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European Journal of Pharmacology 389 (2000) 193–199

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Motor effects of (−)-OSU6162 in primates with unilateral 6-hydroxydopamine lesions

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Received 1 December 1999; accepted 7 December 1999

Abstract

The effects of the novel compound, (−)-OSU6162 ((*S*)-(−)-3-methylsulfonylphenyl-1-propylpiperidine), on rotational behavior induced by dopamine receptor agonists was investigated in common marmosets (*Callithrix jacchus*) with unilateral 6-hydroxydopamine lesions. (−)-OSU6162 per se displayed no effect on the animals' behavior. On the other hand, pretreatment with (−)-OSU6162 attenuated rotational behavior induced by apomorphine (apomorphini hydrochloridum), L-DOPA (3,4-dihydroxyphenylalanine), and the dopamine D2 receptor agonist, quinpirole (*trans*-(−)-4*aR*-4,4*a*,5,6,7,8,8*a*,9-octahydro-5-propyl-1*H*-pyrazolol[3,4-*g*]quinoline hydrochloride), without inducing motor impairment such as akinesia or dystonia. In addition, treatment with (−)-OSU6162 for 5 consecutive days almost completely abolished the rotational behavior provoked by apomorphine and produced a transient subsensitization of such apomorphine-induced effects after it was discontinued. Moreover, pretreatment with (−)-OSU6162 in two monkeys augmented the rotational behavior elicited by the dopamine D1 receptor agonists, SKF-81297 (*R*(+)-6-chloro-7,8,dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide) and A-77636 ((−)-(1*R*,3*S*)-3-adamantyl-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-1*H*-2-benzopyran hydrochloride). The findings indicate that (−)-OSU6162 can exert indirect state-dependent effects that differentially affect dopamine D1 and dopamine D2 receptor agonist-induced behavior.

Keywords: (−)-OSU6162; 6-Hydroxydopamine; Parkinson's disease; Dopamine receptor agonist; Dyskinesia

1. Introduction

It is well-established that degeneration of the nigrostriatal dopamine neuron system is the single most important factor in the underlying pathophysiology of Parkinson's disease (Kish et al., 1988). At the striatal level, dopamine D1 and D2 receptors are highly expressed (Sibley and Monsma, 1992; Strange, 1994) and are consequently the major targets for drugs used in the treatment of Parkinson's disease. To date, L-DOPA (3,4-dihydroxyphenylalanine), the precursor of dopamine, remains the most efficacious antiparkinsonian therapy; however, as the disease progresses, the treatment of chronic levodopa is frequently associated with the development of motor response complications such as L-DOPA-induced dyskinesias (Nutt, 1990). The duration of levodopa therapy and the severity of the disease both seem to be important contributing factors in the development of L-DOPA-induced dyskinesias (Horstink et al., 1990). Despite extensive research, the underlying pathophysiology remains elusive, although dopamine D2 receptor mechanisms have been suggested to be closely linked to this clinical phenomenon (Blanchet et al., 1995; Torstenson et al., 1997). Moreover, dopamine receptor supersensitivity is thought to develop after loss of endogenous dopamine and has been hypothesized to be a crucial factor in the induction of L-DOPA-induced dyskinesias. It has further been suggested that subsensitization of the dopamine D1 receptor occurs after prolonged levodopa therapy, leading to imbalanced dopamine D1/D2 receptor interactions (Engber et al., 1990; Britton et al., 1991; Blanchet et al., 1995).

(−)-OSU6162 ((*S*)-(−)-3-methylsulfonylphenyl-1-propylpiperidine) belongs to a new class of centrally acting compounds with stabilizing effects on dopaminergic systems in vivo (Sonesson et al., 1994, 1997; Tedroff et al., 1998). The mechanisms underlying this pharmacological profile are not completely understood but have been sug-

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0014-2999/00/$ - see front matter
PII: S0014-2999(99)00879-1

gested to involve preferential action on dopamine autoreceptors.

