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European Journal of Pharmacology 350 (1998) 39–45

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Involvement of dopamine receptors in beneficial effects of tachykinins on scopolamine-induced impairment of alternation performance in mice

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Received 11 March 1998; accepted 13 March 1998

Abstract

The involvement of dopamine receptors in the beneficial effects of intracerebroventricular injection of substance P, neurokinin A and senktide on the scopolamine-induced impairment of spontaneous alternation performance was investigated in mice. Scopolamine (1 mg/kg) significantly impaired spontaneous alternation performance, while substance P (0.1 μg), neurokinin A (0.3 μg), senktide (0.003 μg) and *S*(−)-sulpiride (10 mg/kg), a dopamine D_2 receptor antagonist, improved the scopolamine (1 mg/kg)-induced disturbance of spontaneous alternation performance. However, the dopamine D_1 receptor antagonist SCH23390 (7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine maleate) did not influence the scopolamine-induced disturbance of spontaneous alternation performance. The dopamine D_2 receptor agonist RU24213 (*N*-*n*-propyl-*N*-phenylethyl-*p*-(3-hydroxyphenyl)-ethylamine hydrochloride) (1 mg/kg) but not the dopamine D_1 receptor agonist SKF38393 (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine hydrochloride) (3 and 10 mg/kg) reversed the beneficial effects of substance P (0.1 μg) and neurokinin A (0.3 μg) on the scopolamine (1 mg/kg)-induced impairment of spontaneous alternation performance. In contrast, neither SKF38393 (3 and 10 mg/kg) nor RU24213 (0.3 and 1 mg/kg) significantly affected the beneficial effects of senktide (0.003 μg) on the scopolamine (1 mg/kg)-induced impairment of spontaneous alternation performance. Although RU24213 (1 mg/kg) and SCH23390 (0.03 mg/kg) markedly decreased total arm entries, SKF38393 (10 mg/kg), RU24213 (1 mg/kg), SCH23390 (0.03 mg/kg) or *S*(−)-sulpiride (10 mg/kg) had no significant effects on spontaneous alternation performance. These results suggest that stimulation of dopamine D_2 but not D_1 receptors reverses the ameliorative effects of substance P and neurokinin A, whereas neither dopamine D_1 nor D_2 receptors play an important role in the beneficial effects of senktide on the scopolamine-induced impairment of spontaneous alternation performance associated with spatial working memory.

Keywords: Tachykinin; Dopamine receptor; SKF38393; RU24213; Substance P; (Mouse)

1. Introduction

The tachykinins, such as substance P, neurokinin A and neurokinin B, are present in the brain and peripheral tissues. These tachykinins have also been proposed as neurotransmitters and/or neuromodulators in the mammalian nervous system. The receptors appropriate for substance P, neurokinin A and neurokinin B are termed as neurokinin-1 (NK_1), neurokinin-2 (NK_2) and neurokinin-3 (NK_3), respectively (Nakanishi, 1991).

Tachykinins have been demonstrated to influence cholinergic and dopaminergic neurons. Alberch et al. (1993) have reported that the tachykinin NK_3 receptor agonist senktide-induced release of acetylcholine is attenuated, while the tachykinin NK_2 receptor agonist [Nle^{10}]neurokinin A (4–10)-induced release of acetylcholine is facilitated in the brain of 6-hydroxydopamine-treated rats, suggesting that dopaminergic neurons contribute to the mnemonic effects of tachykinins (Schlesinger et al., 1983; Hasenöhrl et al., 1990). It has been reported that tachykinins inhibit the scopolamine-induced impairment of spontaneous alternation performance associated with spatial working memory (Ukai et al., 1995b, 1996). Therefore, it is possible that the beneficial effects of tachykinins on amnesia resulting from cholinergic dysfunction are mediated via dopaminergic neurotransmission. In fact, dopaminergic neurons are reportedly involved in learning and memory. For example, low and high doses of apomorphine differentially affect a single-trial passive

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0014-2999/98/$19.00

avoidance learning (Ichihara et al., 1988). The dopamine D_2 receptor agonist RU24213 (*N*-*n*-propyl-*N*-phenylethyl-*p*-(3-hydroxyphenyl)-ethylamine hydrochloride) but not the dopamine D_1 receptor agonist SKF38393 (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine hydrochloride) reversed the beneficial effects of dynorphin A-(1–13) on the scopolamine-induced disturbance of spontaneous alternation performance (Itoh et al., 1993b). In particular, the dopamine D_2 receptor antagonist *S*(−)-sulpiride, but not the dopamine D_1 receptor antagonist SCH23390 (7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine maleate), attenuates the scopolamine-induced impairment of spontaneous alternation performance (Itoh et al., 1993b).

