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Effects of acute and repeated treatment with a novel dopamine D_2 receptor ligand on L-DOPA-induced dyskinesias in MPTP monkeys

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Abstract

(*S*)-(−)-3-(3-(methylsulfonyl)phenyl)-1-propylpiperidine ((−)-OSU6162) is a phenylpiperidine derivative which exhibits low affinity to the dopamine D_2 receptor in vitro. However, in vivo, positron emission tomography scanning studies show that the compound displaces the selective dopamine D_2 receptor antagonist, raclopride. We have evaluated, in this study, the effect of (−)-OSU6162, on L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesias in a primate model of Parkinson's disease. Five 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated cynomolgus monkeys with a stable parkinsonian syndrome and reproducible dyskinesias to L-DOPA were used in this study. The monkeys were housed in observation cages equipped with an electronic motility monitoring system. They were injected subcutaneously (s.c.) with L-DOPA methyl ester (125 mg per animal) plus benserazide (50 mg per animal; L-DOPA/benserazide) alone or in combination with (−)-OSU6162 (1.0, 3.0, 6.0 or 10 mg/kg, s.c.). Subcutaneous injection of sterile saline was used as control. L-DOPA/benserazide increased locomotion and improved parkinsonism but also induced dyskinesias. Co-administration of (−)-OSU6162 with L-DOPA/benserazide produced a significant reduction in L-DOPA-induced dyskinesias. This improvement in L-DOPA-induced dyskinesias occurred mainly at the onset of the L-DOPA/benserazide effect as reflected by an increase in the duration of the "ON" state without dyskinesias up to 3.4 fold after (−)-OSU6162 co-administration as compared to L-DOPA/benserazide alone. The anti-dyskinetic effect of (−)-OSU6162 was maintained during 14 days and no tolerance to this effect was observed. Our data suggests that (−)-OSU6162 could be of significant clinical value to reduce L-DOPA-induced dyskinesias in fluctuating advanced Parkinson's disease patients.

Keywords: Parkinson's disease; L-DOPA; Dyskinesias; MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine); (−)-OSU6162; Dopamine D_2 receptor

1. Introduction

Abnormal involuntary movements (dyskinesias) are the most common side effect of anti-parkinsonian treatments including both L-3,4-dihydroxyphenylalanine (L-DOPA) and to a lesser extent direct acting dopamine receptor agonists. In addition, the dyskinesias are extremely difficult to control (Marsden, 1994). Peak-dose dyskinesias, the most frequent type, occur typically when anti-parkinsonian relief is maximal and L-DOPA plasma levels are high or above a critical threshold (Muenter et al., 1977). Thus, far, evidence from both clinical observations and experimental studies of L-DOPA-induced dyskinesias suggest that chronic exogenous exposure to dopaminergic drugs, mainly when given intermittently, and a severe dopamine depletion resulting from nigrostriatal denervation are crucial factors (Crossman, 1990). Furthermore, the presence of anatomically intact striatal neurons is also required for the dyskinetic process (Blanchet et al., 1995c). In fact, functional postsynaptic alterations, i.e. altered signal transduction mechanisms in striatal medium-sized neurons, was postulated to underlie L-DOPA-induced dyskinesias (Verhagen Metman et al., 1997).

The exact mechanism by which L-DOPA-induced dyskinesias develop is not clearly understood and there is a pressing need for research in an animal model of Parkin-

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son's disease displaying typical L-DOPA-induced dyskinesias. Dopamine receptor supersensitivity is thought to be one of the major contributing factors for the development of L-DOPA-induced dyskinesias, and dopamine D_1 receptor-mediated mechanisms have traditionally been linked primarily to this phenomenon (Blanchet et al., 1994). However, experimental studies using dopamine D_1 receptor-selective agonists have shown that these drugs have a less dyskinesiogenic potential than L-DOPA or dopamine D_2 receptor-selective agonists (Blanchet et al., 1993; Grondin et al., 1997). On the other hand, dopamine D_2 receptor mechanisms have also been implicated, including the idea that long-term exposure of the dopamine-depleted putamen to exogenous dopaminergic agents causes (either directly or indirectly) a preferential shift in favor of the striatopallidal pathway (inhibition of the dopaminergic effect) the cell bodies of which bear mainly dopamine D_2 receptors (Crossman, 1990). In studies using positron emission tomography (PET), it has been also demonstrated that the progression of Parkinson's disease is probably associated with a similar shift (increase) in the efficacy of dopamine D_2 receptor-mediated mechanisms (Tedroff et al., 1996; Torstenson et al., 1997). Such a shift causes extensive disinhibition of lateral pallidal neurons, which become overactive and depress the subthalamic nucleus resulting in an excessive inhibition of the output nuclei of the basal ganglia. As a consequence of the disinhibition of the thalamus, the motor cortex is overstimulated leading to dyskinesias.

