 5). On the other hand, the 5-HT_3 antagonist ondansetron negligibly affected galantamine-potentiated bradykinesia. We previously demonstrated that the serotonergic potentiation of EPS by 5-HT reuptake inhibitors was reversed by a systemic treatment with, but not by an intrastriatal microinjection of the 5-HT_3 antagonist, suggesting that 5-HT_3 antagonist attenuated EPS through extra-striatal mechanisms (22). This may account for the ineffectiveness of the 5-HT_3 antagonist against the ChEIs' actions since the primary action site of ChEIs in potentiating EPS appears to be within the striatum (cholinergic interneurons).

5. Conclusions

Since antipsychotics are often used in conjunction with anti-Alzheimer drugs to ameliorate psychomotor excitement of BPSD, we evaluated the interaction between anti-Alzheimer and antipsychotic drugs in inducing EPS. The ChEIs, donepezil and galantamine, showed only marginal effects in inducing EPS by themselves, but markedly potentiated haloperidol-induced bradykinesia in dose-dependent and synergistic manners. The potentiation of bradykinesia by galantamine was completely blocked by trihexyphenidyl, but not by mecamylamine, indicating the primary involvement of muscarinic receptors in the potentiation of EPS by ChEIs. In addition, since the stimulation of 5-HT_{1A} receptors or the antagonism of 5-HT_2 and 5-HT_6 receptors effectively reversed ChEIs-enhanced EPS, second generation antipsychotics that can activate 5-HT_{1A} or block 5-HT_2 and 5-HT_6 receptors (e.g., risperidone, lurasidone, olanzapine, and aripiprazole) (14,39,40) appear to have weaker propensities to cause EPS in combined therapy with ChEIs for the treatment of Alzheimer's disease.

Conflict of interest

There are no conflicts of interest to disclose for any of the authors.

Acknowledgments

This work was partly supported by the Smoking Research Foundation. The authors are thankful to Mr. Kentaro Tokudome and Naofumi Kunisawa for their critical reading of and comments on the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jphs.2015.03.004.

References

(1) Silva T, Reis J, Teixeira J, Borges F. Alzheimer's disease, enzyme targets and drug discovery struggles: from natural products to drug prototypes. Ageing Res Rev. 2014;15:116–145.
(2) Lyketsos CG, Sheppard JM, Steinberg M, Tschanz JA, Norton MC, Steffens DC, et al. Neuropsychiatric disturbance in Alzheimer's disease clusters into three groups: the Cache County study. Int J Geriatr Psychiatry. 2001;16:1043–1053.
(3) Aalten P, Verhey FR, Boziki M, Bullock R, Byrne EJ, Camus V, et al. Neuropsychiatric syndromes in dementia. Results from the European Alzheimer Disease Consortium: part I. Dement Geriatr Cogn Disord. 2007;24:457–463.
(4) Gabryelewicz T. Pharmacological treatment of behavioral symptoms in dementia patients. Przegl Lek. 2014;71:215–220.
(5) Fibiger HC. Cholinergic mechanisms in learning, memory and dementia: a review of recent evidence. Trends Neurosci. 1991;14:220–223.
(6) Salamone JD, Correa M, Carlson BB, Wisniecki A, Mayorga AJ, Nisenbaum E, et al. Neostriatal muscarinic receptor subtypes involved in the generation of tremulous jaw movements in rodents implications for cholinergic involvement in parkinsonism. Life Sci. 2001;68:2579–2584.
(7) Kozman MN, Wattis J, Curran S. Pharmacological management of behavioural and psychological disturbance in dementia. Hum Psychopharmacol. 2006;21:1–12.
(8) Schmitt B, Bernhardt T, Moeller HJ, Heuser I, Frölich L. Combination therapy in Alzheimer's disease: a review of current evidence. CNS Drugs. 2004;18:827–844.
(9) Horacek J, Bubenikova-Valesova V, Kopecek M, Palenicek T, Dockery C, Mohr P, et al. Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. CNS Drugs. 2006;20:389–409.
(10) Meltzer HY. The mechanism of action of novel antipsychotic drugs. Schizophr Bull. 1991;17:263–287.
(11) Ohno Y, Ishida-Tokuda K, Ishibashi T, Sakamoto H, Tagashira R, Horisawa T, et al. Potential role of 5-HT_2 and D_2 receptor interaction in the atypical antipsychotic action of the novel succimide derivative, perospirone. Pol J Pharmacol. 1997;49:213–219.
(12) Kapur S, Remington G. Atypical antipsychotics: new directions and new challenges in the treatment of schizophrenia. Annu Rev Med. 2001;52:503–517.
(13) Meltzer HY, Li Z, Kaneda Y, Ichikawa J. Serotonin receptors: their key role in drugs to treat schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27:1159–1172.
(14) Ohno Y. Therapeutic role of 5-HT_{1A} receptors in the treatment of schizophrenia and Parkinson's disease. CNS Neurosci Ther. 2011;17:58–65.
(15) Shimizu S, Mizuguchi Y, Ohno Y. Improving the treatment of schizophrenia: role of 5-HT receptors in modulating cognitive and extrapyramidal motor functions. CNS Neurol Disord Drug Targets. 2013;12:861–869.
(16) Shimizu S, Ohno Y. Improving the treatment of Parkinson's disease: a novel approach by modulating 5-$HT_{(1A)}$ receptors. Aging Dis. 2013;4:1–13.
(17) Smith Y, Villalba R. Striatal and extrastriatal dopamine in the basal ganglia: an overview of its anatomical organization in normal and Parkinsonian brains. Mov Disord. 2008;23:534–547.
(18) Shimizu S, Tatara A, Imaki J, Ohno Y. Role of cortical and striatal 5-HT_{1A} receptors in alleviating antipsychotic-induced extrapyramidal disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34:877–881.