The present study was designed to investigate the involvement of dopaminergic neurotransmission mediated via dopamine D_1 and D_2 receptors in the beneficial effects of substance P, neurokinin A and senktide on amnesia resulting from cholinergic dysfunction.

2. Materials and methods

2.1. Animals

Male mice of the ddY strain (Nihon SLC, Hamamatsu, Japan), weighing between 30 and 40 g were used. They were housed in a group of eight under standard conditions (23 ± 1°C, 50 ± 10% humidity, light/dark cycle with the light on between 0800 and 2000 h) with free access to food and water. The mice were used for the experiments following adaptation to laboratory conditions for at least 1 week and were naive to the test used in the present study. The experiments were conducted between 1000 and 1800 h in a sound-attenuated room.

2.2. Drugs

Substance P (Peptide Institute, Minoh, Japan), neurokinin A and senktide (Research Biochemicals, Natick, MA, USA) were dissolved in sterile isotonic saline solution (Otsuka Pharmaceutical, Tokyo, Japan), while RU24213 (Roussel-Uclaf, Romainville, France), SKF38393 (Research Biochemicals) and scopolamine hydrobromide (Tokyo Chemical Industry, Tokyo, Japan) were dissolved in isotonic saline solution. SCH23390 (Schering, Bloomfield, NJ, USA) and *S*(−)-sulpiride (Research Biochemicals) were dissolved in 8.5% lactic acid and 1.0 M sodium hydroxide in a 3:2 ratio. The tachykinin-related drugs were administered into the lateral ventricle of the brain (i.c.v.) according to the method of Haley and McCormick (1957) in an injection volume of 5 μl/mouse over 1 min through injection needle under brief ether anesthesia as previously described (Itoh et al., 1994). No stereotaxic instruments were used. The site was checked by injecting 5 μl of a 1:10 dilution of ink; examination of the brain showed ink restricted to lateral and 3rd ventricles and severe tissue damage was never observed. Injection of isotonic saline by our procedure was found not to affect spontaneous alternation performance in normal mice (Ukai et al., 1995b). Scopolamine (s.c.), dopamine receptor agonists (s.c.) and antagonists (i.p.) were administered in an injection volume of 0.1 ml/10 g body weight. Doses were expressed in terms of the base.

2.3. Apparatus

Spontaneous alternation performance was assessed in a black-painted Y-maze which was 40 cm long, 10 cm high, 3 cm wide at the bottom and 10 cm wide at the top and positioned at an equal angle.

2.4. Procedures

The testing procedure was based on that of Sarter et al. (1988). Following vehicle or drug injections, each of the mice was placed at the end of one arm and allowed to move freely through the maze for an 8-min test session. The sequence of arm entries was recorded manually. An alternation was defined as the entry into all three arms on consecutive choices. The maximum number of alternations was then the total number of arms entered minus 2, and the percent alternation was calculated as (actual alternations/maximum alternations) × 100. The total number of arm entries was used as an index of locomotor activity. Mice which exhibited arm entries less than eight times during the test were eliminated from the study, because the data obtained from these mice were not considered to reflect precise alternation. Tachykinin-related drugs, dopamine-related drugs and scopolamine were injected 10, 30 and 30 min before measurements, respectively.

2.5. Statistical analysis

The results were expressed as the mean ± S.E.M. and analyzed by a Kruskal–Wallis one-way analysis of variance (ANOVA). Further statistical analysis for post hoc comparisons was done with a Bonferroni's multiple comparison test (two-tailed). The criterion for statistical significance was $P < 0.05$ in all statistical evaluations.

