Pharmacology Biochemistry and Behavior, Vol. 65, No. 3, pp. 503–508, 2000

0091-3057/00/$–see front matter

PII S0091-3057(99)00240-3

Effects of Ropinirole on Various Parkinsonian Models in Mice, Rats, and Cynomolgus Monkeys

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Received 25 September 1998; Revised 8 July 1999; Accepted 6 August 1999

FUKUZAKI, K., T. KAMENOSONO AND R. NAGATA. *Effects of ropinirole on various Parkinsonian models in mice, rats, and cynomolgus monkeys.* PHARMACOL BIOCHEM BEHAV **65**(3) 503–508, 2000.—Ropinirole (4-[2-(dipropylamino)ethyl]-2-indolinone monohydrochloride) a nonergoline dopamine receptor agonist with high affinity for native dopamine D_2-like receptors in human caudate tissue, was tested with respect to the stimulation of postsynaptic brain dopamine receptors in standard preclinical models of Parkinson's disease. Additionally, in these animal models the antiparkinsonian activity of ropinirole was compared to that of bromocriptine. The ED_{50}s (95% confidence limits) of ropinirole and bromocriptine on the turning behavior in 6-OHDA–lesioned rats were 20.17 mg/kg (14.27–26.88 mg/kg) and 11.99 mg/kg (9.37–14.17 mg/kg), respectively. The ED_{50}s (95% confidence limits) of ropinirole and bromocriptine on the catalepsy induced by reserpine were 18.55 mg/kg (15.29–22.99 mg/kg) and 12.56 mg/kg (10.25–14.64 mg/kg), respectively. Ropinirole and bromocriptine had no effect on the tremors induced by oxotremorine in mice, whereas atropine markedly suppressed the tremors. The ED_{50}s (95% confidence limits) of ropinirole and bromocriptine on the tremors in VMT-lesioned monkeys were 0.18 mg/kg (0.12–0.29 mg/kg) and 2.63 mg/kg (1.06–6.45 mg/kg), respectively. In rodent parkinsonian models, bromocriptine was more potent than ropinirole; however, in the nonhuman primate parkinsonian model, ropinirole was a more potent inhibitor of parkinsonian activity than bromocriptine. This study suggests that ropinirole is a dopamine D_2-like receptor agonistic drug of potential use in the treatment of Parkinson's disease. © 2000 Elsevier Science Inc.

Ropinirole Bromocriptine L-DOPA Parkinson's disease Ventromedial tegmentum Tremor Catalepsy Rats Mice Cynomolgus monkeys

PARKINSON'S disease is characterized by a relatively selective loss of neurons in the substantial nigra, and the subsequent severe reduction in transmitter dopamine released from these nerve endings and motor deficits, which become more severe with progression of the disease. The discovery of the role of dopamine neurons in motor function, along with the finding of pathological changes in patients and the subsequent success of the therapy with L-DOPA as an exogenous substitute for the missing dopamine in the basal ganglia, led to the development of many dopamine receptor stimulants for treatment of Parkinsonís disease. However, treatment with L-DOPA is complicated by loss of initial benefit after some years of continuous therapy. With long-term treatment of L-DOPA, most patients have either troublesome fluctuations, troublesome dyskinesia or there is a loss of efficacy (9). The key signs of Parkinson's disease are tremor, akinesia, rigidity, and postural instability. An electrical focal lesion in the brain, neurotoxin to dopaminergic neurons such as 6-hydroxydopamine (6-OHDA), cholinomimetic tremorogenic agents such as oxotremorine, and monoamine-depleting agents such as reserpine are applied to render animal parkinsonism (24). Bromocriptine is the most widely used ergot-derivative dopamine receptor agonist. 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 2-adrenoceptors (2,12, 20,26). To combat this loss of efficacy bromocriptine has been used in Parkinson's disease therapy, usually in combination with L-DOPA. Bromocriptine is the most widely used ergot-derivative dopamine receptor agonist. Brain dopamine receptors have been classified into D_1 and D_2 subtypes according to pharmacological, anatomical, and biochemical criteria. In this classification schema D_1 is the receptor associated with stimulation of adenylate cyclase, whereas D_2 defines receptors that

