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Effects of ropinirole on motor behavior in MPTP-treated common marmosets

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Abstract

The effects of ropinirole (4-[2-(dipropylamino)ethyl]-2-indolinone monohydrochloride), a nonergoline dopamine receptor agonist with a high affinity for native dopamine D_2-like receptors, on Parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 2.5 mg/animal in common marmosets were examined and compared to the effects of bromocriptine. Ropinirole (0.1–3 mg/kg, PO) increased motor activity dose dependently and reversed akinesia or uncoordinated movement in MPTP-treated marmosets. The activities for ropinirole were very similar to those of bromocriptine. Ropinirole had, however, several properties that differed from those of bromocriptine. Ropinirole caused a more rapid onset of anti-Parkinsonian activity compared to bromocriptine, and had a potency more than five times greater than that of bromocriptine in the improvement of motor deficits. The combination of ropinirole and L-DOPA increased the effectiveness of ropinirole or L-DOPA alone, and produced a more marked additive effect on motor activity than did bromocriptine and L-DOPA. Chronic administration of ropinirole for 21 days produced a statistically significant increase in motor activity compared to the initial administration, and akinesia scores, measured through rating the quality of movements, were also improved without obvious dyskinesia. This study suggests that ropinirole is a dopamine D_2-like receptor agonistic drug of potential use in the treatment of Parkinson's disease.

Keywords: Ropinirole; Bromocriptine; L-DOPA; MPTP; Common marmosets; Parkinson's disease; Akinesia; Locomotion

1. Introduction

Parkinson's disease is characterized by a relatively selective loss of neurons in the substantia nigra and a subsequent severe reduction in transmitter dopamine released by these nerve endings. In turn, motor deficits occur, which become more severe with progression of the disease. Dopamine D_1/D_2 receptor excitation contributed by the dopamine formed from L-DOPA in combination with a dopamine D_2 receptor agonist, has been repeatedly shown to relieve Parkinsonian symptoms [14,24,32]. However, treatment with L-DOPA is complicated by the loss of the initial benefit after some years of continuous therapy. With L-DOPA, treatment of longer than 5 years, most patients experience either some fluctuations, some dyskinesia, or loss of efficacy [10].

Bromocriptine is a strong agonist of the D_2-like receptors and a partial antagonist of the D_1-like receptors, and has shown affinity to nondopaminergic receptors, particularly 5-HT_1, 5-HT_2, and α_2- adrenoceptors [4,12,21,34]. Ropinirole is a new nonergoline dopamine agonist that binds specifically to D_2-like receptors with selectivity similar to that of dopamine. The chemical structure of ropinirole has the potential to maintain a structure–activity relationship similar to that of dopamine and other effective dopamine agonists without producing ergot-related adverse effects. In a binding assay, ropinirole showed little or no affinity for other receptor sites, namely: D_1, 5-HT_1, 5-HT_2, benzodiazepine, and GABA receptors or α_1-, α_2-, and β-adrenoceptors [9]. It is reported that ropinirole specifically stimulates the D_2 receptors in both the CNS and peripheral system [8].

In recent clinical trials, ropinirole has shown greater potency in its anti-Parkinsonian effect than bromocriptine [19]. Our goal is to support the results of clinical trials, using the MPTP-treated marmoset. Additionally, ropinirole showed a rank order of affinity of $D_3 > D_2 > D_4$ in binding

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studies. The presence of D_3 receptors in areas of the brain involved in the control of movement, as well as parts of the limbic system, indicates that the D_3 receptor may be involved in motor function and is a target for anti-Parkinsonian drugs [7,9].

In this study, we confirmed the anti-Parkinsonian activity of ropinirole using MPTP-treated common marmosets and compared it to the properties of bromocriptine.

2. Materials and methods

2.1. Animals

Thirty adult common marmosets (Clea Japan) of each sex were used. The marmosets weighed 258–418 g, and were housed in stainless steel cages (52 cm width × 45 cm depth × 62 cm height) with ad lib access to food and water. The animal room was maintained at a constant temperature of 26±2°C and humidity of 50±10%, with a 12-h automatic light cycle (0600 to 1800 h). This study was approved by the Animal Care and Use Committee of SNBL.

2.2. MPTP treatment

Twenty animals were pretreated twice, with an intravenous administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 2.5 mg/animal at a dose of 2.5 mg/kg, with a 1-week interval between administrations (treatment performed under anesthesia with ketamine 7.5 mg/animal iM). The MPTP-treated marmosets were allowed to recover from the acute effects of the treatment for 2 months. Vehicle injections were administered to the 10 remaining normal animals under the same conditions.

