In 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-Treated Primates, the Selective 5-Hydroxytryptamine 1a Agonist (R)-(+-)8-OHDPAT Inhibits Levodopa-Induced Dyskinesia but Only with Increased Motor Disability

Mahmoud M. Iravani, Kayhan Tayarani-Binazir, Wing B. Chu, Michael J. Jackson, and Peter Jenner
Neurodegenerative Disease Research Group, School of Health and Biomedical Sciences, King's College, London, United Kingdom

Received July 7, 2006; accepted September 5, 2006

ABSTRACT

5-Hydroxytryptamine 1a (5-HT1a) receptor agonists, such as sarizotan and tandospirone, are reported to reduce levodopa-induced dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated macaques and in Parkinson’s disease without worsening motor disability. However, these compounds are not specific for 5-HT1a receptors and also possess dopamine antagonist actions. We now report on the effects of (2R)(+-)8-hydroxy-2-(di-n-propylamino)tetralin [(R)(+-)8-OHDPAT], a selective 5-HT1a agonist lacking dopaminergic activity, on motor disability and dyskinesia (chorea and dystonia) in levodopa-primed MPTP-treated common marmosets. Administration of (R)(+-)8-OHDPAT (0.2, 0.6, and 2.0 mg/kg s.c.) in conjunction with levodopa/carbidopa (12.5 mg/kg each p.o.) to levodopa-primed animals, dose-dependently reduced levodopa-induced chorea but did not affect dystonic movements. However, (R)(+-)8-OHDPAT treatment also reduced locomotor activity and the reversal of motor disability. Administration of (R)(+-)8-OHDPAT alone had no effects of motor behaviors. The effects of (R)(+-)8-OHDPAT on levodopa-induced motor behaviors were antagonized by the 5-HT1a receptor antagonist N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyrindilcyclohexanecarbamide maleate (WAY-100635) (1.0 mg/kg s.c.). Administration of (R)(+-)8-OHDPAT (0.6 mg/kg s.c.) also reduced chorea produced by the administration of the D2/D3 dopamine receptor agonist pramipexole (0.06 mg/kg p.o.) to levodopa-primed MPTP-treated animals. However, again the increase in locomotor activity and reversal of motor disability produced by pramipexole were also inhibited. These data suggest that selective 5-HT1a agonists do not provide an effective means of suppressing levodopa-induced dyskinesia, except with worsening of parkinsonism.

Levodopa is the most effective drug for the symptomatic treatment of Parkinson’s disease (PD), because it reverses motor deficits to a greater extent than dopamine agonists, such as ropinirole and pramipexole (Schapira, 2005). However, prolonged levodopa use can lead to the development of dyskinesia in approximately 40% of PD patients (Ahlskog and Muenter, 2001), and these involuntary movements can become treatment-limiting (Brotchie, 2000). The current pharmacological treatment of troublesome dyskinesia involves either a reduction in dopaminergic medication, leading to a worsening of motor performance, or the use of the glutamate antagonist amantadine (Luginger et al., 2000; da Silva-Junior et al., 2005). However, only a number of patients can tolerate effective doses of amantadine, and its effects decline over time (Crosby et al., 2003). As a consequence, novel therapeutic approaches to the suppression of dyskinesia are being sought.

Recently, a variety of studies of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment in adult cynomolgus monkeys primed with levodopa to express dyskinesia and in patients with PD showing involuntary movements have suggested that drugs possessing 5-HT1a receptor agonist activity, such as clozapine, buspirone, tandospirone, sarizotan, and mirtazapine, reduce the duration and intensity of dyskinesia (Bonifati et al., 1994; Durrif et al., 1997; Durrif, 1999; Hadj Tahar et al., 2000; Bibbiani et al., 2001; Kannari et al.,

M.M.I. and K.B.-T. contributed equally to this work.

