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Adenosine A_{2A} receptor antagonists KF17837 and KW-6002 potentiate rotation induced by dopaminergic drugs in hemi-Parkinsonian rats

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Abstract

The effects of novel adenosine A_{2A} receptor antagonists KF17837 ((*E*)-1,3-dipropyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione) and KW-6002 ((*E*)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione), on rotational behavior induced by apomorphine or L-DOPA (L-3,4-dihydroxyphenylalanine) were investigated in rats with unilateral 6-hydroxydopamine lesions. Both KF17837 and KW-6002 slightly induced rotational behavior per se. However, KF17837 and KW-6002 significantly increased the total counts of turning induced by apomorphine at doses of 3 mg/kg, p.o. and 10 mg/kg, p.o., and at doses of 1 mg/kg, p.o. and higher, respectively. KF17837 and KW-6002 also potentiated the rotational behavior induced by L-DOPA at a dose of 3 mg/kg, p.o. Furthermore, i.c.v. injection (10 μg/20 μl) of a selective adenosine A_2 receptor agonist CGS 21680 {2-[*p*-(2-carboxyethyl)phenethylamino]-5′-*N*-ethylcarboxamidoadenosine} partially prevented the rotational behavior induced by apomorphine and this inhibition was reversed by KW-6002 (1 mg/kg, p.o.).

The increase in total counts of apomorphine-induced turning by the adenosine A_{2A} receptor antagonists seems to be mainly attributable to prolongation of turning duration rather than enhancement of intensity. These results suggest that these adenosine A_{2A} receptor antagonists may be useful to ameliorate shortening in the duration of dopaminergic drug response in patients with advanced Parkinson's disease.

Keywords: KF17837 ((*E*)-1,3-dipropyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione); KW-6002 ((*E*)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione); Parkinson's disease; Adenosine A_{2A} receptor antagonist; 6-Hydroxydopamine

1. Introduction

Current treatment of Parkinson's disease is based on dopamine replacement therapy. Nevertheless, benefits of this therapy often become compromised by long-term complications, including the onset of dyskinesia and wearing-off fluctuations (Marsden et al., 1982). Thus, a mechanism that targets a nondopaminergic receptor is an attractive alternative approach; adenosine A_{2A} receptor antagonists are candidates for such novel therapy (Richardson et al., 1997; Kuwana et al., 1999).

Adenosine A_{2A} receptors are particularly abundant in the caudate-putamen, nucleus accumbens, and olfactory tubercle in several species (Schiffmann et al., 1990; Dixon et al., 1996). In the caudate-putamen, adenosine A_{2A} receptor mRNA has been detected in γ-aminobutyric acid (GABA)ergic striatopallidal medium-sized spiny neurons (Schiffmann and Varderhaeghen, 1993; Fredholm et al., 1994; Mori et al., 1996). There is also functional evidence for the presence of adenosine A_{2A} receptor on striatal cholinergic nerve terminals (Kawaguchi et al., 1995; Kurokawa et al., 1996; Richardson et al., 1997). These adenosine A_{2A} receptors have a profound influence on motor functions via the modulation of basal ganglia output pathways (Ochi et al., 2000).

We have recently developed orally active adenosine A_{2A} receptor antagonists KF17837 ((*E*)-1,3-dipropyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione) and KW-6002 ((*E*)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione) (Shiozaki et al., 1999a). These adenosine A_{2A} receptor antagonists ameliorate motor dysfunctions of drug-induced catalepsy models and MPTP (1-methyl-4-phenyl-1,2,3,6-