To further evaluate whether (−)-OSU6162 has any effect on postsynaptic dopamine D2 receptor function, we examined the effects of (−)-OSU6162 on the agonist-induced rotational behavior of dopamine receptors in the common marmoset (*Callithrix jacchus*) with 6-hydroxydopamine lesions. Using unilateral 6-hydroxydopamine-induced destruction of the nigrostriatal neurons that contain dopamine, a model of unilateral parkinsonism can be created (Annett et al., 1992). The resulting supersensitivity of dopamine receptor function is evaluated by the rotational behavior provoked by dopamine receptor agonists (Ungerstedt, 1971).

The present investigation presents the results from the first exploratory studies investigating the effects of (−)-OSU6162 in primates with experimental nigral lesions of the dopaminergic system. The study focuses on rotational behavior induced by dopamine receptor agonists and on changes after pretreatment with (−)-OSU6162.

2. Materials and methods

2.1. Animals

Ten common marmosets (four females and six males picked by random order for each experiment) weighing 270–450 g each were used in the study. Six were housed in pairs of two, and the other four were housed individually, all in a temperature-controlled (25 ± 1°C) and humidity-controlled (50% relative humidity) environment with a 12-h day–night cycle (the light was on from 6 a.m. to 6 p.m.). The marmosets received a fortified milk solution with bread in the morning and fresh fruit in the afternoon. The monkeys had free access to water at all times. The study was approved by the Animals Ethics Committee at Uppsala University.

2.2. 6-Hydroxydopamine lesions

The animals were placed in a Kopf stereotaxic instrument under ketamine at 80 mg/kg (Ketalar®, 50 mg/ml, Parke-Davis) and xylazine at 4.5 mg/kg (Rompur®, vet. 20 mg/ml, Bayer) anesthesia. Prior to induction of anesthesia, the animals were pretreated with desipramine (25 mg/kg, i.m.). Aseptic conditions were maintained during surgery. 6-hydroxydopamine HBr with ascorbic acid (Research Biochemicals, Natick, MA, USA) was dissolved in saline to a concentration of 4 mg/ml and intracerebrally injected into five sites of the nigrostriatal bundle using the same coordinates and method reported by Annett et al. (1992).

The experiments were started at least 16 months after the intracerebral injections. None of the animals had been given any drugs for at least 3 months before the present investigation. Two weeks before the start of the experiments, the animals were tested for responsiveness to apomorphine at a concentration of 0.2 mg/kg. Apomorphine HCl (Apomorphini hydrochloridum 1/2 AQ, Apoteksbolaget) was dissolved in sterile water up to a concentration of 0.15 mg/ml. The animals were put into individual aluminum observation cages (46.5 × 46.5 × 62 cm) with stainless steel grid doors (46.6 × 62 cm) and observed for 60 min after an injection of apomorphine at a concentration of 0.2 mg/kg subcutaneously (s.c.). Only animals showing more than 275 contralateral rotations every 60 min in response to apomorphine were used in subsequent tests.

2.3. Drugs

All drug solutions used in the study were prepared on the day of the experiment, and only one experiment was performed on each monkey per day.

2.3.1. Dopaminomimetics

Five milligrams of L-DOPA (Research Biochemicals) was dissolved in a 5% glucose solution to a concentration of 1.6 mg/ml and administered intraperitoneally (i.p.).

Apomorphine HCl (Apoteksbolaget) was dissolved in sterile water to a concentration of 0.15 mg/ml, and 0.2 mg/kg was administered s.c. for the experiments.

2.3.2. Dopamine D2 receptor agonist

Quinpirole (*trans*-(−)-4*aR*-4,4*a*,5,6,7,8,8*a*,9-octahydro-5-propyl-1*H*-pyrazolol[3,4-*g*]quinoline hydrochloride, Research Biochemicals) solution was made with acid water to a concentration of 1.5 mg/ml and kept stored at −80°C. This solution was dissolved with 0.9% saline on the day of the experiment to a concentration of 0.15 mg/ml. For the experiments, 0.15 mg/kg was given i.p.