3. Results

3.1. Effects of SCH23390 and S(−)-sulpiride on scopolamine-induced impairment

Although not significant, SCH23390 (0.01 and 0.03 mg/kg) showed a tendency to inhibit the scopolamine (1 mg/kg)-induced decrease in percent alternation (Fig. 1A). SCH23390 (0.01 and 0.03 mg/kg) significantly inhibited

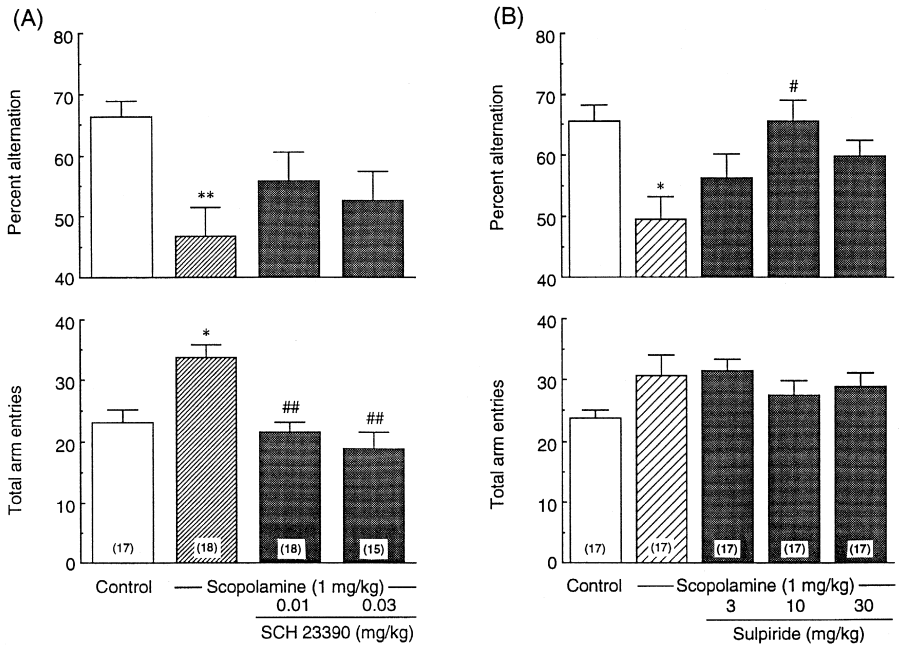

Fig. 1. Effects of SCH23390 (A) or *S*(−)-sulpiride (B) on scopolamine-induced impairment of spontaneous alternation performance and total arm entries in mice. Each value represents the mean ± S.E. SCH23390 (i.p.), *S*(−)-sulpiride (i.p.) and scopolamine (s.c.) were administered 30 min before behavioral measurements. The number of mice used is shown in parentheses. $*P < 0.05$; $**P < 0.01$ vs. control, $\#P < 0.05$; $\#\#P < 0.01$ vs. scopolamine alone.

the scopolamine (1 mg/kg)-induced increase in total arm entries ($H = 19.84$, $P < 0.01$) (Fig. 1A). Mice could not receive more than 0.03 mg/kg doses of SCH23390 because of its sedative effects. *S*(−)-sulpiride (10 mg/kg) significantly inhibited the scopolamine (1 mg/kg)-induced decrease in percent alternation ($H = 13.18$, $P < 0.05$) (Fig. 1B) without affecting the scopolamine (1 mg/kg)-induced alteration in total arm entries (Fig. 1B).