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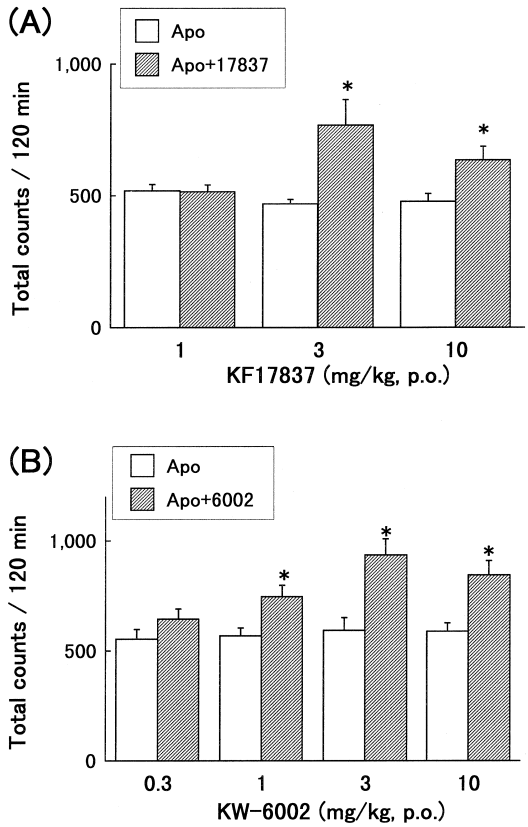


Fig. 1. Effects of KF17837 (A) and KW-6002 (B) on total counts of turning after apomorphine (0.1 mg/kg, s.c.) injection in 6-hydroxydopamine lesioned rats. KF17837 or KW-6002 was administered orally 30 min before the apomorphine injection. Each column and bar represents the mean ± S.E.M. of total counts of turning in 120 min after apomorphine injection. Significant differences from treatment of apomorphine alone were assessed by paired *t*-test ($n = 8$, $^{*}P < 0.05$).

tetrahydropyridine) or reserpine-induced Parkinsonian models in mice (Shiozaki et al., 1999b). More recently, we have reported that the combination of KW-6002 with dopaminergic drugs yields synergistic anti-Parkinsonian activity without an aggravation of dyskinesia in MPTP-treated common marmosets (*Callithrix jacchus*) (Kanda et al., 1998a,b, 2000).

In the present study, we investigated the effects of adenosine A_{2A} receptor antagonists KF17837 and KW-6002 in rats with a 6-hydroxydopamine lesion of the medial forebrain bundle, because this animal model of Parkinson's disease is one of the most reliable for the assessment of efficacy of candidate compounds (Ungerstedt and Arbuthnott, 1970). The study focuses on alterations of dopamine receptor agonist apomorphine or L-DOPA (L-3,4-dihydroxyphenylalanine) induced rotational behavior by KF17837 or KW-6002. We also investigated whether the potentiation of rotational behavior by these compounds is due to the increase of intensity or the prolongation of turning duration.