Article, publication date, and citation information can be found at http://jpet.aspetjournals.org.
doi:10.1124/jpet.106.110429.

ABBREVIATIONS: PD, Parkinson’s disease; 5-HT, 5-hydroxytryptamine (serotonin); 8-OHDPAT, 8-hydroxydipropylaminotetralin; (S)-(S)-8-OHDPAT, R,S-(+-)8-OHDPAT; (R)(+-)8-OHDPAT, (2R)(+-)8-hydroxy-2-(di-n-propylamino)tetralin; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; WAY-100635, N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyrindilcyclohexanecarbamide maleate; 6-OHDA, 6-hydroxydopamine.
Implement of vitamin D3 and had free access to water. On experimental daily on a diet of fresh fruit, nuts, Mazuri food pellets, and a sup-
either in pairs or individually at a temperature of 25
weighing between 350 and 430 g, were used. Marmosets were housed
using the selective 5-HT1a receptor antagonist WAY-100635
-suppressed is unclear. 
Animals

Materials and Methods

Animals

Adult common marmosets of either sex (Callithrix Jacchus; n = 6), weighing between 350 and 430 g, were used. Marmosets were housed either in pairs or individually at a temperature of 25 ± 1°C with 50% relative humidity on a 12-h light/dark cycle. Animals were fed once daily on a diet of fresh fruit, nuts, Mazuri food pellets, and a supplement of vitamin D3 and had free access to water. On experimental days, the animals were fed after completion of behavioral testing. Animals were previously treated with MPTP hydrochloride (2.0 mg/kg s.c., dissolved in 0.9% sterile saline; Sigma-Aldrich, Poole, Dorset, UK) daily for 5 consecutive days. These animals had previ-

Behavioral Assessment

Behavioral assessments including locomotor activity, motor dis-
ability, and dyskinesia were performed in activity cages equipped with an array of eight infrared photo sensors (Perspecx fronted al-
uminum cages, 50 × 60 × 70 cm), The number of beam interruptions due to movement was counted and summed in bins of 10-min inter-
vals using an analog-to-digital converter attached to an Intel-based compatible computer. Motor activity was measured over a period of 6 h and expressed both as the time course measuring the number of beam interruption occurring in 10-min time segments or as the total number of beam interruptions over the test period. Assessments of motor disability and dyskinesia were carried out using an observer rating scale as described previously (Irvani et al., 2003).

Pramipexole-Induced Locomotor Activity, Motor Disability, and Dyskinesia.

To determine the effects of 5-HT1a receptor activation on motor behaviors were mediated by 5-HT1a receptor activation, the selective 5-HT1a antagonist WAY-100635 (1 mg/kg s.c.; Sigma-Aldrich) was administered 30 min before the administration of an intermediate dose of (+)-8-OHDPAT (0.6 mg/kg) and levodopa.

The Effect of (+)-8-OHDPAT Alone and on Levodopa-Induced Locomotor Activity, Motor Disability, and Dyskinesia.

Eight weeks after MPTP treatment, animals were treated with 12.5 mg/kg levodopa methyl ester plus 12.5 mg/kg carbidopa by oral gavage on a daily basis (Irvani et al., 2003). Carbidopa was admin-
istered 30 to 45 min before levodopa treatment. When animals be-
came dyskinetic (between 28 and 56 days), daily administration of levodopa/carbidopa was changed to once a week. From this point on, subsequent once-a-week levodopa/carbidopa administration induced reproducible levels of dyskinesia identical to that produced at the end of the daily priming period.

Experimental Design

Drug Treatments. All doses used in this study were derived either from our previous studies in common marmosets (Irvani et al., 2003) or were obtained from preliminary studies in which adjustments were made to commonly used drug dose ranges in rats.