2.3.3. Dopamine D1 receptor agonists

SKF-81297 (*R*(+)-6-chloro-7,8,dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide, Research Biochemicals) and A-77636 ((−)-(1*R*,3*S*)-3-adamantyl-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-1-*H*-2-benzopyran hydrochloride, Research Biochemicals) were both dissolved in 0.9% saline to concentrations of 0.3 mg/ml and 1.1 mg/ml, respectively. For the experiments, the animals received SKF-81297 at a concentration of 0.3 mg/kg, i.p., or A-77636 at a concentration of 1.1 mg/kg, s.c.

2.3.4. (−)-OSU6162

(−)-OSU6162 ((*S*)-(−)-3-methylsulfonylphenyl-1-propylpiperidine, Department of Pharmacology, Göteborg University, Sweden) was given at three different doses i.p. to each monkey. (−)-OSU6162 was prepared with 0.9% saline to the concentrations of 1 mg/ml (for 1 mg/kg dosing) and 2 mg/ml (for 3 and 10 mg/kg dosing) on the day of the experiment.

2.4. Drug treatments and behavioral assessments

On the day of the experiment, the animals were put in a separate observation cage that measured 62 × 46.5 × 46.5 cm and had stainless steel bars in the front. The other three sides and the roof were made out of metal sheets. An initial period of 10 min was permitted for habituation to the cage before drug dosing and observation. Baseline measurements were made for all dopaminomimetics administered in the study. After each drug was administered, ipsi- and contralateral turns were counted by visual inspection in 5-min periods for 60–120 min (60 min for apomorphine; 120 min for all other dopamine receptor agonists). Only full turns were counted. Ipsilateral turns were subtracted from the total number of contralateral turns.

2.5. Treatment protocols

Four different protocols were used to explore the efficacy of (−)-OSU6162.

2.5.1. Protocol 1

To investigate whether (−)-OSU6162 had any effect on rotational behavior when it was administered alone, all animals were pretreated with (−)-OSU6162 (1, 3, and 10 mg/kg) given 30 min before administration of 3.1 ml of 0.9% saline i.p. (same volume as the L-DOPA solution).

2.5.2. Protocol 2

To investigate the effect of (−)-OSU6162 on rotational behavior induced by apomorphine, L-DOPA, and quinpirole, (−)-OSU6162 was administered 30 min before the dopaminomimetics were administered in increasing doses of 1, 3, and 10 mg/kg. The results were compared to the baseline for each drug.

2.5.3. Protocol 3

The efficacy of different doses of (−)-OSU6162 on rotational behavior induced by dopamine D1 receptor agonists was assessed. For baseline measurements, the monkeys were observed after single daily injections of SKF-81297 or A-77636 for 4 consecutive days. Following these 4 consecutive days, the monkeys were again challenged with apomorphine and then allowed a resting period of at least 1 week. A similar protocol was then carried out but this time with pretreatment on days 2–4 with (−)-OSU6162 at three doses of 3, 1 or 10 mg/kg.

2.5.4. Protocol 4

The effect of repeated treatment with (−)-OSU6162 at a concentration of 10 mg/kg on apomorphine-induced rotational behavior was examined.

First, to evaluate the effect of chronic treatment with apomorphine per se, a baseline assessment including behavioral assessment for 6 consecutive days with single apomorphine injections was made. After this period, (−)-OSU6162 was co-administered with apomorphine and given s.c. for 5 consecutive days. This 5-day period was immediately followed by 3 days of single apomorphine injections to evaluate if repeated treatment with (−)-OSU6162 could induce any long-term effects on rotational behavior.

In all four protocols, evaluation of rotational behavior was performed as described above. At least 2 weeks were allowed between the protocols.

2.6. Statistical analysis

Data were analyzed using a one-way analysis of variance (ANOVA) with repeated measurements. The Fisher PLSD test was used for post-hoc testing. The accepted level of significance was $P < 0.05$.

3. Results

All dopaminergic agonists tested produced a marked stimulatory effect on contraversive rotational behavior in each monkey. This behavioral response was seen within 5–10 min after administration of all dopamine receptor agonists investigated, and maximum stimulation of rotational behavior occurred within the first hour after injection of drugs.