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are uncoupled or coupled to adenylate cyclase in an inhibitory way (13). 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 (8). It is reported that ropinirole specifically stimulates the D_2 receptors in both the CNS and peripheral system (6). The purpose of the present study was to conduct a pharmacological evaluation of the antiparkinsonian effect of ropinirole, a D_2-like receptor agonist, in the standard preclinical models of Parkinson's disease. Furthermore, this effect was compared to that of bromocriptine.

METHOD

Animals

Male mice and male rats that were 6 weeks of age (Charles River Japan, Inc.) were used. The animals were quarantined and acclimated for at least a 1-week period. Only animals that showed normal growth and body weight during this period were selected for use in this study. Animals were maintained in stainless steel cages (19.5 cm width, 32.5 cm depth, and 18.0 cm height) with ad lib access to food and water. The temperature and humidity of the laboratories were maintained at 22 ± 2°C and 50 ± 10%, respectively, with a 12-h automatic light cycle (0600–1800 h).

Male cynomolgus monkeys (*Macaca fascicularis*) that were 3–7 years old (SNBL) and weighed 4.1–5.5 kg were used. The animals were quarantined and acclimated for at least a 1-month period. Fifteen healthy male cynomolgus monkeys that showed normal growth and body weight during this period were selected for use in this study. Animals were housed individually in stainless steel cages (70 cm width, 68 cm depth, and 77 cm high). The temperature and humidity of the laboratories were maintained at 26 ± 2°C and 50 ± 10%, respectively, with a 12-h automatic light cycle (0600–1800 h).

This study was approved by the Animal Care and Use Committee of SNBL.

Effects on turning behavior in 6-OHDA–lesioned rats. Rats were lesioned by the method described by Ungerstedt (37). 6-OHDA was dissolved in 0.9% saline, and ascorbic acid (0.2 mg/ml) was added to prevent auto-oxidation. Animals were anesthetized by diethyl ether, and the head was fixed in a standard stereotaxic apparatus. Referring to the stereotaxic atlas of the rat brain as described by König and Klippel (17), a unilateral lesion was made by 6-OHDA on the right side of the substantia nigra (A: 2.4, L: 2.0, H: −2.4 mm). 6-OHDA (8 μg/4 μl), calculated as base, was injected unilaterally at an injection speed of 1 μl/min speed. Seven days after 6-OHDA treatment, rats were challenged with apomorphine (1 mg/kg, IP). Fifty rats, which displayed contralateral turning behavior, were used in the present study. Ten animals were selected for use in each group. If the same animals were used more than once in this study, they were allowed to recover for 6 days or more. This experiment finished until 28 days after 6-OHDA treatment. The direction of turning and the number of turns during 3 min were recorded at 0.5, 1, 2, 3, 4, and 5 h after administration.

Effects on catalepsy in reserpine-treated rats. Rats that had cataleptic reactions 17 h after an injection of reserpine (5 mg/kg, IP) were used. Ten animals were used in each group. The upper limbs of the animals were placed on a horizontal bar (2-mm diameter) 13 cm high at 0.5, 1, 2, 3, and 4 h after the ropinirole or bromocriptine injection, and the anticatalepsy effect was examined. The criterion of positive catalepsy response was determined to be showing a hold posture for over 30 s.

Effects on tremor in oxotremorine-treated mice. Ten mice were used in each group. Ropinirole, bromocriptine, L-DOPA, and atropine were administered to mice 30 min before an oxotremorine injection. The tremor was scored visually in individual animals at 10, 20, and 30 min after oxotremorine (0.5 mg/kg, IP) administration using a rating scale of 0 to 3, as described by Coward (5): 0 = no tremor; 1 = occasional isolated twitches; 2 = moderate or intermittent tremor associated with short periods of quiescence; 3 = pronounced continuous tremor.