2.3. Motor behavior

Locomotion was measured in an activity cage (46 cm width × 56 cm depth × 62.5 cm height) equipped with two photocell sensor units mounted on the outer wall 2 cm above each perch. Interruptions of the infrared light beams were recorded on electromechanical counters and automatically printed every 15 min. The animals were allowed at least 1 h to acclimatize to the activity cage. Subsequently, marmosets were orally administered 10 ml/kg of one of the following: ropinirole at 0.1–3 mg/kg, bromocriptine at 0.5–10 mg/kg, or 0.5% carboxymethylcelullose (CMC).

An increase in interruption counts twice that of the control was considered to indicate an improvement in motor activity. The ED_{50} for motor activity was calculated by the Probit method.

The spontaneous behavior of the animals was then observed over the ensuing 5 h and recorded on videotape. To evaluate drug-induced improvement in the quality of motor behavior, akinetic scores were recorded 15, 30, 60, 120, 180, 240, and 300 min after administration by observation of the video recording, and analyzed blind. During the observation period, the animals had free access to food and water. Akinesia was assessed according to the following rating scale [22,23]: −1 = excited behavior; 0 = normal behavior; 1 = quiet but

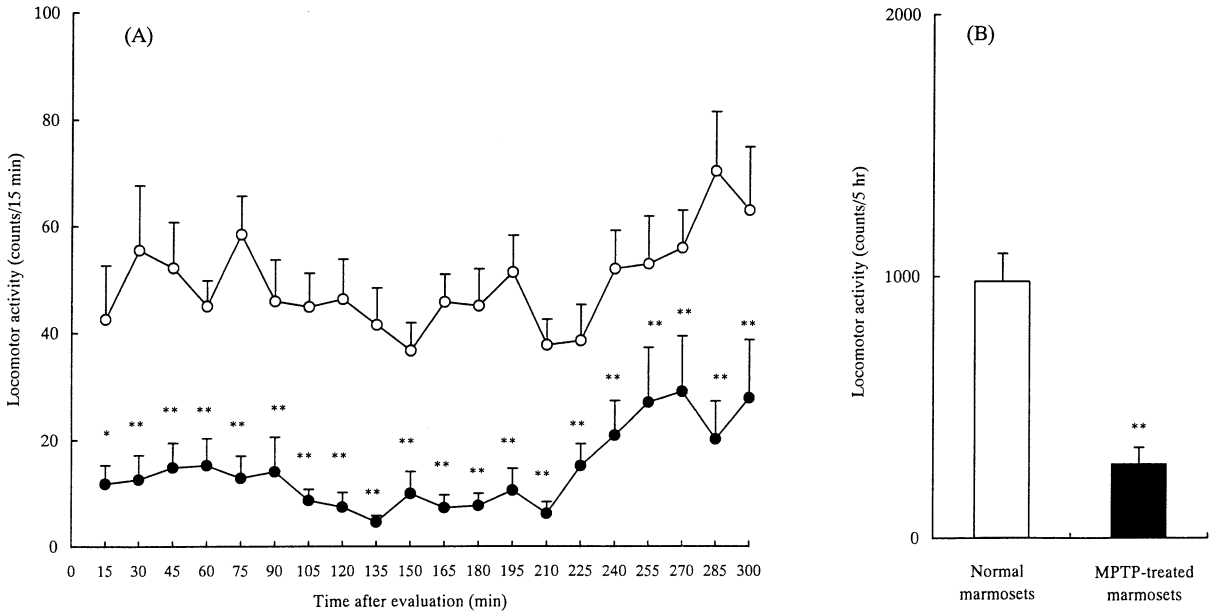

Fig. 1. Time course of spontaneous locomotor activity in normal and MPTP-treated common marmosets (A) and the cumulative motor activity counts were determined from the total of each 15 min count for 5 h (B). Animals were allowed to acclimatize for 60 min prior to initiation of the locomotor activity evaluation. The locomotor activity counts were recorded every 15 min for 5 h. Each point and bar represents the mean ± SEM (n = 20). Key to symbols: normal marmoset (○), MPTP-treated marmoset (●). Each column and bar represents the mean ± SEM (n = 20). **, * Significantly different from normal animals at $p < 0.01$ and $p < 0.05$, respectively, Mann–Whitney U-test.

shows a normal repertoire of movement; 2 = moves freely, but is clumsy when making complicated movements, such as climbing down the cage wall; 3 = makes fewer and slower movements and is obviously clumsy in executing complex movement, such as jumping up to a perch or moving on the perch; 4 = makes few movements unless disturbed, and then the movements are slow and limited to a small region of the cage; 5 = akinetic and does not move even when disturbed.