2. Materials and methods

2.1. Animals

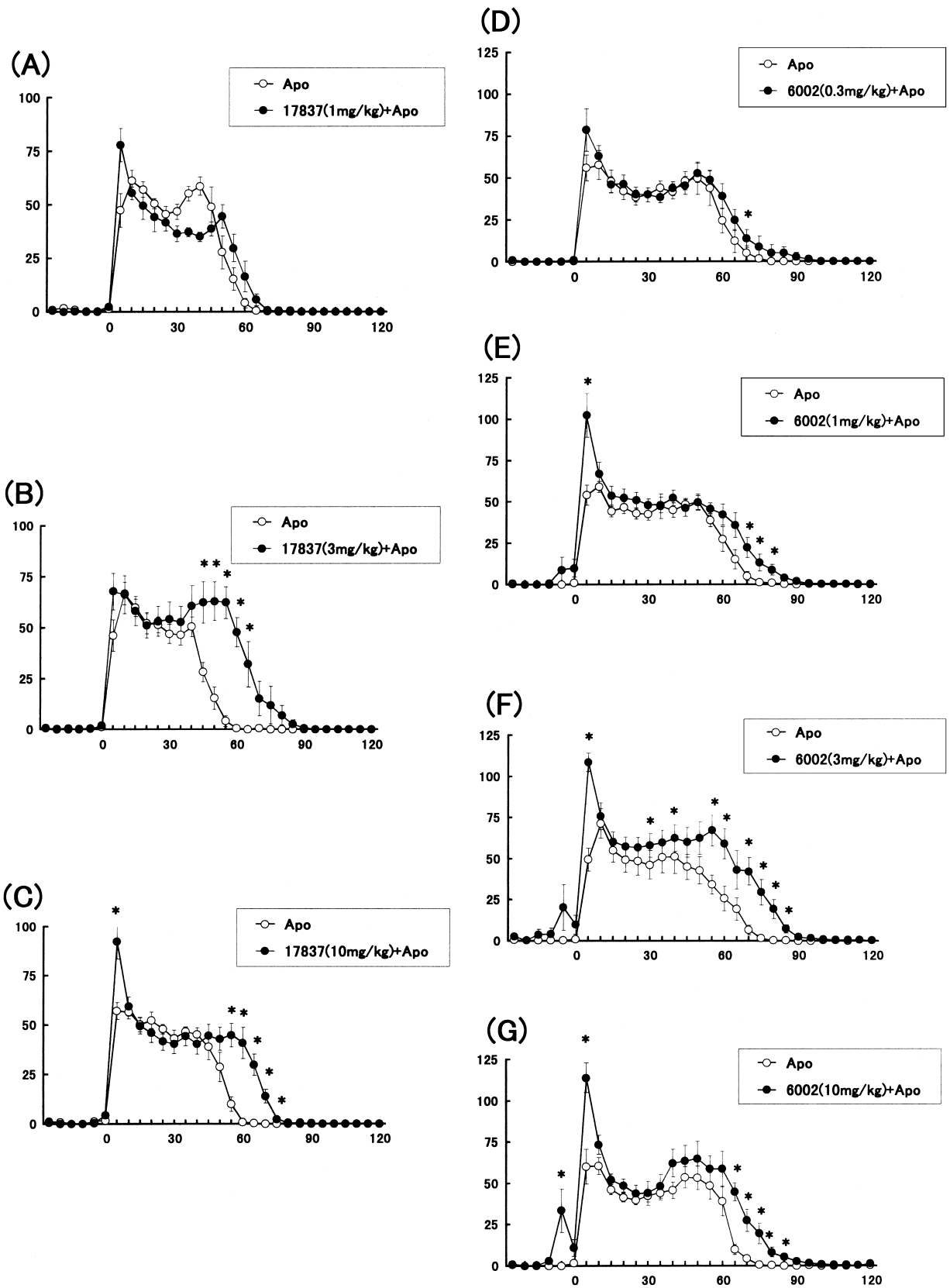
Male Sprague–Dawley rats (180–200 g; SLC, Hamamatsu, Japan) were housed five per cage and maintained in a facility with controlled humidity (50–60%) and temperature (22–24°C) on a 12:12 h light/dark cycle (lights on at 7:00 a.m.) with free access to food (FR-2, Funabashi Farm; Funabashi, Japan) and water until experimental use. The experimental protocols were approved by the Animal Ethics Committee at Kyowa Hakko Kogyo, and were in accordance with the Guiding Principles for the Care and Use of Laboratory Animals endorsed by the Japanese Pharmacological Society.

2.2. Compounds

The following compounds were used: (*E*)-1,3-dipropyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione [KF17837 (*E* isomer > 99.9%); Kyowa Hakko Kogyo, Japan], (*E*)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione [KW-6002 (*E* isomer > 99.9%); Kyowa Hakko Kogyo], 2-[*p*-(2-carboxyethyl)phenethylamino]-5′-*N*-ethylcarboxamidoadenosine hydrochloride (CGS 21680; Research Biochemicals, MA, USA), apomorphine hydrochloride (apomorphine; Sandoz, Basel, Switzerland), L-3,4-dihydroxyphenylalanine (L-DOPA; Kyowa Hakko Kogyo), D,L-serine 2-[(2,3,4-trihydroxyphenyl)methyl] hydrazide hydrochloride (benserazide; Kyowa Hakko Kogyo), desipramine hydrochloride (desipramine; Sigma, St. Louis, MO), 6-hydroxydopamine hydrobromide (Sigma). KF17837, KW-6002 and L-DOPA (administered with benserazide at the ratio of 4:1) were suspended in 0.3% Tween 80 or 0.3% sodium carboxymethylcellulose. CGS 21680 and apomorphine were dissolved in saline. Desipramine was dissolved in distilled water. 6-hydroxydopamine hydrobromide was dissolved in saline solution containing L-ascorbic acid (Wako, Osaka, Japan). KF17837, KW-6002 and L-DOPA were administered p.o. in a volume of 5 ml/kg. CGS 21680 was