The Effect of (+)-8-OHDPAT Alone and on Levodopa-Induced Locomotor Activity, Motor Disability, and Dyskinesia. After an acclimatization period of 60 min in locomotor activity cages, the effect of oral administration of levodopa alone or together with subcutaneous dose of (+)-8-OHDPAT on motor activity and motor disability was examined for a period of 5 h. Subsequently, (+)-8-
OHDPAT (0.2, 0.6, and 2.0 mg/kg s.c.) was administered together with levodopa (12.5 mg/kg) plus the peripheral decarboxylase inhibit-
or carbidopa (12.5 mg/kg) by oral gavage. An equivalent volume of 10% sucrose solution was administered by oral gavage as levodopa/ carbidopa control. Likewise, an equivalent volume of saline was administered s.c. as 8-OHDPAT control. There was a washout period of 2 days between each experiment.

The Effect of WAY-100635 on (+)-8-OHDPAT Together with Levodopa. To examine whether the effects of (+)-8-OHDPAT on mo-
tor behaviors were mediated by 5-HT1a receptor activation, the selective 5-HT1a antagonist WAY-100635 (1.0 mg/kg s.c.; Sigma-Aldrich) was administered 30 min before the administration of an intermediate dose of (+)-8-OHDPAT (0.6 mg/kg) and levodopa.

The Effect of (+)-8-OHDPAT on Pramipexole-Induced Locomotor Activity, Motor Disability, and Dyskinesia. To deter-
mine the effects of 5-HT1a receptor activation on the direct stimula-
tion of dopamine D1/D3 receptors, we studied the effect of an intermediate dose of (+)-8-OHDPAT (0.6 mg/kg) (Tocris Cookson, Inc., Bristol, UK) on locomotor activity, motor disability, and dyskinesia evoked by a D1/D3 agonist, pramipexole (0.06 mg/kg p.o.). To avoid D2/D3 receptor-mediated vomiting response in common marmosets, pramipexole was administered 1 h after 1 mg/kg domperi-
done [4-(5-chloro-2-oxo-1-benzimidazolyl)-1-[3-(2-oxobenzimid-
azolyl)propyl]piperidine] pretreatment. In control experiments, an equivalent volume of saline was administered instead of (+)-8-OHDPAT.

Priming for Dyskinesia Induction

Adult common marmosets (Callithrix Jacchus; n = 6), weighing between 350 and 430 g, were used. Marmosets were housed either in pairs or individually at a temperature of 25 ± 1°C with 50% relative humidity on a 12-h light/dark cycle. Animals were fed once daily on a diet of fresh fruit, nuts, Mazuri food pellets, and a supplement of vitamin D3 and had free access to water. On experimental days, the animals were fed after completion of behavioral testing. Animals were previously treated with MPTP hydrochloride (2.0 mg/kg s.c., dissolved in 0.9% sterile saline; Sigma-Aldrich, Poole, Dorset, UK) daily for 5 consecutive days. These animals had previ-
ously been used for pharmacological studies but had received no drug treatment for approximately 2 months. Experiments were carried out in accordance with the “Animals (Scientific Procedures) Act 1986” and Home Office regulations (license number PPL 70/4986) and with local Ethical Committee approval.

The Effect of (+)-8-OHDPAT Alone and on Levodopa-Induced Locomotor Activity, Motor Disability, and Dyskinesia. After an acclimatization period of 60 min in locomotor activity cages, the effect of oral administration of levodopa alone or together with subcutaneous dose of (+)-8-OHDPAT on motor activity and motor disability was examined for a period of 5 h. Subsequently, (+)-8-
OHDPAT (0.2, 0.6, and 2.0 mg/kg s.c.) was administered together with levodopa (12.5 mg/kg) plus the peripheral decarboxylase inhibit-
or carbidopa (12.5 mg/kg) by oral gavage. An equivalent volume of 10% sucrose solution was administered by oral gavage as levodopa/ carbidopa control. Likewise, an equivalent volume of saline was administered s.c. as 8-OHDPAT control. There was a washout period of 2 days between each experiment.