2.4. Combination with L-DOPA

The acute effects of a combined administration of ropinirole and L-DOPA on motor behavior were examined in MPTP-treated marmosets, and compared to the acute effects of a combination of bromocriptine and L-DOPA. Preliminary studies were performed to determine the doses of ropinirole, bromocriptine, and L-DOPA required to induce anti-Parkinsonian activity in MPTP-treated animals. Ropinirole and bromocriptine were administered at 0.2 and 0.5 mg/kg, respectively, and L-DOPA was administered at 40 mg/kg.

2.5. Chronic treatment with ropinirole

A preliminary study was performed to determine the dose level of ropinirole that would produce a significant increase in motor activity in MPTP-treated or normal marmosets. From the results of the preliminary study, dose levels of 0.2 and 1 mg/kg of ropinirole were selected for MPTP-treated and normal animals, respectively. MPTP-treated and normal animals received an oral administration of ropinirole once daily for 21 days. The vehicle was administered in the same manner to MPTP-treated marmosets.

2.6. Drugs and solutions

Bromocriptine mesylate and L-DOPA were purchased from Sigma (St. Louis, MO); MPTP, hydrochloride was purchased from Research Biomedicals International (Natick, MA); and ropinirole hydrochloride was generously supplied by SmithKline Beecham Seiyaku K.K. (Tokyo, Japan).

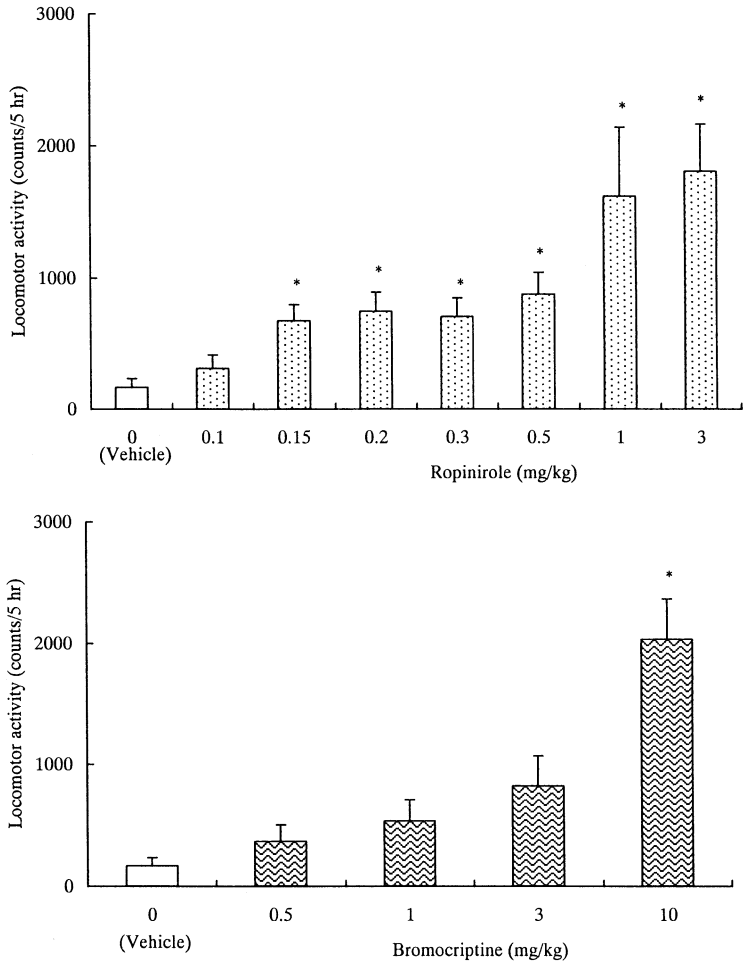

Fig. 2. Acute effects of ropinirole and bromocriptine on locomotor activity in MPTP-treated marmosets. The vehicle and all drugs were administered orally. Animals were allowed to acclimate for 60 min prior to initiation of the locomotor activity evaluation. The cumulative motor activity counts were determined from the total of each 15 min count for 5 h. Each bar represents the mean ± SEM (n = 4). * $p < 0.05$ compared to vehicle-treated animals, Mann–Whitney U-test.

Ropinirole was dissolved in a 0.5% CMC (CMC sodium) solution, while bromocriptine and L-DOPA were suspended in a 0.5% CMC solution. Ropinirole and bromocriptine were administered orally to animals. MPTP was dissolved in a 0.9% saline solution.

2.7. Statistical analysis

The data were analyzed using the Kruskal–Wallis one-way ANOVA test followed by the Mann–Whitney *U*-test ($p<0.05$).