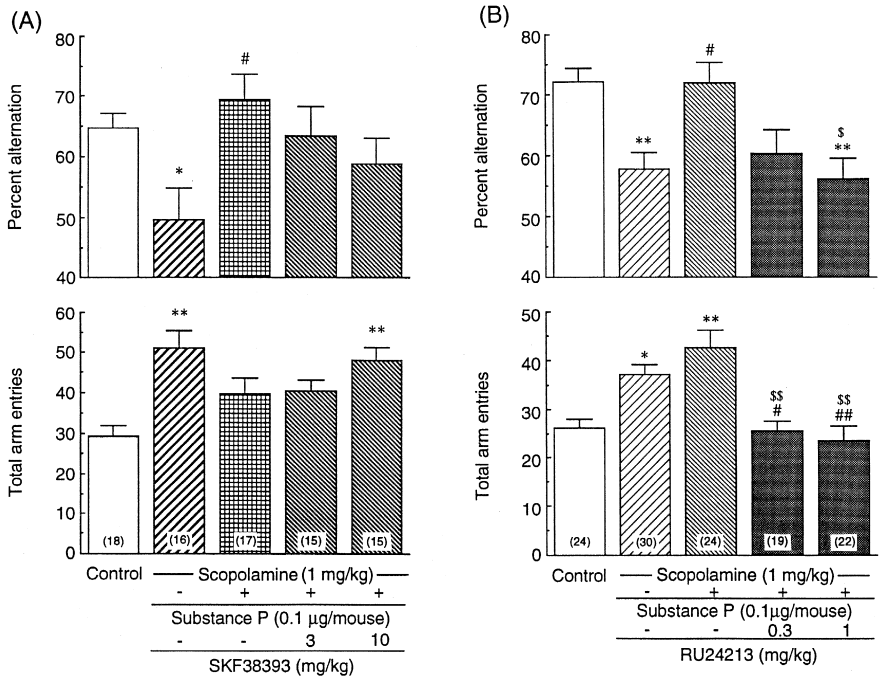

Fig. 2. Effects of substance P combined with SKF38393 (A) or RU24213 (B) on scopolamine-induced impairment of spontaneous alternation performance and total arm entries in mice. Each value represents the mean ± S.E. Substance P (i.c.v.), SKF38393 (s.c.), RU24213 (s.c.) and scopolamine (s.c.) were administered 10, 30, 30 and 30 min before behavioral measurements, respectively. The number of mice used is shown in parentheses. $*P < 0.05$; $**P < 0.01$ vs. control, $\#P < 0.05$; $\#\#P < 0.01$ vs. scopolamine alone, $\$P < 0.05$; $\$\$P < 0.01$ vs. scopolamine plus substance P.

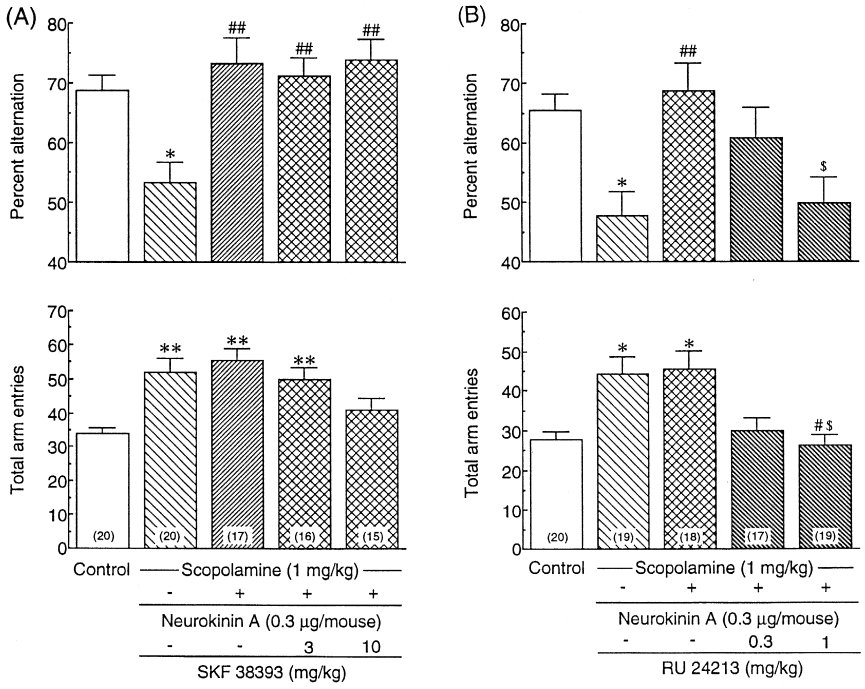

Fig. 3. Effects of neurokinin A combined with SKF38393 (A) or RU24213 (B) on scopolamine-induced impairment of spontaneous alternation performance and total arm entries in mice. Each value represents the mean ± S.E. Neurokinin A (i.c.v.), SKF38393 (s.c.), RU24213 (s.c.) and scopolamine (s.c.) were administered 10, 30, 30 and 30 min before behavioral measurements, respectively. The number of mice used is shown in parentheses. $*P < 0.05$; $**P < 0.01$ vs. control, $\#P < 0.05$; $\#\#P < 0.01$ vs. scopolamine alone, $\$P < 0.05$ vs. scopolamine plus neurokinin A.