3.1. Effects of single injections of (−)-OSU6162 (Protocol 1)

Following injection of (−)-OSU6162 at doses of 1, 3 or 10 mg/kg, no effects on either gross behavior or contra- or ipsilateral turning behavior were noted upon visual inspection.

3.2. Effects of (−)-OSU6162 on rotational behavior induced by apomorphine, L-DOPA, and quinpirole (Protocol 2)

Administration of L-DOPA induced a marked stimulatory effect on rotational behavior. Following pretreatment with (−)-OSU6162, the onset of rotational behavior was delayed, and this behavior was attenuated during the 1-h observation period. This inhibition showed a clear dose–response association, with an ED_{50} occurring at approximately 3 mg/kg (Fig. 1). A similar dose–response-like relationship was also observed for quinpirole-induced rotational behavior after pretreatment with (−)-OSU6162 (Fig. 1). The ED_{50} for this effect was calculated to be 5 mg/kg. Following the highest doses of (−)-OSU6162, normal behavior, with symmetrical use of limbs and without signs of motor impairment or any other gross behavioral disturbances, was observed.

No significant dose-related effect was seen on apomorphine-induced rotational behavior after pretreatment with

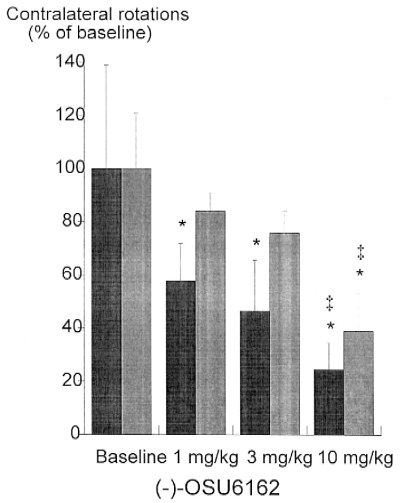

Fig. 1. Bar graph representing pooled data on rotational behavior induced by L-DOPA (5 mg) (gray bars) and by quinpirole (0.15 mg/kg) (hatched bars) at baseline and following pretreatment with (−)-OSU6162 at concentrations of 1, 3, and 10 mg/kg in common marmosets with unilateral 6-hydroxydopamine lesions. Values are means ± S.E.M. ($n = 5$; $^{*}P < 0.05$ versus baseline and $^{‡}P < 0.05$ versus 1.0 mg/kg (−)-OSU6162).

(−)-OSU6162. In three animals, (−)-OSU6162 produced a marked inhibitory effect that was similar to that seen with L-DOPA or quinpirole, and in the other two animals, (−)-OSU6162 pretreatment induced an increase in rotational behavior.

3.3. Effects of (−)-OSU6162 on rotational behavior induced by SKF-81297 and A-77636 (Protocol 3)

Only two out of five animals showed rotational behavior in response to SKF-81297 at the dose we used here. At higher doses, rotational behavior could be induced in all animals, but since the animals that responded to the lower dose had repeated seizures at the higher doses, we used the lower dose in this investigation in order to obtain the highest number of animals with a behavioral response without seizures.

The two monkeys that responded to SKF-81297 were observed after single daily injections of this drug for 4 consecutive days. The rotational behavior provoked by the compound rapidly decreased from the level seen on the first day (Fig. 2A). The responsiveness to SKF-81297 was regained after challenging the monkeys with apomorphine and allowing a period for recovery.

Pretreatment with (−)-OSU6162 induced a striking increase in rotational behavior and prevented the desensitization to the dopamine D1 receptor agonist, SKF-81297, seen at baseline. The effects of (−)-OSU6162 on these measures showed no obvious dose dependency.

Two monkeys that showed marked rotational behavior in response to A-77636 were used for the experiments with this compound. Similar to the results seen with SKF-81297, decreased rotational behavior was observed after repeated treatment with A-77636 (Fig. 2B). This effect was prevented by pretreatment with (−)-OSU6162 at a concentration of 3 mg/kg on the second day of A-776363 treatment; however, (−)-OSU6162 at concentrations of 1 or 10 mg/kg failed to augment rotational behavior on days 3 and 4.