3. Results

3.1. Effects of ropinirole and bromocripitine on motor behavior

After MPTP treatment, the animals showed characteristic Parkinsonian/akinetic behavior. Primarily, the animals were immobile and rigid with flexed hind quarters, postural tremors and a loss of vocalization. Following a 2-month recovery period from the MPTP treatment, the animals were immobile, and slumped on either the perch or floor of the housing cage. In comparison to the control animals, the MPTP-treated animals exhibited few eye and head movements, characterized by making eye contact with novel stimuli and/or blinking. When initially placed into the activity cage, MPTP-treated animals showed little mobility and the quality of their locomotion differed considerably, in that the movements of the MPTP-treated animals were slower and uncoordinated in comparison to the control animals. These animals also showed tremor when extending their forelimbs. When the locomotor activity of MPTP-treated animals was scored, a significant decrease was noted in comparison to the activity of the control animals (Fig. 1).

An oral administration of ropinirole increased motor activity counts for 5 h in a dose-dependent fashion, and the effects were significant at doses of 0.15–3 mg/kg.

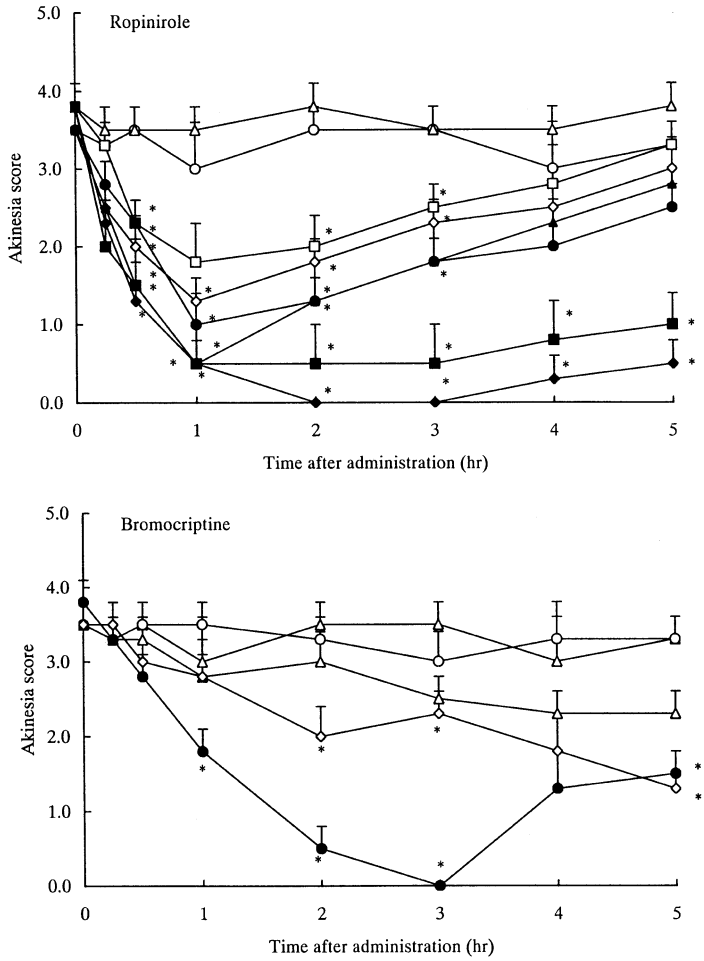

Fig. 3. Effect of ropinirole and bromocriptine on the akinetic score in MPTP-treated marmosets. The vehicle and all drugs were administered orally. Animals were allowed to acclimate for 60 min prior to initiation of the locomotor activity evaluation. The akinetic scores were estimated at 15 and 30 min, and 1, 2, 3, 4, and 5 h after injection. Each point and bar represents the mean ± SEM (n = 4). * $p < 0.05$ compared to vehicle-treated animals, Mann–Whitney *U*-test. Key to symbols: vehicle (○); ropinirole: 0.1 mg/kg (△), 0.15 mg/kg (□), 0.2 mg/kg (✧), 0.3 mg/kg (●), 0.5 mg/kg (▲), 1 mg/kg (■), 3 mg/kg (✦); bromocriptine: 0.5 mg/kg (△), 1 mg/kg (□), 3 mg/kg (✧), 10 mg/kg (●).