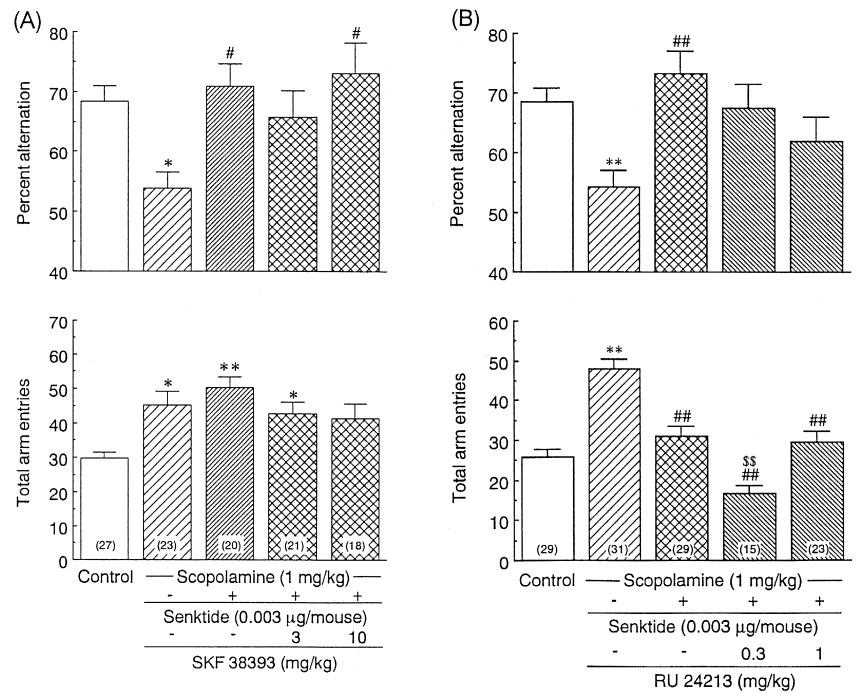

Fig. 4. Effects of senktide combined with SKF38393 (A) or RU24213 (B) on scopolamine-induced impairment of spontaneous alternation performance and total arm entries in mice. Each value represents the mean ± S.E. Senktide (i.c.v.), SKF38393 (s.c.), RU24213 (s.c.) and scopolamine (s.c.) were administered 10, 30, 30 and 30 min before behavioral measurements, respectively. The number of mice used is shown in parentheses. $*P < 0.05$; $**P < 0.01$ vs. control, $\#P < 0.05$; $\#\#P < 0.01$ vs. scopolamine alone, $\$\$P < 0.01$ vs. scopolamine plus senktide.

3.2. Effects of SKF38393 and RU24213 on effects of substance P

Substance P (0.1 μg) significantly reduced the scopolamine (1 mg/kg)-induced decrease in percent alternation (Fig. 2). SKF38393 (3 and 10 mg/kg) did not markedly influence the effects of substance P (0.1 μg) ($H = 12.93$, $P < 0.05$ for percent alternation) (Fig. 2A), whereas RU24213 (1 mg/kg) significantly inhibited the effects of substance P (0.1 μg) ($H = 22.48$, $P < 0.01$ for percent alternation) (Fig. 2B).

RU24213 (0.3 and 1 mg/kg) ($H = 31.38$, $P < 0.01$) (Fig. 2B) but not SKF38393 (3 and 10 mg/kg) ($H = 21.76$, $P < 0.01$) (Fig. 2A) markedly reversed the effects of substance P (0.1 μg) on the scopolamine (1 mg/kg)-induced increase in total arm entries (Fig. 2).