It was not possible to initiate any rotational behavior with (−)-OSU6162 (1–10 mg/kg) in combination with SKF-81297 or A-77636 in monkeys that did not show any such response to these compounds at baseline (data not shown).

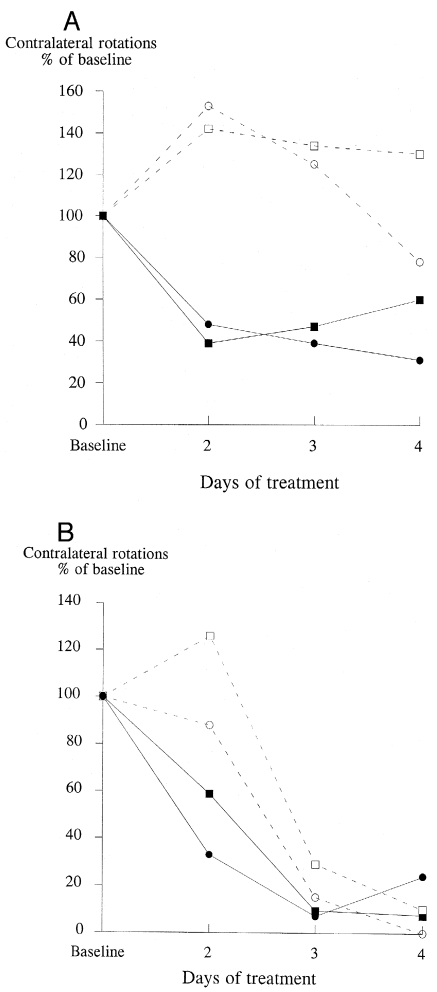

Fig. 2. (A) Graph of the mean changes in rotational behavior in two monkeys (squares illustrating monkey no. 1 and circles illustrating monkey no. 2) after treatment for 4 consecutive days with one daily dose of SKF-81297 (0.3 mg/kg) (filled symbols) and after pre-treatment with (−)-OSU6162 (open symbols) at three different doses: 3 mg/kg on day 2, 1 mg/kg on day 3, and 10 mg/kg on day 4. (B) Graph of the mean changes in rotational behavior in two monkeys (squares illustrating monkey no. 1 and circles illustrating monkey no. 2) after treatment for 4 consecutive days with one daily dose of A-77636 (1.1 mg/kg) (filled symbols) and after pre-treatment with (−)-OSU6162 (open symbols) at three different doses: 3 mg/kg on day 2, 1 mg/kg on day 3, and 10 mg/kg on day 4.

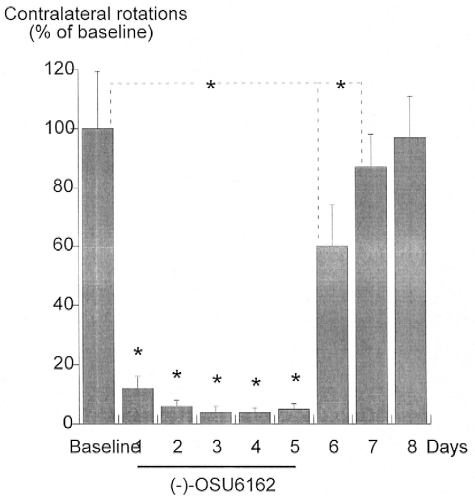

Fig. 3. The effect of 5 days of combined (−)-OSU6162 (10 mg/kg) and apomorphine (0.2 mg/kg) treatments (days 1–5) on rotational behavior. (−)-OSU6162 was administered concomitantly with apomorphine. The baseline value comprises the mean number of contralateral turns from each of 6 days of induction by repeated treatment with apomorphine + vehicle. Values are mean ± S.E.M. ($n = 3$; $^{*}P < 0.05$).