The ED_{50} of ropinirole was 0.109 mg/kg at the 95% confidence level on motor activity from 0.088 to 0.111 mg/kg (Fig. 2). At 0.2–3 mg/kg, motor activity increased almost immediately after administration of ropinirole, reaching a peak between 60 and 120 min. Statistically significant increases were observed at the highest doses (1–3 mg/kg) almost continually until 5 h after dosing. Even the lowest dose, 0.1 mg/kg, remained slightly higher than the control through most of the observation period. Bromocriptine also increased motor activity in a dose-dependent fashion. The ED_{50} of bromocriptine was 0.504 mg/kg at the 95% confidence level on motor activity from 0.498–1.285 mg/kg (Fig. 2). Doses of 0.5 to 10 mg/kg also increased motor activity at 90 to 120 min after administration in almost all cases. The highest dose of bromocriptine, 10 mg/kg, increased motor activity almost continually for 5 h. Ropinirole (1.0 mg/kg) significantly increased locomotor activity from the first measurement period (from immediately after administration to 15 min after administration). This effect reached a peak level 1–2 h after administration. Bromocriptine (3.0 mg/kg) increased locomotor activity from approximately 2.5 h after administration, and this effect persisted 5 h after administration.

The akinetic score was also decreased by the administration of ropinirole or bromocriptine. A statistically significant reversal of akinesia was observed at 0.15 to 3.0 mg/kg of ropinirole. The reversal was noted from 0.5 h to 5 h after administration at 1.0 and 3.0 mg/kg, and behavior was almost normal. No stereotypical behavior was observed at any dose of ropinirole. A statistically significant reversal of akinesia was noted 2, 3, and 5 h after administration at 3.0 to 10 mg/kg of bromocriptine (Fig. 3).

The onset of bromocriptine effects on locomotor behavior and anti-Parkinsonian activity was very slow when compared to ropinirole. Additionally, the dose of bromocriptine needed to achieve effects similar to that of ropinirole was higher.

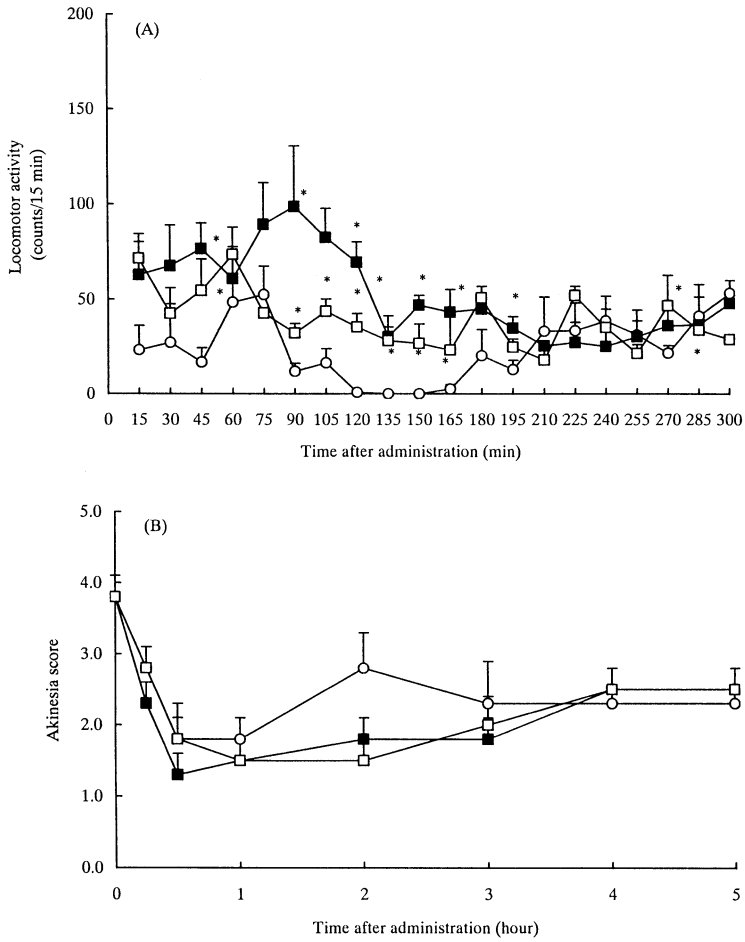

Fig. 4. Acute effects of combined administration of ropinirole (0.2 mg/kg) or bromocriptine (0.5 mg/kg) with L-DOPA (40 mg/kg) on motor activity (A) and the akinetic score (B) in MPTP-treated common marmosets. The vehicle and all drugs were administered orally. Ropinirole or bromocriptine was given in a combined injection with L-DOPA. Animals were allowed to acclimate for 60 min prior to initiation of the locomotor activity evaluation. The locomotor activity counts were recorded every 15 min for 5 h, and the akinetic scores were estimated at 15 and 30 min, and 1, 2, 3, 4, and 5 h after injection. Each point and bar represents the mean ± SEM ($n = 4$). * Significantly different from the L-DOPA + vehicle-treated animals at $p < 0.05$, Mann–Whitney U-test. Key to symbols: vehicle + L-DOPA (○), ropinirole + L-DOPA (■), bromocriptine + L-DOPA (□).