The Effect of WAY-100635 on (+)-8-OHDPAT Together with Levodopa. To examine whether the effects of (+)-8-OHDPAT on mo-
tor behaviors were mediated by 5-HT1a receptor activation, the selective 5-HT1a antagonist WAY-100635 (1 mg/kg s.c.; Sigma-Aldrich) was administered 30 min before the administration of an intermediate dose of (+)-8-OHDPAT (0.6 mg/kg) and levodopa.

The Effect of (+)-8-OHDPAT on Pramipexole-Induced Locomotor Activity, Motor Disability, and Dyskinesia. To deter-
mine the effects of 5-HT1a receptor activation on the direct stimula-
tion of dopamine D1/D3 receptors, we studied the effect of an intermediate dose of (+)-8-OHDPAT (0.6 mg/kg) (Tocris Cookson, Inc., Bristol, UK) on locomotor activity, motor disability, and dyskinesia evoked by a D1/D3 agonist, pramipexole (0.06 mg/kg p.o.). To avoid D2/D3 receptor-mediated vomiting response in common marmosets, pramipexole was administered 1 h after 1 mg/kg domperi-
done [4-(5-chloro-2-oxo-1-benzimidazolyl)-1-[3-(2-oxobenzimid-
azolyl)propyl]piperidine] pretreatment. In control experiments, an equivalent volume of saline was administered instead of (+)-8-OHDPAT.

Behavioral Assessment

Behavioral assessments including locomotor activity, motor dis-
ability, and dyskinesia were performed in activity cages equipped with an array of eight infrared photo sensors (Perspecx fronted al-
uminum cages, 50 × 60 × 70 cm), The number of beam interruptions due to movement was counted and summed in bins of 10-min inter-
vals using an analog-to-digital converter attached to an Intel-based compatible computer. Motor activity was measured over a period of 6 h and expressed both as the time course measuring the number of beam interruption occurring in 10-min time segments or as the total number of beam interruptions over the test period. Assessments of motor disability and dyskinesia were carried out using an observer rating scale as described previously (Irvani et al., 2003).

On experimental days, motor disability (score 0 to 18) and dyski-
ness (score 0 to 4) was scored every 30 min for a period of up to 300 min. The motor disability scores and dyskinesia (chorea, score 0–4; and dystonia, score 0–4) were either presented graphically as time
course graphs or expressed as the mean total disability for each experimental day.

Data Analysis

Results are expressed as mean ± S.E.M. Data from motor activity was analyzed using a repeated measures one-way analysis of variance for comparison of the effect of different doses of (+)-8-OHDPAT with vehicle-treated controls at each time point. On obtaining a significant F-value, a Newman-Keuls multiple comparison test was performed. The nonparametric motor disability, chorea, and dystonia scores were compared using a Friedman’s test followed by Dunn’s multiple comparison test. When only two treatments were compared, a Wilcoxon matched pair test was used. All statistical analyses were performed using Prism version 4.0 software (GraphPad Software, Inc. San Diego, CA).

Results

Effect of Levodopa on Motor Behavior. Administration of levodopa plus carbidopa (both 12.5 mg/kg p.o.) increased locomotor activity for approximately 4 h with the peak effect occurring at 120 to 150 min after drug treatment (Fig. 1a). Levodopa administration also reduced motor dis-
ability (total motor disability scores/5 h: vehicle-treated, 150 ± 5; levodopa, 91 ± 5, p < 0.01; Fig. 1b). Levodopa administration produced marked dyskinesia, chorea, and dystonia, which was not present in vehicle-treated animals (total dyskinesia score/5 h: levodopa, 19.7 ± 3, p < 0.01).