Effects of tremor in VMT-lesioned cynomolgus monkeys. Fifteen monkeys were anesthetized by ketamine hydrochloride, and their heads were fixed into the standard stereotaxic apparatus. Referring to the stereotaxic atlas of the monkey brain of Szabo and Cowan (36), a unilateral lesion was made by electrocoagulation (3 mA, 30 s) on the right side of the VMT (A:1.6, L:6.0, H: −8.0 mm). Immediately after coagulation, ipsilateral dilated pupils and contralateral hypokinesia were observed. Two to three days after the operation, animals had a characteristic postural tremor of the contralateral upper and lower limbs. The animals were restrained in a monkey chair, and an evaluation of spontaneous tremors was performed after adaptation to the restraint. Tremors were scored according to the following rating scale (16): 0 = no tremor; 1 = the observer could not feel vibrations when handling the limbs of the animals, but upon close observation there was a small but visible continuous tremor; 2 = the observer felt slight vibrations and could easily observe small tremors; 3 = the observer felt obvious vibrations and could observe limb tremor. Three animals were used in each group. The tremors and vibrations were observed twice for 10 s, with a 30-s interval between each observation point. The average score from two examinations was taken, and animals with an average tremor score of over 2.0 were selected for this study. All animals selected underwent a 2-week postoperation recovery period. The observer also recorded the clinical signs including emetic behavior.

Following evaluation of the spontaneous tremor, the effect of the test drug was examined at 0.5, 1, 2, 3, and 4 h after administration. The tremor score after drug administration was expressed as a percentage of the pretreatment score. If the same animals were used more than once in this study, they were allowed to recover for 6 days or more.

Drugs and Solutions

Ropinirole hydrochloride was generously supplied by SmithKline Beecham Seiyaku K.K. (Tokyo, Japan); bromocriptine mesylate and L-DOPA were purchased from Sigma Chemical Co. (St. Louis, MO). Ropinirole was dissolved in 0.5% CMC (carboxymethylcellulose sodium) solution, and bromocriptine and L-DOPA were suspended in 0.5% CMC solution. Ropinirole, bromocriptine, and L-DOPA were administered orally to animals. The administration volume was 10 ml/kg for rats and mice, and 5 ml/kg for cynomolgus monkeys.

Apomorphine hydrochloride, reserpine, oxotremorine hydrobromide, and atropine sulfate were purchased from Sigma Chemical Co. (St. Louis, MO), and 6-hydroxydopamine (6-

OHDA) was purchased from Aldrich Chem. Co. (Milwaukee, WI). Apomorphine, reserpine, atropine, and oxotremorine were dissolved in 0.9% saline. 6-OHDA was dissolved in 0.9% saline solution containing 0.02% ascorbic acid.

Statistical Analysis

The data represent mean ± SD. The data were analyzed by the Kruskal–Wallis one-way ANOVA test followed by the Mann–Whitney *U*-test. The percentage incidence of turning behavior and catalepsy were analyzed by Fisher's exact direct probability test. A risk percentage of P values less than 0.05 was considered to be statistically significant. The ED_{50} and 95% confidence limits were calculated by the Probit method (10) using the number of animals with positive responses.

RESULTS

Effects on Turning Behavior in 6-OHDA–Lesioned Rats

6-OHDA–lesioned rats received apomorphine (1 mg/kg, IP) to induce contralateral turning behavior (45.2 ± 4.2 turns/3 min; $n = 50$). Ropinirole did not induce turning behavior at 5 mg/kg. At 10 mg/kg, turning behavior was noted in 3 of 10 animals 1 or 2 h after administration. With increasing doses of ropinirole, the frequency and duration of turning behavior increased. At 50 mg/kg, all animals showed turning and a peak in the turning behavior (43.5 ± 10.3 turns/3 min) was noted 1 h after administration. Statistically significant increases in the percentage incidence of animals showing contralateral rotation were observed at 30 to 50 mg/kg (Fig. 1). The ED_{50} of ropinirole was 20.17 mg/kg with 95% confidence limits from 14.27 to 26.88 mg/kg.