(19) Van Dam D, Abramowski D, Staufenbiel M, De Deyn PP. Symptomatic effect of donepezil, rivastigmine, galantamine and memantine on cognitive deficits in the APP23 model. Psychopharmacology (Berl). 2005;180:177–190.
(20) Koda K, Ago Y, Kawasaki T, Hashimoto H, Baba A, Matsuda T. Galantamine and donepezil differently affect isolation rearing-induced deficits of prepulse inhibition in mice. Psychopharmacology (Berl). 2008;196:293–301.
(21) Ohno Y, Imaki J, Mae Y, Takahashi T, Tatara A. Serotonergic modulation of extrapyramidal motor disorders in mice and rats: role of striatal 5-HT_3 and 5-HT_6 receptors. Neuropharmacology. 2011;60:201–208.
(22) Tatara A, Shimizu S, Shin N, Sato M, Sugiuchi T, Imaki J, et al. Modulation of antipsychotic-induced extrapyramidal side effects by medications for mood disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2012;38:252–259.
(23) Ohno Y, Ishida K, Ikeda K, Ishibashi T, Okada K, Nakamura M. Evaluation of bradykinesia induction by SM-9018, a novel 5-HT_2 and D_2 receptor antagonist, using the mouse pole test. Pharmacol Biochem Behav. 1994;49:19–23.
(24) Damsma G, de Boer P, Westerink BH, Fibiger HC. Dopaminergic regulation of striatal cholinergic interneurons: an in vivo microdialysis study. Naunyn Schmiedebergs Arch Pharmacol. 1990;342:523–527.
(25) DeBoer P, Abercrombie ED. Physiological release of striatal acetylcholine in vivo: modulation by D_1 and D_2 dopamine receptor subtypes. J Pharmacol Exp Ther. 1996;277:775–783.
(26) Samochocki M, Höffle A, Fehrenbacher A, Jostock R, Ludwig J, Christner C, et al. Galantamine is an allosterically potentiating ligand of neuronal nicotinic but not of muscarinic acetylcholine receptors. J Pharmacol Exp Ther. 2003;305:1024–1036.
(27) Ago Y, Koda K, Takuma K, Matsuda T. Pharmacological aspects of the acetylcholinesterase inhibitor galantamine. J Pharmacol Sci. 2011;116:6–17.
(28) Takeda M, Tanaka T, Okochi M. New drugs for Alzheimer's disease in Japan. Psychiatry Clin Neurosci. 2011;65:399–404.
(29) Giacobini E. Selective inhibitors of butyrylcholinesterase: a valid alternative for therapy of Alzheimer's disease? Drugs Aging. 2001;18:891–898.
(30) Ago Y, Koda K, Ota Y, Kita Y, Fukada A, Takuma K, et al. Donepezil, but not galantamine, blocks muscarinic receptor-mediated in vitro and in vivo responses. Synapse. 2011;65:1373–1377.
(31) Neumaier JF, Sexton TJ, Yracheta J, Diaz AM, Brownfield M. Localization of 5-HT_7 receptors in rat brain by immunocytochemistry, in situ hybridization, and agonist stimulated cFos expression. J Chem Neuroanat. 2001;21:63–73.
(32) Hedlund PB, Kelly L, Mazur C, Lovenberg T, Sutcliffe JG, Bonaventure P. 8-OH-DPAT acts on both 5-HT_{1A} and 5-HT_7 receptors to induce hypothermia in rodents. Eur J Pharmacol. 2004;487:125–132.
(33) Ohno Y, Shimizu S, Imaki J, Ishihara S, Sofue N, Sasa M, et al. Evaluation of the antibradykinetic actions of 5-HT_{1A} agonists using the mouse pole test. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1302–1307.
(34) Alex KD, Pehek EA. Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. Pharmacol Ther. 2007;113:296–320.
(35) Ishibashi T, Ikeda K, Ishida K, Yasui J, Tojima R, Nakamura M, et al. Contrasting effects of SM-9018, a potential atypical antipsychotic, and haloperidol on c-fos mRNA expression in the rat striatum. Eur J Pharmacol. 1996;303:247–251.
(36) Ishida K, Ohno Y, Ishibashi T, Nakamura M. Effects of SM-9018, a novel 5-HT_2 and D_2 receptor antagonist, on electrically-evoked [3H]acetylcholine release from rat striatal slices. Gen Pharmacol. 1996;27:1203–1207.
(37) Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry. 1996;153:466–476.
(38) Bonsi P, Cuomo D, Ding J, Sciamanna G, Ulrich S, Tscherter A, et al. Endogenous serotonin excites striatal cholinergic interneurons via the activation of 5-HT_{2C}, 5-HT_6, and 5-HT_7 serotonin receptors: implications for extrapyramidal side effects of serotonin reuptake inhibitors. Neuropsychopharmacology. 2007;32:1840–1854.
(39) Ohno Y, Tatara A, Shimizu S, Sasa M. Management of cognitive impairments in schizophrenia: the therapeutic role of 5-HT receptors. In: Sumiyoshi T, editor. Antipsychotic drugs: pharmacology, side effects and abuse prevention. NY: Nova Science Publishers, Inc.; 2012. p. 323–328.
(40) Newman-Tancredi A. The importance of 5-HT_{1A} receptor agonism in antipsychotic drug action: rationale and perspectives. Curr Opin Investig Drugs. 2010;11:802–812.