3.3. Effects of SKF38393 and RU24213 on effects of neurokinin A

Neurokinin A (0.3 μg) markedly inhibited the scopolamine (1 mg/kg)-induced decrease in percent alternation without affecting the scopolamine (1 mg/kg)-induced increase in total arm entries. SKF38393 (3 and 10 mg/kg) did not influence the effects of neurokinin A (0.3 μg) on the scopolamine (1 mg/kg)-induced decrease in percent alternation ($H = 23.74$, $P < 0.01$), while a 10 mg/kg dose of SKF38393 showed a tendency to inhibit the scopolamine (1 mg/kg)-induced increase in total arm entries ($H = 24.80$, $P < 0.01$) (Fig. 3A). RU24213 (1 mg/kg) significantly reversed the effects of neurokinin A (0.3 μg) ($H = 19.94$, $P < 0.01$ for percent alternation; $H = 19.85$, $P < 0.01$ for total arm entries) (Fig. 3B).

3.4. Effects of SKF38393 and RU24213 on effects of senktide

SKF38393 (3 and 10 mg/kg) did not significantly influence the effects of senktide (0.003 μg) on the scopolamine (1 mg/kg)-induced decrease in percent alternation ($H = 21.52$, $P < 0.01$) (Fig. 4A). RU24213 (0.3 and 1 mg/kg) failed to inhibit the effects of senktide (0.003 μg) on the scopolamine (1 mg/kg)-induced decrease in percent alternation ($H = 18.83$, $P < 0.01$) (Fig. 4B).

RU24213 (0.3 mg/kg) ($H = 50.21$, $P < 0.01$) (Fig. 4A) but not SKF38393 (3 and 10 mg/kg) ($H = 15.29$, $P < 0.01$) (Fig. 4B) markedly attenuated the effects of senktide (0.003 μg).

3.5. Effects of dopamine receptor agonists and antagonists alone

Although SKF38393 (10 mg/kg), RU24213 (1 mg/kg), SCH23390 (0.03 mg/kg) or *S*(−)-sulpiride (10 mg/kg) did not significantly influence percent alternation ($H = 4.06$, $P > 0.05$), RU24213 (1 mg/kg) and SCH23390 (0.03 mg/kg) significantly decreased total arm entries ($H = 24.22$, $P < 0.05$) (Fig. 5).

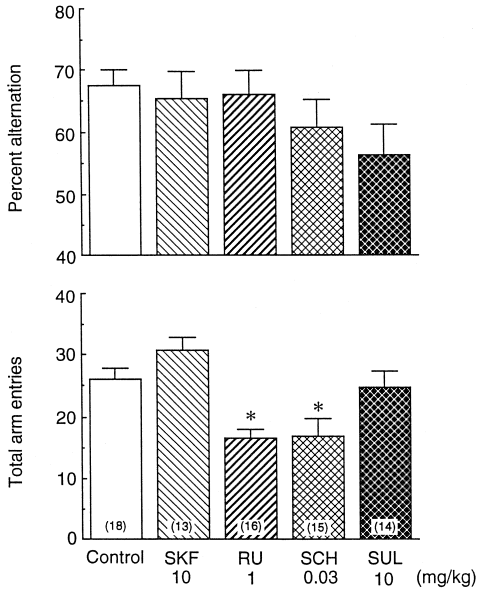

Fig. 5. Effects of SKF38393, RU24213, SCH23390 or *S*(−)-sulpiride on scopolamine-induced impairment of spontaneous alternation performance and total arm entries in mice. Each value represents the mean ± S.E. SKF38393 (s.c.), RU24213 (s.c.), SCH23390 (i.p.), *S*(−)-sulpiride (i.p.) and scopolamine (s.c.) were administered 30 min before behavioral measurements. The number of mice used is shown in parentheses. * $P < 0.05$ vs. control.

SKF38393 (10 mg/kg) or RU24213 (1 mg/kg) did not produce any marked effects on behavioral responses, such as grooming, circling and wall-climbing as observed in the Y-maze.

4. Discussion

Spontaneous alternation performance is based on the tendency of rodents to enter an arm of a Y-maze that was least recently explored, i.e., the arm that was not entered in the last two choices. This performance associated with spatial working memory has been shown to be disturbed by ischemia (Itoh et al., 1993a) and amnesic drugs such as scopolamine (Sarter et al., 1988), pirenzepine (Ukai et al., 1995a), morphine (Stone et al., 1991), [D-Ala^2,*N*-MePhe^4,Gly-ol]enkephalin (Itoh et al., 1994) and dizocilpine (Parada-Turska and Turski, 1990).