Fig. 2. Effects of KF17837 and KW-6002 on apomorphine (0.1 mg/kg, s.c.)-induced contralateral turning behavior in 6-hydroxydopamine lesioned rats. The abscissa indicates the time (min) after apomorphine injection. KF17837 [1 mg/kg (A), 3 mg/kg (B), 10 mg/kg (C)] or KW-6002 [0.3 mg/kg (D), 1 mg/kg (E), 3 mg/kg (F), 10 mg/kg (G)] was administered orally 30 min before the injection of apomorphine. Each point represents the mean ± S.E.M. of counts in each 5-min period. Significant differences from corresponding control were assessed by two-way repeated-measure ANOVA followed by paired *t*-test ($n = 8$, $^{*}P < 0.05$).

dissolved at 1 μg/2 μl and 20 μl was injected intracerebroventricularly (i.c.v.) using the method of Haley and McCormack (1957). Apomorphine was dissolved at 0.1 mg/5 ml and administered s.c. in a volume of 5 ml/kg.



2.3. 6-hydroxydopamine lesion

Rats (220–260 g) were anaesthetized with sodium pentobarbital (30 mg/kg, i.p.) and placed in a stereotaxic frame (Narishige, Tokyo, Japan). 6-hydroxydopamine (6-hydroxydopamine hydrobromide, 8 μg in 2 μl saline containing 0.05% ascorbic acid) was injected over 2 min (at a rate of 1 μl/min) into the left medial forebrain bundle (A/P-2.5, L/M-1.8, and V/D-8.9, from bregma point and surface of the skull; according to the atlas of Paxinos and Watson, 1986). Thirty minutes before the stereotaxic injection, the rats received an injection of desipramine hydrochloride (25 mg/kg, i.p.) to protect the noradrenergic neurons. At least 6 days after 6-hydroxydopamine injections, the lesioned animals were tested by injecting apomorphine (0.1 mg/kg, s.c.) and recording rotational behavior in a rotometer (Ungerstedt and Arbuthnott, 1970).

2.4. Evaluation of turning behavior

More than 2 weeks after the lesion, rats were screened on the basis of their contralateral rotation (1 rotation count was defined as a 360° turn) in response to apomorphine (0.1 mg/kg). Any rat not showing at least 300 contralateral rotation counts during the 1 h testing period was eliminated from the study. For behavioral observation, rats were placed in hemispherical bowls (30 × 30 cm) and turning behavior was quantified by automated rotometers (produced in Kyowa Hakko Kogyo). Turning was recorded in 5-min intervals over a 2- or 3-h period. On test days, rats were weighed and placed into test bowls and allowed to acclimatise for at least 30 min before testing. Apomorphine and L-DOPA were administered 30 min after treatment with KF17837 or KW-6002. At least 6 days were allowed to elapse between experiments. To exclude a factor of priming effect, drug (KF17837 and KW-6002) treatments were administered to all animals within a group in a randomized order, with each rat serving as its own control. The intensity of the response was measured by the number of contralateral turning during any 5 min interval. The duration of the response was measured by the time between the first 5 min interval when the rate of turning attained half its eventual average value and the first interval when the rate again declined to half its average value.

2.5. Antagonism experiments

KW-6002 was tested in combination with a selective agonist at the adenosine A_2 receptor, CGS 21680. 6-Hydroxydopamine lesioned rats, which produced at least 300 contralateral rotations in 1 h after apomorphine injection (0.1 mg/kg, s.c.), were anaesthetized with sodium pentobarbital (Nembutal sodium solution), 40 mg/kg, i.p., and then placed in a stereotaxic frame. A microinjection guide cannula (23-gauge stainless steel tubing, Eicom, Kyoto, Japan) was implanted into the lateral ventricle (A/P 0.8, L/M-1.5 and V/D-3.5, according to the atlas of Paxinos and Watson, 1986). The cannula was secured with two skull screws and dental cement. Before beginning an experiment, animals were allowed at least 1 week to recover from the surgery. CGS 21680 (10 μg/20 μl) was injected into the lateral ventricle using a 50 μl Hamilton microsyringe over 1 min. In the control animals, 20 μl of vehicle (saline) was injected into the lateral ventricle instead of CGS 21680. CGS 21680 and KW-6002 were administered 10 and 40 min before the injection of apomorphine, respectively.