Bromocriptine did not induce turning behavior at 5 mg/kg, whereas, at 10 to 20 mg/kg, bromocriptine dose dependently induced contralateral turning behavior. Statistically significant increases in the percentage incidence of animal rotations were seen at 15 and 20 mg/kg (Fig. 1). The ED_{50} of bromocriptine was 11.99 mg/kg, with 95% confidence limits from 9.37 to 14.17 mg/kg.

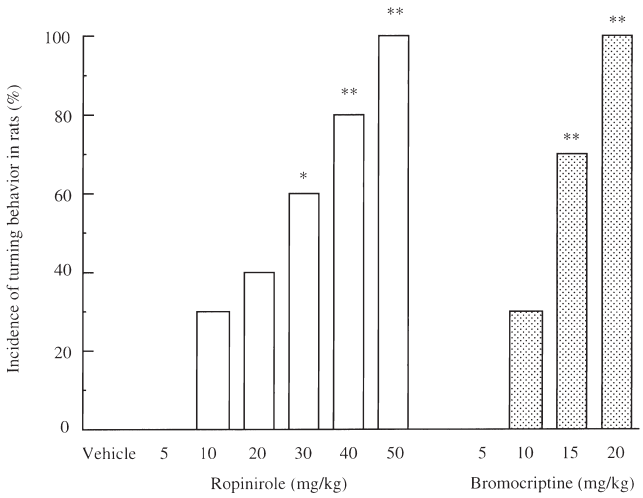

FIG. 1. Effects of ropinirole or bromocriptine on the turning behavior in rats unilaterally denervated with 6-OHDA. Seven days after 6-OHDA treatment, rats were challenged with apomorphine (1 mg/kg, IP). After the animals received apomorphine, contralateral turning behavior was induced (45.2 ± 4.2 turns/3 min). Ropinirole, bromocriptine, or the vehicle were administered orally from 14 days to 28 days after 6-OHDA treatment. The direction of turning and the number of turns in a 3-min period were recorded at 0.5, 1, 2, 3, 4, and 5 h after administration. Each bar represents the percentage incidence of turning behavior ($n = 10$). *$p < 0.05$, **$p < 0.01$ compared to vehicle-treated animals, Mann–Whitney *U*-test.

Effects on Catalepsy in Reserpine-Treated Rats

Ropinirole, at a dose level of 5 mg/kg, failed to suppress catalepsy. Compared with the vehicle group (all animals showed catalepsy), statistically significant decreases in the incidence of animals showing catalepsy occurred at 20 and 30 mg/kg (Fig. 2). The peak effects of ropinirole appeared approximately 30 min after administration, and the potency and duration of anticatalepsy action of ropinirole increased dose dependently. The ED_{50} of ropinirole was 18.55 mg/kg, with 95% confidence limits from 15.29 to 22.99 mg/kg.

Bromocriptine at a dose level of 5 mg/kg failed to suppress catalepsy. Compared with the vehicle, bromocriptine at doses of 15, 20, and 30 mg/kg significantly suppressed catalepsy (Fig. 2). The peak effects of bromocriptine appeared approximately 3 h after administration, and the potency and duration of the anticatalepsy action of bromocriptine increased dose dependently. The ED_{50} of bromocriptine was 12.56 mg/kg, with 95% confidence limits from 10.25 to 14.64 mg/kg.

Effects on Tremors in Oxotremorine-Treated Mice

Both ropinirole and bromocriptine, at a dose of 100 mg/kg, failed to suppress tremors in oxotremorine-treated mice. Atropine, however, dose dependently suppressed the tremors at 1 to 20 mg/kg, and statistical significance was noted at each dose level. L-DOPA, at 300 mg/kg, significantly suppressed the tremors (Fig. 3).