In the present study, scopolamine (1 mg/kg) decreased spontaneous alternation performance while increasing locomotor activity as indexed by total arm entries. Substance P (0.1 μg), neurokinin A (0.3 μg) and senktide (0.003 μg) inhibited the scopolamine (1 mg/kg)-induced impairment of spontaneous alternation performance as previously reported (Ukai et al., 1995b, 1996). Furthermore, the ameliorative effects of substance P (0.1 μg) and neurokinin A (0.3 μg) are mediated via tachykinin NK_1 and NK_2

receptors, respectively (Ukai et al., 1995b, 1996), while those of senktide (0.003 μg) are evoked through the mediation of receptors other than a tachykinin NK_3 type (Ukai et al., 1996).

There are several reports that the pharmacological effects of tachykinins are involved in cholinergic neurotransmission. For example, substance P injected into the medial frontal cortex increases the carbachol-induced boxing behavior (Crawley et al., 1985). [Nle^{10}]Neurokinin A (4–10), a tachykinin NK_2 receptor agonist, and senktide induce acetylcholine release from rat neostriatal slices (Alberch et al., 1993; Arenas et al., 1993). Despite that, systemic administration of substance P decreases extracellular concentrations of acetylcholine in the neostriatum and nucleus accumbens (Boix et al., 1994). Thus, the beneficial effects of substance P, neurokinin A and senktide may result from activation of cholinergic neurons, although the cholinomimetic action of substance P, neurokinin A and senktide on behavior in normal mice is not seen.

S(−)-sulpiride (10 mg/kg), but not SCH23390 (0.01 and 0.03 mg/kg), inhibited the scopolamine (1 mg/kg)-induced impairment of spontaneous alternation performance. These results are in accordance with that haloperidol and *S*(−)-sulpiride inhibit the scopolamine-induced impairment of working memory (McGurk et al., 1988; Itoh et al., 1993b). In vivo microdialysis study displays that haloperidol and *S*(−)-sulpiride, but not SCH23390, facilitate acetylcholine release in the brain (Imperato et al., 1993). The present results show that the dopamine D_2 receptor agonist RU24213, but not the dopamine D_1 receptor agonist SKF38393, blocked the ameliorative effects of substance P and neurokinin A on the scopolamine-induced impairment of spontaneous alternation performance. These results suggest that stimulation of dopamine D_2 receptors attenuates the beneficial effects of substance P and neurokinin A. However, SKF38393 or RU24213 did not block the beneficial effects of senktide. In slice preparations, the [Nle^{10}]neurokinin A (4–10)-induced increase in acetylcholine release is augmented, whereas the senktide-induced increase in acetylcholine release is attenuated in 6-hydroxydopamine-treated rats and in rats treated with repeated administrations of haloperidol (Alberch et al., 1993), implying that the reduction of dopaminergic neurotransmission through dopamine D_2 receptors enhances the tachykinin NK_2 receptor agonist-induced release of acetylcholine, and conversely attenuates the tachykinin NK_3 receptor agonist-induced release of acetylcholine. In addition, the doses of dopamine receptor agonists and antagonists administered in the study are fully influential in dopaminergic neurotransmission (Itoh et al., 1993b).

We measured total arm entries to examine the effects of drugs on locomotor activity in the present study, although the effects of the tachykinins except for neurokinin A on the scopolamine-induced increase in total arm entries seemed to be inconsistent. Senktide (0.003 μg) dose-dependently attenuated the scopolamine-induced disturbance of spontaneous alternation performance, whereas such a drug failed to influence the increase in total arm entries. These results further support the view that spontaneous alternation performance is not based simply on locomotor activity (Itoh et al., 1994). In contrast, typical behavioral patterns, such as grooming after treatment with SKF38393 (10 mg/kg), and circling and wall-climbing after treatment with RU24213 (1 mg/kg), were not so evident in the Y-maze.

In conclusion, the activation of dopamine D_2 receptors disturbs the beneficial effects of agonists for tachykinin NK_1 and NK_2 receptors on the scopolamine-induced impairment of spontaneous alternation performance associated with spatial working memory, whereas the ameliorative effects of the tachykinin NK_3 receptor agonist senktide are mediated via some pharmacological mechanisms other than its effects on dopaminergic neurotransmission through dopamine D_1 and D_2 receptors.

Acknowledgements

This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

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