2.6. Data analysis and statistics

The mean ± S.E.M. of the number of rotation counts was calculated. Total counts data were analyzed by paired *t*-test. To compare the values at each time point, the data were analyzed by two-way analysis of variance (ANOVA) for repeated measurement, and when significant differences were found, the effects of drugs at individual time points were compared with corresponding control values using paired *t*-test. The level of statistical significance was set at $P < 0.05$ for all analyses.

3. Results

3.1. Effects of adenosine A_{2A} receptor antagonists on apomorphine-induced rotation

Apomorphine (0.1 mg/kg, s.c.) produced intense contralateral turning for approximately 60 min. The maximal magnitude exceeded 50 counts in 5 min and the total counts were approximately 500 in 120 min. By contrast, oral administration of KF17837 (1–10 mg/kg) or KW-6002 (0.1–1 mg/kg) per se did not induce turning behavior. KW-6002 only produced contralateral rotations at higher doses (3 mg/kg and 10 mg/kg), although these effects were relatively weak and statistically significant only at 25 min after the administration of KW-6002.

Administration of KF17837 at doses of 3 mg/kg, p.o. and 10 mg/kg, p.o., or KW-6002 at doses of 1 mg/kg, p.o. and higher significantly increased the total counts (in 120 min) of contralateral rotations induced by apomorphine (Fig. 1). In Fig. 2, the effects of drug treatment were statistically significant at all doses except at 1 mg/kg, p.o. of KF17837 (panel A; $P = 0.8621$ by two-way ANOVA). Animals given KF17837 and KW-6002 together with apomorphine had a longer response duration to apomorphine than those receiving apomorphine alone (Fig. 2B–G). KF17837 and KW-6002 (both compounds at 3 mg/kg, p.o.) maximally prolonged the duration of motor response to apomorphine by 44% and 25%, respectively (Table 1).

Table 1
Effects of adenosine A_{2A} receptor antagonists KF17837 and KW-6002 on the duration of apomorphine-induced turning behavior

Compound (mg/kg)		Turning duration (min)		Prolongation of duration (% increase)
		Apo	Apo + A_{2A} antagonist	
KF17837	1	50	55	10
	3	45	65	44
	10	50	65	30
KW-6002	0.3	55	60	9
	1	60	65	8
	3	60	75	25
	10	60	70	17

Prolongation of duration indicates percentage increase of turning duration by apomorphine (Apo) + adenosine A_{2A} receptor antagonist (A_{2A} antagonist) KF17837 or KW-6002 compared with apomorphine alone.

3.2. The combination effects of KW-6002 and selective adenosine A_2 receptor agonist CGS 21680 on apomorphine-induced turning behavior

Pretreatment with CGS 21680 (10 μg/20 μl, i.c.v.) significantly reduced the contralateral rotations induced by apomorphine (Fig. 3). This effect of CGS 21680 could be partially reversed by coadministration of the adenosine A_{2A} receptor antagonist KW-6002 (1 mg/kg, p.o.) (Fig. 3).

3.3. Effects of adenosine A_{2A} receptor antagonists on L-DOPA-induced rotation

KF17837 (3 mg/kg, p.o.) tended to potentiate rotational behavior induced by L-DOPA (3–30 mg/kg, p.o.), although the effect was statistically significant only in the case of 10 mg/kg, p.o. of L-DOPA (Fig. 4A). On the other hand, KW-6002 (3 mg/kg, p.o.) significantly increased the total counts of rotation induced by 3 mg/kg, p.o. or 10 mg/kg, p.o. doses of L-DOPA, but it did not affect rotational behavior induced by 30 mg/kg, p.o. of L-DOPA (Fig. 4B).