Effects on Tremors in VMT-Lesioned Cynomolgus Monkeys

In monkeys with VMT lesions, the vehicle did not influence the spontaneous tremor at all. Ropinirole, at a dose level of 0.05 mg/kg, failed to suppress the tremors. Compared with

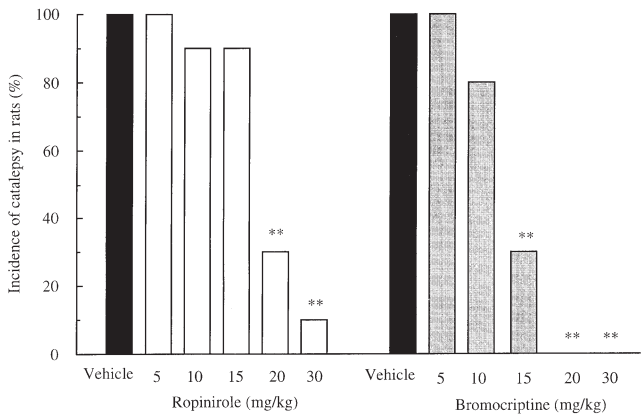

FIG. 2. Effects of ropinirole or bromocriptine on the reserpine-induced catalepsy in rats. All drugs or the vehicle were administered orally 17 h after an injection of reserpine (5 mg/kg, IP). The upper limbs of the animals were placed on a horizontal bar (2 mm diameter) 13 cm high at 0.5, 1, 2, 3, and 4 h after administration of the test drugs, and the anticatalepsy potency was examined. A positive catalepsy response was a hold posture of over 30 s. Each bar represents the percentage incidence of catalepsy ($n = 10$). **$p < 0.01$ compared to vehicle-treated animals, Mann–Whitney *U*-test.

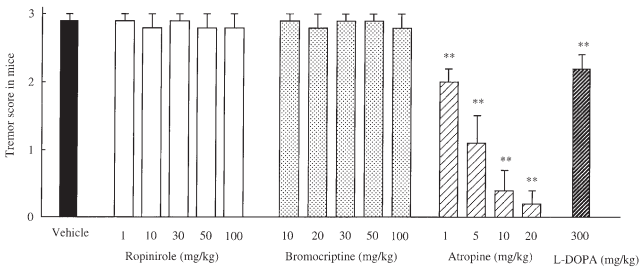

FIG. 3. Effects of ropinirole, bromocriptine, atropine, or L-DOPA on the oxotremorine induced tremor in mice. All drugs or the vehicle were administered orally to mice 30 min before an oxotremorine (0.5 mg/kg, IP) injection. The tremor was scored visually in individual animals at 10, 20, and 30 min following the oxotremorine administration using a rating scale of 0 to 3 (4). Each bar represents the mean ± SD ($n = 10$). $^{**}p < 0.01$ compared to vehicle-treated animals, Mann–Whitney *U*-test.

the vehicle control group (score = 100%), ropinirole at dose levels of 0.2 mg/kg (score = 61.1%) and 0.3 mg/kg (score = 24.4%) significantly suppressed the tremors 30 min after administration. The antitremor effect maintained for 60 min after administration, and the potency and duration of antitremor activity increased in a dose-dependent manner (Fig. 4). Bromocriptine (1–10 mg/kg) also dose dependently suppressed the tremors in VMT-lesioned monkeys, and the peak effects appeared about 60 or 120 min after administration (Fig. 4).

The tremor score was calculated using the minimum score (maximum suppressed score) from each animal during 4 h of observation. The ED_{50}s (95% confidence limits) of ropinirole and bromocriptine on the tremors in VMT-lesioned monkeys were 0.18 mg/kg (0.12–0.29 mg/kg) and 2.63 mg/kg (1.06–6.45 mg/kg), respectively. In general behavior observations, no abnormalities were noted in the ropinirole-treated animals, and