Effect of (+)-8-OHDPAT Alone on Motor Behavior. Administration of (+)-8-OHDPAT (0.6 mg/kg s.c. + vehicle p.o.) had no significant effect on locomotor activity. Motor activity was similar to that observed after vehicle administration [locomotor counts: vehicle alone, 1172 ± 475, 6 h; 0.6 mg/kg s.c. (+)-8-OHDPAT, 1514 ± 319, 6 h, p > 0.05; Fig. 1e]. In contrast, treatment with (+)-8-OHDPAT increased the severity of motor disability, with immobility and sedation observed in the first hour after treatment [total motor disability score/5 h: vehicle alone, 150 ± 5; 0.6 mg/kg (+)-8-OHDPAT, 194 ± 6, p < 0.01; Fig. 1f]. Administration of (+)-8-OHDPAT produced an abnormal body posture consisting of elevated hindquarters and lowered head.

Effect of (+)-8-OHDPAT on Levodopa-Induced Motor Behavior. Administration of (+)-8-OHDPAT (0.2, 0.6, and 2.0 mg/kg) dose-dependently reduced levodopa-induced locomotor activity, although this was only significant at the highest dose of (+)-8-OHDPAT (2.0 mg/kg) used [levodopa alone, 8478 ± 1017, 6 h; 2.0 mg/kg levodopa + (+)-8-OHDPAT, 1776 ± 253, 6 h, p < 0.01; Fig. 2, a and b]. Activity was not significantly different from that observed in animals receiving vehicle treatment alone (vehicle 1172 ± 475, 6 h, p > 0.05). There was a dose-dependent shift of the peak motor response to the right (0.2 mg/kg: 240–270 min; 0.6 mg/kg: 300–360 min; and 2.0 mg/kg: no discernable peak response observed compared with vehicle-treated animals alone). The reduction of motor disability produced by levodopa administration was reversed dose-dependently by (+)-8-OHDPAT treatment. After administration of 0.2 and 0.6 mg/kg (+)-8-OHDPAT, motor disability was enhanced to a level not significantly different from that of vehicle treatment. (+)-8-OHDPAT (2.0 mg/kg) increased motor disability, and this was significantly greater than observed in vehicle-treated animals (total motor disability/5 h: vehicle, p < 0.01) [see Fig. 2, c and d] (total motor disability/5 h: levodopa alone, 1172 ± 475, 6 h; levodopa + 0.2 mg/kg (+)-8-OHDPAT, 130 ± 8, p < 0.01; levodopa + 0.6 mg/kg (+)-8-OHDPAT, 158 ± 5, p < 0.01; levodopa + 2.0 mg/kg (+)-8-OHDPAT, 205 ± 4, p < 0.01] (Fig. 2c). At a 2.0-mg/kg dose of (+)-8-OHDPAT, movement was generally confined to the cage floor, and some marmosets developed a characteristic elevated hindquarter and head-down posture. Overall, animals displayed poor alertness and slow or absent reactions.

All of the doses of (+)-8-OHDPAT resulted in decreased levodopa-induced dyskinesia (both dystonia and chorea; Fig. 3); however, this effect was statistically significant only at 0.6 mg/kg [total dyskinesia score/5 h: levodopa alone, 19.7 ± 3.7; levodopa + 0.2 mg/kg (+)-8-OHDPAT, 13.8 ± 2.1, p > 0.05; levodopa + 0.6 mg/kg (+)-8-OHDPAT, 8.17 ± 3.15, p < 0.05; and levodopa + 2.0 mg/kg (+)-8-OHDPAT, 18.2 ± 7.5, p < 0.05] (Fig. 2d). However, all of the doses of (+)-8-OHDPAT were found to significantly reduce chorea [Fig. 3, a and b; total chorea/5 h: levodopa alone, 20 ± 4; levodopa + 0.2 mg/kg (+)-8-OHDPAT, 9 ± 2; levodopa + 0.6 mg/kg (+)-8-OHDPAT, 4.2 ± 2; levodopa + 2.0 mg/kg (+)-8-OHDPAT, 2.3 ± 1.2]. At the highest dose used, (+)-8-OHDPAT had no significant effect on dystonia expression [Fig. 3, c and d; total dystonia/5 h: levodopa alone, 13 ± 5; levodopa + 0.2 mg/kg
Effect of Pramipexole on Motor Behavior.
Pramipexole (0.06 mg/kg p.o.) administration increased locomotor activity to a greater degree and for a longer duration than levodopa treatment. The pramipexole peak effects was reached later at approximately 120 to 150 min after administration (Fig. 4, a and b). Pramipexole induced a similar level of reversal of motor disability (Fig. 4, c and d) and expression of dyskinesia (Fig. 5; chorea and dystonia) as observed after levodopa administration.