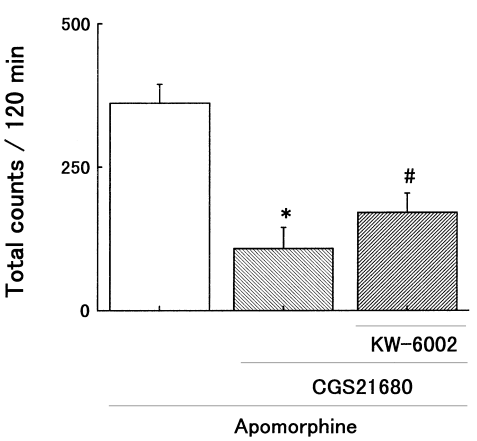


Fig. 3. Effects of CGS 21680 (10 μg/20 μl, i.c.v.) and KW-6002 (1 mg/kg, p.o.) on apomorphine (0.1 mg/kg, s.c.)-induced turning behavior in 6-hydroxydopamine lesioned rats. Each column and bar represents mean ± S.E.M. of total counts of turning in 120 min after apomorphine injection. Significant differences from treatment of apomorphine alone ($^{*}P < 0.05$) or CGS 21680 plus apomorphine treatment ($^{\#}P < 0.05$) were assessed by paired t-test ($n = 10$).

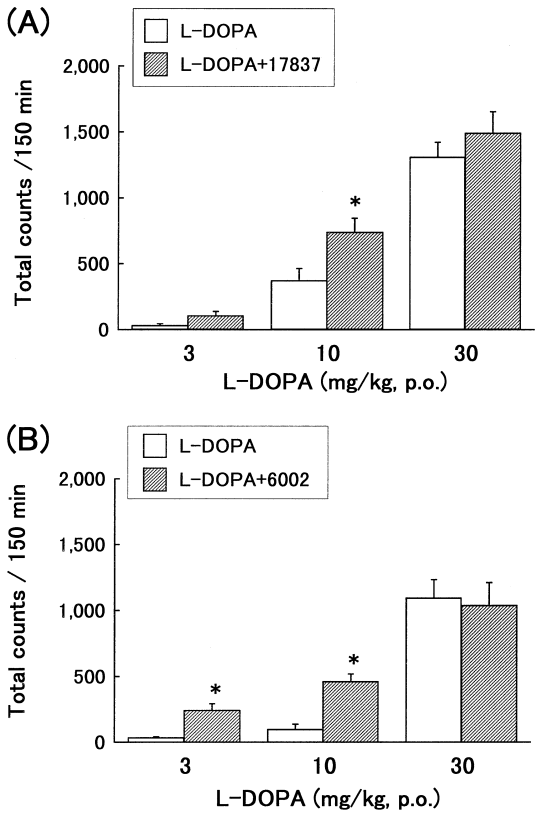


Fig. 4. Effects of KF17837(A) and KW-6002(B) on total counts of turning after L-DOPA administration in 6-hydroxydopamine lesioned rats. KF17837 or KW-6002 was administered orally 30 min before the administration of L-DOPA. Each column and bar represent the mean ± S.E.M. of total counts of turning in 150 min after L-DOPA administration. Significant differences from treatment of L-DOPA alone were assessed by paired t-test ($n = 8$–10, $^{*}P < 0.05$).

4. Discussion

KF17837 and KW-6002 are novel orally active adenosine A_{2A} receptor antagonists that may be therapeutically beneficial in preventing Parkinsonian symptoms (Richardson et al., 1997; Kuwana et al., 1999). Previously it has been shown that these adenosine A_{2A} receptor antagonists produce marked and sustained improvement of motor functions in mouse and monkey models of Parkinson's disease (Kanda et al., 1998a,b, 2000; Shiozaki et al., 1999a). In this study, we demonstrated that KF17837 and KW-6002 have potentiating effects on apomorphine-induced rotation in 6-hydroxydopamine-lesioned rats. Furthermore, these adenosine A_{2A} receptor antagonists potentiated the rotational behavior induced by the current gold standard drug used for treating Parkinson's disease, namely L-DOPA.