3.4. Effects of repeated treatment with (−)-OSU6162 (Protocol 4)

Three monkeys that had previously been shown to respond to (−)-OSU6162 with marked decreases in apomorphine-induced turning behavior were included in this protocol.

Six consecutive days of treatment with single injections of apomorphine did not significantly affect the magnitude of rotational behavior, but adding (−)-OSU6162 (10 mg/kg) treatment effectively decreased rotational behavior induced by apomorphine (Fig. 3). However, there were no clinical signs of impairment or parkinsonism, and in animals exhibiting complete inhibition of rotational behavior, clinical examination revealed normal motor function with symmetrical use of the limbs and without signs of motor impairment such as akinesia or dystonia. After (−)-OSU6162 treatment was discontinued, the number of contralateral rotations induced by apomorphine was lower than expected (as determined from test–retest variability at baseline) on the first day after discontinuation and then gradually returned to baseline levels during the next 2 days (Fig. 3).

4. Discussion

(−)-OSU6162 belongs to a new class of centrally acting dopaminergic compounds. Despite low binding affinity to dopamine D2 receptor in vitro, (−)-OSU6162 is highly active in vivo, both in the synthesis and turnover of dopamine and by inducing stabilizing effects on psychomotor function in behavioral tests, without inducing hypolocomotion or catalepsy (Sonesson et al., 1994; Sonesson, 1995). Such stabilizing properties have also been shown in positron emission tomography (PET) studies, where (−)-OSU6162 was shown to decrease the spread in L-[^{11}C]DOPA influx between primates through a presynaptic action without affecting the average value (Tedroff et al., 1998); thus, (−)-OSU6162 was first considered to act preferentially on presynaptic dopamine autoreceptors.

The present investigation was undertaken as a pilot investigation to assess the potential postjunctional effects of (−)-OSU6162. The pharmacological profile indicates that (−)-OSU6162 can differentially affect rotational behavior induced by dopamine D1 and D2 receptor agonists in marmosets with unilateral 6-hydroxydopamine lesions. (−)-OSU6162 by itself apparently did not affect motor function in the monkeys within the dose range tested. This is consistent with a previous finding in healthy common marmosets, where (−)-OSU6162 at a concentration of 3 mg/kg given once daily for 14 consecutive days produced no effects on locomotor activity (unpublished data). Despite the lack of behavioral effects per se, pretreatment with (−)-OSU6162 produced a dose-dependent decrease in rotational behavior induced by L-DOPA and quinpirole and a decrease in rotational behavior induced by apomorphine in three out of five animals. (−)-OSU6162 pretreatment also increased the rotational response induced by dopamine D1 receptor agonists.

However, recent data indicate profound postsynaptic effects by (−)-OSU6162 in PET studies as well as in behavioral studies in primates (Ekesbo et al., 1997; Neu et al., 1997). Furthermore, (−)-OSU6162 has been shown to induce differential effects on postsynaptic dopamine D1 and D2 receptor binding in PET studies in which (−)-OSU6162, given in doses yielding about 80% displacement of [^{11}C]raclopride, increased [^{11}C]SCH23390 binding in the striatum of rhesus monkeys (Ekesbo et al., 1999).

The manner in which (−)-OSU6162 affects rotational response to L-DOPA and quinpirole was found to be dose-dependent. After the highest dose of (−)-OSU6162 given in conjunction with L-DOPA, two animals showed normal motor function with symmetrical use of the limbs. This response is in agreement with previous behavioral studies in which (−)-OSU6162 attenuated L-DOPA-induced dyskinesias in parkinsonian monkeys without appreciably affecting the antiparkinsonian response (Ekesbo et al., 1997). In this respect, the pharmacological profile of (−)-OSU6162 differs considerably from those of the neuroleptics, which are more prone to induce cataleptogenic effects. This suggests that the mechanism of action involves receptor state-dependent effects at both pre- and postjunctional levels.