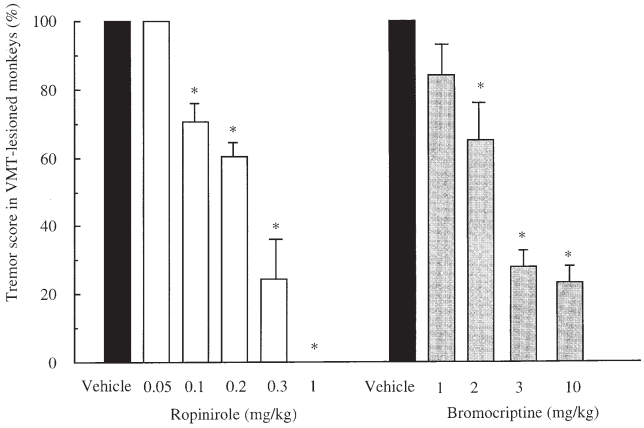

FIG. 4. Effects of ropinirole or bromocriptine on the tremor in VMT-lesioned monkeys. All drugs or the vehicle were administered orally. Tremors were judged by observation, and are represented as a percentage of the pretreatment value. Tremors were examined 0.5, 1, 2, 3, and 4 h after administration of the test drug, and the score was calculated using the lowest score of each animal during the 3-h observation period. Each point and bar represents the mean ± SD ($n = 3$). $^{*}p < 0.05$ compared to vehicle-treated animals, Mann–Whitney *U*-test.

antitremor doses of ropinirole did not induce oral movement, salivation, retching or vomiting; however, retching behavior was noted in the animals treated with 1 or 3 mg/kg of bromocriptine.

DISCUSSION

It is known that in patients with Parkinson's disease there is a marked deficiency in the dopaminergic innervation of the basal ganglia owing to degeneration of the neurons in the substantia nigra, resulting in parkinsonism, such as akinesia, rigidity, and tremor; and that dopamine receptor agonists are effective treatments for Parkinson's disease. Animal models with parkinsonian-like tremors can be produced by making an electrocoagulation in the unilateral VMT, or by treatment with MPTP, harmaline, or tremorine. Among these, the persistent resting tremor of the contralateral limbs of the VMT-lesioned monkey was reported to closely resemble those seen in patients with Parkinson's disease (25,30). As anti-Parkinson's disease drugs suppress these tremors in VMT-lesioned cynomolgus monkeys, the model can be used to evaluate the actions of the drugs for potential use in humans (11,23). Particularly, selective D_2 receptor stimulation exerts antitremor activity in this model (16). In this study, ropinirole at doses of 0.1 and 0.2 mg/kg significantly suppressed the tremors and the peak effects of ropinirole appeared about 30 min after administration. The potency and duration of the antitremor activity increased in a dose-dependent manner, and the ED_{50} value was 0.18 mg/kg. Bromocriptine also suppressed tremor in a dose-dependent manner, and the ED_{50} was 2.63 mg/kg. Ropinirole had approximately 14 times more potency than bromocriptine, and had a rapid onset of antitremor activity compared with bromocriptine.

The effects of ropinirole and bromocriptine on general behavior were quite different. Antitremor doses of ropinirole did not result in any observed abnormalities such as retching or vomiting in clinical signs, while bromocriptine induced emetic behavior when antitremor effects were observed. Emesis is induced by most dopamine receptor agonists, and is mediated by dopamine receptor sites located outside the blood–brain barrier in the postrema area. The emetic responses triggered by D_2 receptor stimulation may secondarily cause an increase of abdominal afferent vagal activity. Bromocriptine increased the 5-HIAA concentration in the ileum, and serotonin turnover (5-HIAA/5-HT) was increased the activities of tryptophan hydroxylase and monoamine oxidase in anesthetized rats (22). Conversely, ropinirole specifically stimulates the D_2 receptors in both the CNS and peripheral system, and showed little or no affinity for other receptor sites (6,8). In the present study, antitremor doses of ropinirole did not result in any observed abnormalities such as retching or vomiting in clinical signs, while bromocriptine-induced emetic behavior when antitremor effects were observed. One possible reason why ropinirole showed no emetic side effects in this model may be that it has less influence on serotonin-mediated responses than does bromocriptine with equipotent antiparkinsonian doses.