A similar effect to that exhibited by the adenosine A_{2A} receptor antagonists in 6-hydroxydopamine models in the present study has been reported using other agents possessing the property of adenosine A_{2A} receptor antagonism. For example, methylxanthines, such as theophylline and caffeine, which have antagonistic effects on adenosine receptors besides inhibiting phosphodiesterase have been reported to induce rotation and enhance rotational behavior elicited by dopamine receptor agonists in rats with a unilateral lesion of the nigrostriatal dopamine system (Fuxe and Ungerstedt, 1974; Garrett and Holzman, 1995; Jiang et al., 1993). Although the precise mechanism by which these effects are mediated is not fully understood, it is believed to be, at least in part, by blockade of adenosine A_{2A} receptor because these methylxanthine-mediated rotations were antagonized by a selective adenosine A_2 receptor agonist CGS21680.

More recently, Pinna et al. (1996) and Fenu et al. (1997) reported that intraperitoneal injection of another selective adenosine A_{2A} receptor antagonist, SCH58261, also potentiated the contralateral turning behavior induced by dopamine D_1 receptor agonist SKF38393 or L-DOPA, although SCH58261 alone did not induce any motor asymmetry. Similarly in our experiments, adenosine A_{2A} receptor antagonists KF17837 and KW-6002 per se did not induce marked turning behavior, suggesting that antagonism of adenosine A_{2A} receptors alone does not produce rotation in the hemi-Parkinsonian model. The turning behavior in unilaterally lesioned animals is due to stimulation of supersensitive postsynaptic striatal dopamine receptors (Ungerstedt, 1971; Fuxe and Ungerstedt, 1974). Therefore, one possible explanation is that compounds that do not target the dopaminergic system directly do not yield a striatal imbalance, and consequently do not cause rotations in these models. On the other hand, it is possible that adenosine A_{2A} receptor antagonists augment the striatal imbalance caused by dopaminergic drugs.

Overall intensity of the response to apomorphine was not changed greatly by KF17837 and KW-6002, although an increase in peak effect was seen (only at 5 min point after treatment of apomorphine). Thus, we think that the observed enhancement by these adenosine A_{2A} receptor antagonists on the total rotational response to apomorphine can be mainly attributed to a specific effect on turning duration. Surprisingly, the effect of KF17837 on turning duration was greater than that of KW-6002 (KF17837 prolonged the duration by 44%; KW-6002 prolonged the duration by 25%, at 3 mg/kg, p.o., respectively; Table 1). Previously, we have reported that KW-6002 is more potent than KF17837 at inhibiting drug-induced catalepsy (Shiozaki et al., 1999a). Because of its higher potency, KW-6002 may not only prolong the duration but also potentiate the intensity (especially this is clearly observed in 3 mg/kg, p.o. of KW-6002), which may mask the effect on turning duration to some degree. Alternatively, the apparent differences in the prolongation of turning duration by KF17837 and KW-6002 could be due to differences in the degree of dopaminergic denervation in the animal groups in which these compounds were assessed, since the turning duration induced by apomorphine per se was longer in the animal group used for the evaluation of KW-6002 (Fig. 2).

Finally, the findings of this study may have important implications for the symptomatic treatment of Parkinson's disease. Most early Parkinson's disease patients derive sustained and steady benefit from L-DOPA throughout the day. However, as Parkinson's disease progresses, the duration of benefit shortens (called wearing-off phenomena). A drug capable of selectively reversing the underlying reduction in the duration of L-DOPA anti-Parkinsonian action without augmenting its response intensity might have considerable value, because the wearing-off phenomena would diminish without the risk of inducing peak dose dyskinesia (Papa et al., 1995). Thus, KF17837 and KW-6002 may be useful as adjuncts in the treatment of advanced Parkinson's disease.

In conclusion, this study has shown that the selective adenosine A_{2A} receptor antagonists KF17837 and KW-6002 potentiate the motor effect of apomorphine and L-DOPA in an experimental model of Parkinson's disease. If similar effects occur in humans, these adenosine A_{2A} receptor antagonists could offer a novel, nondopaminergic approach to the treatment of Parkinson's disease.

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