In contrast to the effect of (−)-OSU6162 on L-DOPA- and quinpirole-induced rotational behavior, where a dose-dependent decrease was evident in all animals, (−)-OSU6162 decreased apomorphine-induced rotational behavior in only three out of five animals. In the other two

animals, the rotational response was increased. It is known that L-DOPA activates both dopamine D1 and D2 receptor, as does apomorphine. It could be speculated that apomorphine was more potent in activating the dopamine D1 receptor in animals when the increased apomorphine-induced rotational response was induced by (−)-OSU6162 pretreatment.

In order to evaluate the effects of repeated dosing, animals were treated for 6 days with a combined apomorphine and (−)-OSU6162 treatment. (−)-OSU6162 at a concentration of 10 mg/kg given together with apomorphine was highly effective in attenuating rotational behavior. After (−)-OSU6162 treatment was discontinued, the apomorphine response was lower than expected from the baseline studies and then gradually returned to normal during the following days. Thus, (−)-OSU6162 could induce a transient subsensitization of apomorphine response following repeated treatment. This finding could not possibly be due to prolonged therapeutic plasma concentrations or active metabolites. Studies in rodents suggest that (−)-OSU6162 has a short plasma half-life, about 90 min, and no active metabolites and that a 24-h wash-out should be sufficient to rule out any possible interference from any drug remaining in the plasma (Waters et al., unpublished data). We speculate that (−)-OSU6162 might induce changes in striato-fugal neurons, which is reflected by the lowered response to single administrations of apomorphine. This is in agreement with recent observations in Huntington's disease patients, where single doses of (−)-OSU6162 produced a marked decrease in chorea that was considerably longer than expected from the drug half-life in plasma (Tedroff et al., 1999).

Repeated treatment with the dopamine D1 receptor agonists, SKF-81297 and A-77636, for 4 consecutive days resulted in a significant reduction in rotational response, which occurred as early as the second day of treatment with both drugs. Such dopamine D1 receptor agonist behavioral tolerance and desensitization has been well-documented in vivo and in vitro (Winkler et al., 1988; Britton et al., 1991; Lin et al., 1996). (−)-OSU6162 was highly effective in reversing this desensitization on the second day (3 mg/kg) with both drugs studied. However, (−)-OSU6162 failed to augment this decreased response to A-77636 on the third and fourth days (1 mg/kg and 10 mg/kg). The long activity of A-77636 (Kebabian et al., 1992) probably contributes to the weaker ability of (−)-OSU6162 to reverse desensitization since continued activation of the dopamine D1 receptor leads to inability of the receptor to recover its responsiveness (Lin et al., 1996). It is possible that (−)-OSU6162 (3 mg/kg) given on the second day would have prevented such behavioral tolerance to the compound, whereas the lower dose given on the third day (1 mg/kg) was ineffective.

The effects of (−)-OSU6162 seen on motor response to dopamine receptor agonists are not unique. Antagonists of *N*-methyl-D-aspartate (NMDA) receptors, such as MK-801, have also been shown to accentuate dopamine D1 receptor responses and to attenuate dopamine D2 receptor responses (Starr, 1995). The finding that (−)-OSU6162, which lacks binding affinity for the dopamine D1 receptor, can have a similar pharmacological profile presumably demonstrates the close interplay between NMDA- and dopamine-mediated effects in striato-fugal projections and that it is possible to target such mechanisms in different ways.

In summary, the present investigation demonstrates that (−)-OSU6162 can differentially affect dopamine receptor agonist-induced rotational behavior in marmosets with unilateral 6-hydroxydopamine lesions. Despite negligible behavioral effects when administered alone, (−)-OSU6162 is able to modify dopaminergic neurotransmission. The trend towards an augmentation of dopamine D1 receptor-mediated responses and the attenuation of dopamine D2 receptor-mediated responses is in agreement with PET investigations on non-human primates. The pharmacological profile suggests that (−)-OSU6162 treatment has potential as an adjunct to L-DOPA treatment in advanced Parkinson's disease, as well as in a variety of disorders for which an underlying instability of the dopaminergic system can be assumed.

Acknowledgements

This study was supported by grants from the NHR Foundation and the Tricentennial Fund of the Bank of Sweden.

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