3.2. Combination of ropinirole or bromocriptine with L-DOPA

In comparison to a single treatment of L-DOPA at 40 mg/kg (vehicle combination) in MPTP-treated marmosets, locomotor activity increased significantly with a combined administration of L-DOPA plus 0.2 mg/kg of ropinirole or 0.5 mg/kg of bromocriptine (Fig. 4). The cumulative locomotor activity for 5 h increased significantly ($p<0.05$) with a combined administration of L-DOPA plus ropinirole, but L-DOPA at 40 mg/kg plus bromocriptine did not significantly increase activity in comparison to the vehicle combination. The combined administration of ropinirole or bromocriptine with L-DOPA reversed the akinesia of parkinsonism induced by MPTP in marmosets.

3.3. Effects of chronic ropinirole treatment on motor behavior

Chronic ropinirole (0.2 mg/kg/day, for 21 days, PO) significantly increased locomotor activity in MPTP-treated marmosets in comparison to the vehicle. Days 1, 3, 7, and 21 showed a statistically significant increase in activity. At 7 days after cessation of treatment, activity decreased and returned to a level equal to the vehicle or pretreatment value (Fig. 5).

The effects of chronic ropinirole treatment (a daily dose of 0.2 mg/kg for 21 days) on the akinetic score in MPTP-treated marmosets showed a similar time course on all experimental days. Ropinirole (0.2 mg/kg PO) on days 1–21 decreased the total akinetic scores for 5 h to almost the same levels as day 1. On days 7 and 14 after cessation, ropinirole treated animals showed similar akinetic scores as

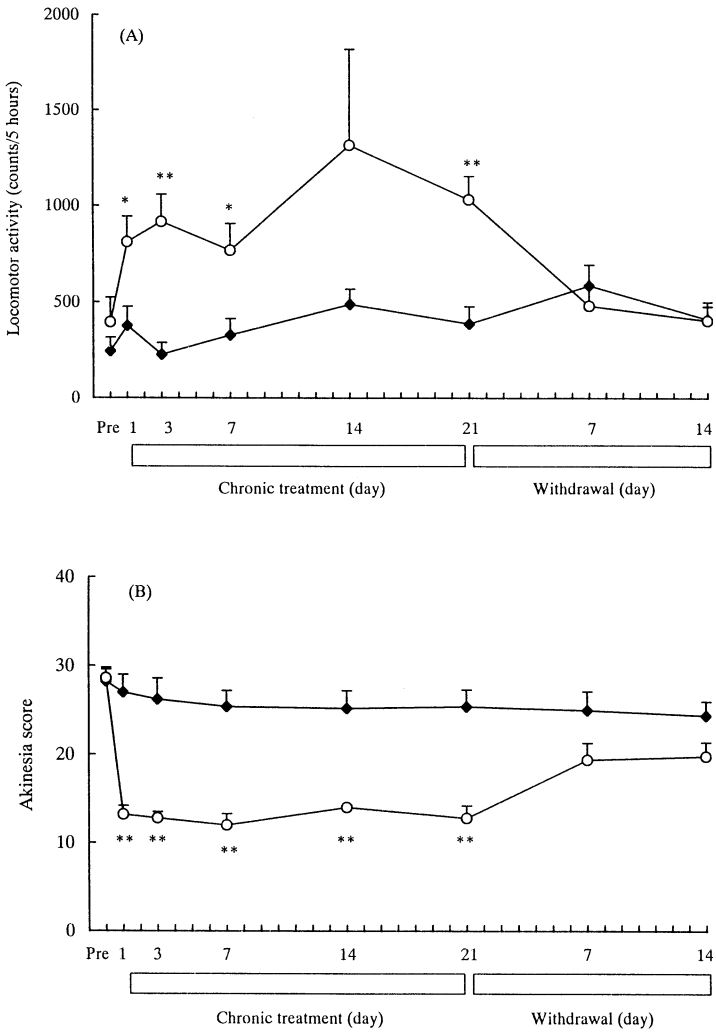

Fig. 5. Effects of chronic ropinirole on motor activity (A) and total akinetic score (B) in MPTP-treated marmosets. Ropinirole (○) or the vehicle (✦) was administered orally. MPTP-treated animals were injected once a day with 0.2 mg/kg of ropinirole for 21 days. On the day of the motor activity measurement, the animals were allowed 60 min prior to the injection to adapt to the novel environment. The cumulative motor activity counts were determined as a total of each 15-min count for 5 h. Each point and bar represents the mean ± SEM (n = 5). *, ** Significantly different from the vehicle at $p < 0.05$ and $p < 0.01$, respectively, Mann–Whitney U-test.

those that received vehicle. The time course of akinetic scores in animals treated with ropinirole (0.2 mg/kg) on days 1–21 showed no change (Fig. 5). Neither MPTP-treated nor normal control animals showed dyskinesia, such as protrusion of the tongue or inappropriate opening of the mouth, or chorea/choreoathetosis/dystonia of the limbs on chronic administration.