Effect of (+)-8-OHDPAT on Pramipexole-Induced Motor Behaviors. Administration of (+)-8-OHDPAT (0.6 mg/kg) resulted in a marked reduction of the pramipexole-induced increase in motor activity (Fig. 6, a and b). In addition, (+)-8-OHDPAT treatment worsened motor disability [total motor disability/6 h: pramipexole, 78 ± 3 counts, pramipexole + (+)-8-OHDPAT, 149.5 ± 8, p < 0.01] (Fig. 4, c and d), such that it was more significant than in vehicle-treated animals. Treatment with (+)-8-OHDPAT reduced the pramipexole-induced dyskinesia expression (Fig. 5, e and f). However, when the effect of (+)-8-OHDPAT on dystonia and...
chorea components of dyskinesia was examined in isolation, a moderate but significant reduction of chorea was observed (Fig. 5, a and b), whereas this effect did not reach statistical significance in dystonia (Fig. 5, c and d).

**Effects of WAY-100635 on Motor Behavior.** Administration of WAY-100635 (1.0 mg/kg) with levodopa had no effect on motor activity or motor disability or dyskinesia. However, coadministration of WAY-100635 together with levodopa plus (+)-8-OHDPAT resulted in the return of dyskinesia to the level of levodopa alone (Fig. 6). The administration of WAY-100635 (1.0 mg/kg s.c.) fully blocked the effects of 0.6 mg/kg (+)-8-OHDPAT on levodopa-induced locomotor activity [total motor activity/6 h: levodopa alone, 8478 ± 101; levodopa + 0.6 mg/kg (+)-8-OHDPAT + 1 mg/kg WAY-100635, 6588 ± 1436, p > 0.05] (Fig. 6).

After WAY-100635 (1.0 mg/kg) pretreatment, the effects of 0.6 mg/kg (+)-8-OHDPAT on motor disability was reversed significantly to the level of levodopa + vehicle levels [total motor disability/5 h: 0.6 mg/kg (+)-8-OHDPAT, 158 ± 5; WAY-100635, 121 ± 5, p < 0.01, and from levodopa, 90.5 ± 5 total score for 5 h, to WAY-100635, 121 ± 5 total score for 5 h, p < 0.05].

WAY-100635 blocked the effect of (+)-8-OHDPAT on levodopa-induced dyskinesia (Fig. 7). Whereas the effect of (+)-8-OHDPAT on dystonia was not affected by WAY-100635 (Fig. 7, c and d), chorea intensity was restored to the level close to that of levodopa alone [total chorea/5 h: levodopa + vehicle, 20 ± 4; WAY-100635 + (+)-8-OHDPAT + levodopa, 12 ± 2.6 total score for 5 h, p > 0.05]. Reduction of chorea expression by (+)-8-OHDPAT was significantly reversed after WAY-100635 treatment [total chorea/5 h: levodopa + 0.6 mg/kg (+)-8-OHDPAT, 4.2 ± 1.9; 1 mg/kg WAY-100635 + 0.6 mg/kg + levodopa, 12 ± 2.6, p < 0.05] (Fig. 7, a and b).