Ropinirole, even at 100 mg/kg, failed to suppress tremors in oxotremorine-treated mice. Oxotremorine is an extremely potent muscarinic receptor agonist, and its tremorogenic activity appears to be mediated primarily through central cholinergic stimulation (3,7). Previous findings have shown that tremors induced by oxotremorine are blocked by atropine and β-adrenergic blockers; however, dopamine agonists do not suppress the tremors (5,15). These results suggest that ropinirole has no effect on the muscarinic receptor.

Long-term treatment with a selective antagonist acting on D_1 or D_2 dopamine sites results in a specific upregulation of either class of dopamine receptors (19,21,31). In addition, behavioral studies also demonstrated that denervation supersensitivity develops in rat striatum after unilateral 6-OHDA lesion, as shown by the contralateral turning upon systemic administration of dopamine agonists (1,13,37). Drugs that release dopamine from neurons, such as amphetamine, can do so only on the intact side and cause ipsilateral turning. The induction of contralateral turning in this model is thought to be due to direct stimulation of denervated supersensitive dopamine receptors on the lesioned side (37). The induction of contralateral turning suggests that ropinirole is a direct dopamine agonist, and the potency was similar to bromocriptine. Reserpine-induced catalepsy, caused by the depletion of brain monoamine, can be blocked by dopamine agonists. Ropinirole and bromocriptine dose dependently suppressed the catalepsy induced by reserpine in mice, and its potency was similar for both drugs.

The ED_{50} of ropinirole on turning behavior in 6-OHDA–lesioned rats was 20.17 mg/kg, and its value on the catalepsy induced by reserpine was 18.55 mg/kg. Conversely, the ED_{50} on the tremors in VMT-lesioned monkeys was 0.18 mg/kg. It is unclear, but interesting, that ropinirole is a much more potent inhibitor of parkinsonian activity in the nonhuman primate model than in the rodents model. The metabolism profile of ropinirole is almost the same in rats and monkeys (32). The difference in the potency of antiparkinsonian activity, therefore, was not related to the metabolism profile of ropinirole. Recently, dopamine D_3, D_4, and D_5 receptors were cloned in addition to dopamine D_1 and D_2 receptors (34,35,38), 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 (33). Ropinirole is a nonergoline dopamine receptor agonist with a high affinity for native dopamine D_2-like receptors in human caudate tissue (8). 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 (4). 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 (14). 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 indicate that the D_3 receptor may be involved in motor function, and is a target for antiparkinsonian drugs. One possible reason why ropinirole showed a more potent inhibitor in the nonhuman primate parkinsonian model than the rodent parkinsonian models may be that the distribution of D_3 receptors in the brain of the primate is more widespread than in the rat.

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 with 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 (18). In this study, the antitremor activity of ropinirole was greater than that of bromocriptine in the VMT-lesioned cynomolgus monkey. Additionally, in MPTP-treated common marmosets, the potency of ropinirole on impaired locomotor activity and akinesia was greater than that of bromocriptine (Fukuzaki et al., in preparation). This suggests that the nonhuman parkinsonian model is superior to the rodent model in examining the potency of antiparkinsonian activity for dopamine agonists. 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 and in several nonhuman primate species after MPTP and L-DOPA treatments. 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 (27–29). This suggests that ropinirole is a drug of potential use in the treatment of Parkinson's disease.

In conclusion, ropinirole has shown antiparkinsonian activity in various animal parkinsonian models with the exception of the oxotremorine-induced tremor. The potency of ropinirole was less than that of bromocriptine in the nonprimate animal model, whereas, the antitremor activity of ropinirole was greater than that of bromocriptine in the VMT-lesioned cynomolgus monkey.

ACKNOWLEDGEMENTS

We wish to thank Dr. Go Kito and Mr. Adrian Boyle, Shin Nippon Biomedical Laboratories Ltd., for reading the manuscript.

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