4. Discussion

The results of this study demonstrate that ropinirole has strong anti-Parkinsonian activity in MPTP-treated marmosets. In humans and other primates, intravenous administration of MPTP produces motor deficits characteristic of those seen in patients with Parkinson's disease. Deficits associated with Parkinson's disease are due to a relatively selective loss of neurons in the substantia nigra and a subsequent severe reduction in transmitter dopamine released by these nerve endings. Anti-Parkinsonian drugs such as L-DOPA and dopamine receptor agonists are effective in treating the persistent motor deficits produced by MPTP treatment in primates. Therefore, at the present time, the MPTP model is the best animal model for Parkinson's disease, although justifiable doubts persist as to whether MPTP is a causal factor in Parkinson's disease [11].

In clinical trials, ropinirole at doses ranging from 4 to 8 mg a day has been beneficial for most patients suffering from Parkinson's disease [17,18,36], these doses are lower than the doses of bromocriptine required to achieve similar effects. The purpose of the study was to compare the long-term efficacy and safety of ropinirole with that of bromocriptine over 3 years in patients with early Parkinson's disease and limited or previous dopamine therapy. Both dopamine agonists are effective in the early treatment of a high proportion of Parkinson's disease patients; effectiveness persists for at least 3 years. Those who completed the study had a significantly better functional status on ropinirole than on bromocriptine [19]. In our study, the onset of the action of bromocriptine on locomotor behavior and anti-Parkinsonian activity was very slow compared to that of ropinirole. The reason for this difference may be that compared with bromocriptine, ropinirole is absorbed rapidly after oral administration [20]. Furthermore, the ED_{50} values of ropinirole and bromocriptine on motor activity in MPTP-treated marmosets were 0.109 mg/kg (0.367 μmol/kg) and 0.504 mg/kg (0.671 μmol/kg), respectively. These suggested that a higher dose of bromocriptine was needed to achieve effects similar to that of ropinirole.

Additionally, L-DOPA is widely used in the treatment of Parkinson's disease and gives benefits for some years, but dyskinesia occurs in the majority of patients with Parkinson's disease chronically treated with L-DOPA, as in several nonhuman primate species after MPTP and L-DOPA treatment. A reduction of L-DOPA in the treatment of Parkinson's disease may be beneficial. Ropinirole induced significantly less dyskinesia than L-DOPA in MPTP-treated marmosets [26–28]. The present study demonstrates that locomotor activity increased significantly with a combined administration of L-DOPA plus ropinirole or bromocriptine in comparison to a single treatment of L-DOPA. Each dose level of ropinirole and bromocriptine represented approximately half the maximum permitted daily clinical dose level. The cumulative locomotor activity for 5 h increased significantly ($p<0.05$) with a combined administration of L-DOPA plus ropinirole, but L-DOPA at 40 mg/kg plus bromocriptine did not significantly increase activity in comparison to the vehicle combination.

It is suggested that ropinirole at 0.2 mg/kg alone was effective in increasing locomotor activity, whereas bromocriptine at 0.5 mg/kg alone was insufficient to significantly increase locomotor activity in cumulative locomotor activity over 5 h in this study. The reason for this difference may be that compared with bromocriptine, ropinirole is absorbed rapidly after oral administration [20]. Additionally, ropinirole showed selectivity for the human D_3 receptor over human D_2 receptors in radioligand binding studies (20-fold); whereas, bromocriptine showed no selectivity. The combined administration of ropinirole or bromocriptine with L-DOPA reversed the akinesia of Parkinsonism induced by MPTP in marmosets. This suggests that ropinirole is a drug with a potential for use in the treatment of Parkinson's disease. The combined administration of ropinirole or bromocriptine with L-DOPA reversed the akinesia of Parkinsonism induced by MPTP in marmosets. This suggests that ropinirole is a drug with a potential for use in the treatment of Parkinson's disease.