**Discussion**

In this study, the more potent enantiomer of (+)-8-OHDPAT, R-(+)-8-OHDPAT was shown to dose-dependently reduce levodopa-induced dyskinesia in MPTP-treated levodopa-primed common marmosets but only at the expense of reduced motor activity and increased motor disability. The antidyskinetic effect of (+)-8-OHDPAT was most marked on chorea without being significantly effective in suppressing dystonia. During the study, an unusual behavioral effect of (+)-8-OHDPAT administration was noticed in which some animals developed abnormal body postures. At 2.0 mg/kg (+)-8-OHDPAT, marmosets would shuffle along the cage floor while adopting a characteristic hindquarter elevation.
and head-down posture, and although the marmosets were mobile, they were clearly not responsive to external stimuli and did not make any head-checking movements. In rodents, activation of 5-HT1A receptors can induce serotoninergic syndromes, such as flat body posture, reciprocal forepaw treading, and head weaving (Smith and Peroutka, 1986; Yamada et al., 1988; Hoyer et al., 2002). Previously, we also observed head-weaving movement in 3,4-methylenedioxymethamphetamine-treated marmosets (Iravani et al., 2003). It seems likely that the behavioral abnormalities observed following (+)-8-OHDPAT treatment reflect a facet of a serotoninergic syndrome, which may have contributed to the overall appearance of dystonia and its rating.

There have been previous reports of the ability of other 5-HT1A receptor agonists to inhibit levodopa-induced dyskinesia in MPTP-treated macaques and in PD (Bibbiani et al., 2001; Kannari et al., 2002; Olanow et al., 2004). Activation of 5-HT1A autoreceptors reduces the release of levodopa-derived dopamine in the striatum (Kannari et al., 2001; Yamato et al., 2001). Therefore, administration of (+)-8-OHDPAT (and other 5-HT1A agonists) may decrease dopaminergic activation of postsynaptic receptors resulting from exogenous levodopa administration. Indeed, the reduction in dyskinesia produced by (+)-8-OHDPAT was accompanied by an increase in motor deficits. Reduction of levodopa-induced locomotor activity by (+)-8-OHDPAT and its almost complete inhibition by the highest dose (2.0 mg/kg) suggest that 5-HT1A receptor activation prevents dopamine release. If so, then the reduction of motor activity and dyskinesia may both be due to a reduction of levodopa-derived dopamine activity. In contrast, Bibbiani et al. (2001) found that the 5-HT1A agonist sarizotan did not significantly increase parkinsonian symptoms or reduce the antiparkinsonian effect of levodopa in MPTP-treated monkeys, which is at odds with the findings of this study and also with the findings of a clinical study conducted by Kannari et al. (2002) using tandospirone. These authors showed that, although tandospirone was able to alleviate levodopa-induced dyskinesia, half of the 10 patients receiving this drug also experienced worsening of parkinsonian features. In a more recent study (Bara-Jimenez et al., 2005), it was shown that coadministration of Sarisotan with intravenous levodopa reduced levodopa-induced dyskinesia and prolonged its antiparkinsonian response.