There are many reports regarding the role of dopamine D_1 and D_2 agonists in the amelioration of Parkinson's disease. The stimulation of either central dopamine D_1 or D_2 agonists is required to produce anti-Parkinsonian effects and hyperactivity in MPTP-treated monkeys [2]. The values of locomotor activity at 3 mg/kg ropinirole and 10 mg/kg bromocriptine of MPTP-treated animals are significantly higher than in the normal animals. The increased locomotor activity reflected agonist-induced hyperactivity. However, there was no evidence of excited or stereotypical behavior when general behavior was carefully observed by videotape during the measurement of locomotor activity. The usual dosage range was 0.25–8 mg, three times daily for 2 years. The most frequently observed adverse effects were nausea, somnolence, and dizziness [20]. There was no evidence of aggressiveness or increased irritability.

These findings suggested that there is little possibility of high doses of ropinirole producing adverse side effects such as aggressiveness or increased irritability. This may account for the D_3 receptor, because ropinirole showed selectivity for the human D_3 receptor over human D_2 receptors in radioligand binding studies. Conversely, the dopamine D_2 agonist suppressed resting tremors dose dependently in MPTP-treated monkeys, whereas the D_1 agonist by itself had no effects; yet it potentiated the effects of small doses of

D_2 agonist [13,35]. Recently, dopamine D_3, D_4, and D_5 receptors were cloned in addition to dopamine D_1 and D_2 receptors [31,33] and five dopamine subtypes were identified, namely, D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4), based upon analysis of their amino acid sequences and functional properties [30].

Ropinirole is a non-ergoline dopamine receptor agonist with a high affinity for native dopamine D_2-like receptors in human caudate tissue [9]. In the microphysiometer assay, which measures rates of extracellular acidification following receptor stimulation, ropinirole was shown to be a full D_3 receptor agonist, retaining 10-fold selectivity over D_2 and 50-fold selectivity over D_4 receptors [7]. The distribution of D_3 receptors in the brain of the primate is more widespread than in the rat and more closely resembles the distribution found in the human brain [16]. The presence of D_3 receptors in areas of the brain involved in the control of movement, as well as parts of the limbic system, indicates that the D_3 receptor may be involved in motor function and is a target for anti-Parkinsonian drugs. Recently, ropinirole showed selectivity for the human D_3 receptor over human D_2 receptors in radioligand binding studies (20-fold); however, bromocriptine showed no selectivity (2-fold) [6]. It has been proposed that the presence of dopamine D_3 receptors in the area of the primate brain that is involved in the control of movement, as well as parts of the limbic system, might indicate that the D_3 receptor is a target for anti-Parkinsonian drugs [15]. For this reason, ropinirole is superior to bromocripitine as monotherapy in patients with early Parkinson's disease, and in the present primate study.

In the progression of Parkinson's disease, free radicals are currently regarded as an important factor [1,3,5]. Although L-DOPA is widely used in the treatment of Parkinson's disease and gives benefits for some years, the possibility exists that L-DOPA is a source of free radical formation, and may accelerate neural injury and, consequently, the progression of Parkinson's disease [25]. Thus, a reduction of L-DOPA in the treatment of Parkinson's disease may be beneficial. The combined administration of ropinirole and L-DOPA suggested that the dopamine newly synthesized from L-DOPA may potentiate the effect of ropinirole by stimulating the D_1 and D_2 dopamine receptors. The combined therapy would make it possible to reduce the clinical dose of L-DOPA without impairing the therapeutic effect.

It is reported that when L-DOPA was given intravenously for more than 8 days to patients with Parkinson's disease, the L-DOPA requirements increased progressively within 7 days [29]. Therefore, we performed a chronic study with ropinirole to determine if a tolerance to the drug develops in MPTP-treated marmosets. Ropinirole administered in the chronic study produced a statistically significant increase in motor activity after 21 days of administration, but the improvement in akinesia was steady for all of the 21 days without obvious dyskinesia, which suggests that tolerance to the anti-Parkinsonian activity does not develop. Dyskinesia occurs in the majority of patients with Parkinson's disease chronically treated with L-DOPA, and also occurs in several nonhuman primate species after MPTP and L-DOPA treatments. However, in this study, treated animals did not develop dyskinesia, as characterized by erratic movements of the mouth and limbs. Chronic doses of ropinirole have been compared with L-DOPA, bromocripitine, or vehicle treatment using doses adjusted to equate symptomatic relief. L-DOPA treatment was associated with the development of dyskinesia, and bromocripitine induced significantly less dyskinesia than L-DOPA, but rates of dyskinesia were lowest with ropiniriole [26,28]. Therefore, it is hoped that ropinirole, which did not lead to tolerance or dyskinesia, will be helpful in relieving the unpleasant side effects of L-DOPA. This suggests that ropinirole is a drug of potential use in the treatment of Parkinson's disease.

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