There are reports that serotoninergic drugs can regulate the release of dopamine in the striatum (Guan and McBride, 1989; Wong et al., 1995; Sershen et al., 2000), although there are conflicting reports on exactly how the activation of 5-HT
receptors can lead to changes in striatal extracellular dopamine levels. 8-OHDPAT has been shown to selectively activate somatodendritic 5-HT$_{1A}$ autoreceptors in the dorsal raphe nucleus, inhibiting serotoninergic neuronal activity and thus reducing 5-HT release from the terminals (Hjorth and Magnusson, 1988; Gobert et al., 1995). This in turn can lead to the disinhibition of dopaminergic neurones and increase dopamine release in the striatum in nonlesioned rats (Dugast et al., 1998; Ng et al., 1999). Alternatively, 8-OHDPAT acting on 5-HT$_{1A}$ receptors can decrease dopamine release in the striatum (Santiago et al., 1998) by inhibiting tyrosine hydroxylation and thus reducing dopamine synthesis (Johnson et al., 1993). Therefore, the reason for (+)-8-OHDPAT worsening of motor disability may be a 5-HT$_{1A}$-mediated reduction in levodopa-derived dopamine release. However, this is unlikely because (+)-8-OHDPAT similarly affected the motor responses to a dopamine D$_2$/D$_3$ agonist, pramipexole. When tested against pramipexole, (+)-8-OHDPAT exerted a significant inhibitory effect on pramipexole-induced locomotor activity and motor disability. The fact that (+)-8-OHDPAT was able to alter motor responses to a postsynaptic dopamine receptor agonist indicates that inhibition of levodopa-derived dopamine release is not the sole mechanism of action of (+)-8-OHDPAT. Furthermore, based on the similarities between the effects of (+)-8-OHDPAT on levodopa and pramipexole and the blockade by WAY-100635, 5-HT$_{1A}$ receptor activation also is unlikely to be involved in any alterations to the metabolism of levodopa.

8-OHDPAT may be a partial dopamine receptor agonist (Ahlenius et al., 1990; Hajos-Korsos and Sharp, 1996; Matsuzewich et al., 1999); however, the possibility that (+)-8-OHDPAT might be acting as a dopamine receptor antagonist can also be discounted because the R-isomer of 8-OHDPAT, which shows little or no affinity for the dopamine receptors or partial agonism at 5-HT$_{1A}$ receptors, was used. A further possibility may be activation of 5-HT$_7$ receptors by 8-OHDPAT. These receptors are postsynaptic and can be found in several brain areas, although mainly in the thalamus, hypothalamus, and cortical areas, but modest densities have also been shown in the limbic system, substantia nigra, dorsal raphe nuclei, and the striatum (Vanhoenacker et al., 2000; Hoyer et al., 2002). Whether or not this extends to the antidysskinetic property of (+)-8-OHDPAT is unknown, because there is no selective 5-HT$_7$ receptor agonist currently available.

It is possible that (+)-8-OHDPAT may be acting on postsynaptic 5-HT$_{1A}$ receptors to inhibit striatal medium spiny projection neurons directly; however, the numbers of postsynaptic receptors in the striatum are reported to be low (Barnes and Sharp, 1999). However, in a recent study it has been proposed that the antidysskinetic property of sarizotan is probably due to inhibition of the corticostrital glutamatergic

![Fig. 6. Reversal of (+)-OHDPAT effects by WAY-100635. a to d, administration of 1 mg/kg WAY-100635 led to reversal of 8-OHDPAT-induced suppression of motor activity (a and b) and motor disability (c and d). Mean motor activity and motor disability response over the period of 5 h are shown in b and d, respectively. *p < 0.05, n = 6.](image-url)
transmission, which leads to reduction of GABAergic output to the basal ganglia (Antonelli et al., 2005). This study also suggests that, as well as being a potent 5-HT1a agonist, sarizotan may also be an agonist at dopamine D3 and D4 receptors and also act as a partial D2 agonist.

In conclusion, on the evidence of this study, (-)-8-OHDPAT lacks therapeutic potential in the treatment of levodopa-induced dyskinesia because, although (-)-8-OHDPAT is able to significantly reduce dyskinesia, it worsens motor disability and reduces locomotor activity. In addition, the induction of serotonergic behavioral syndromes and sedation/immobility, coupled with an unclear mechanism of action, are problems that remain inherent with its use.

Fig. 7. Reversal of (+)-8-OHDPAT effects on levodopa-induced increase in dyskinesia by WAY-100635. a to d, administration of WAY-100635 led to a marked reversal of (+)-8-OHDPAT-induced chorea suppression (a and b) but not dystonia (c and d). WAY-100635 only modestly but significantly reversed the antidyskinetic effects of (+)-8-OHDPAT (e and f). *P < 0.05, n = 6.

References