(−)-OSU6162 is a substituted (*S*)-3-phenylpiperidine derivative ((*S*)-(−)-3-(3-(methylsulfonyl)phenyl)-1-propylpiperidine) which exhibits low affinity binding to the dopamine D_2 receptor in vitro (Sonesson et al., 1994). Nevertheless, in a recent in vivo PET investigation, (−)-OSU6162 was shown to dose-dependently displace [^{11}C]raclopride (dopamine D_2 receptor antagonist) binding from the striatum by approximately 80% (Ekesbo et al., 1999; Neu et al., 1997). Furthermore, (−)-OSU6162 increased [^{11}C]R(+)-7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydroxy-1*H*-3-benzazepine maleate, (SCH-23390, dopamine D_1 receptor antagonist) binding, which may indicate a potentiating effect on dopamine D_1 receptor mediated functions (Ekesbo et al., 1999, 2000). Using PET scanning and L-[^{11}C]DOPA, Tedroff et al. (1998) have investigated some of the effects of (−)-OSU6162 on central dopaminergic function in anaesthetized female rhesus monkeys. (−)-OSU6162 displayed a dopaminergic tone-dependent effect with a reduction in the striatal L-[^{11}C]DOPA influx rate in monkeys with high baseline values and an increased striatal L-[^{11}C]DOPA influx rate in animals with low baseline values. In behavioral tests, the compound exhibits a unique normalizing profile on psychomotor activity by exerting a combination of stimulatory and inhibitory effects (Sonesson et al., 1994). Indeed, in addition to its low cataleptogenic potential, (−)-OSU6162 attenuates L-DOPA- and quinpirole (dopamine D_2 receptor agonist)-induced contraversive circling behavior in unilaterally 6-hydroxydopamine-lesioned common marmosets and increases such behavior induced by a dopamine D_1 receptor agonist (Ekesbo et al., 2000; Tedroff et al., 1997). This unique pharmacological profile suggests that (−)-OSU6162 belongs to a new class of functional modulators of dopaminergic systems, having psychomotor state-dependent normalizing properties on D_2 dopaminergic tone (Tedroff et al., 1998; Sonesson, 1995; Sonesson et al., 1997).

The aim of the present study was to evaluate the effects of (−)-OSU6162 on the anti-parkinsonian response and dyskinesias produced by L-DOPA/benserazide in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated cynomolgus monkeys.

2. Materials and methods

2.1. Animals and pretreatments

The experiments were performed on five (acute study) to six (chronic study) adult female cynomolgus (*Macaca fascicularis*) monkeys weighing 3.3–4.3 kg in accordance with the standards of the Canadian Council on Animal Care. The animals were housed separately in observation cages in a temperature-controlled room and exposed to a 12-h light/dark cycle (lights on 6 a.m.–6 p.m.). They were fed once daily in the afternoon and water was provided ad libitum. All animals were exposed to the neurotoxin MPTP (Sigma-Aldrich Canada, Oakville, Ontario) dissolved in sterile water and injected subcutaneously (s.c.) at weekly intervals (2–3 mg/injection) until sustained parkinsonian features with action tremor appeared. The cumulative dose and the time necessary to achieve this goal varied between 9–23.5 mg and 4–32 weeks, respectively. Animals were scored on a regular basis using a disability scale described below, where the normal state extends from 0 to 2 and maximal disability is 16 points. Once a bilateral parkinsonian syndrome had stabilized (i.e. unchanged disability score of 8 or more over several weeks), monkeys began chronic daily oral treatment with L-DOPA/benserazide (100/25 mg; Prolopa®) (Hoffmann-La Roche, Mississauga, Ontario) to induce dyskinesias. All monkeys developed dyskinesias of a predominantly choreic nature within a few months which were thereafter reproducible to subsequent doses of L-DOPA/benserazide or dopamine receptors agonists. At that point, they were put on a maintenance oral dose of L-DOPA/benserazide administered two or three times a week to maintain priming.

2.2. Experimental treatments

During the acute study, L-DOPA methyl ester (L-DOPA; 125 mg per animal, Sigma, St-Louis, MO) was dissolved

in 0.9% sterile saline (1 ml) and administered s.c.-together with benserazide (50 mg, s.c., Hoffmann-La Roche, Montréal, Québec; L-DOPA/benserazide 125/50 mg). (−)-OSU6162 (Pharmacia and Upjohn, Kalamazoo, MI) was dissolved in 0.9% sterile saline and administered s.c., on separate days, at increasing doses: 1, 3, 6 or 10 mg/kg in combination with L-DOPA/benserazide at the doses indicated above. (−)-OSU6162 was also administered alone at the dose of 6 mg/kg. Subcutaneous injection of sterile saline was used as control. During the experiments, drugs were injected in the morning and the spontaneous behavior of the animals was observed for 4 h (during the ON state) until the effects of a given drug disappeared.

For the repeated treatment, (−)-OSU6162 (3 mg/kg) was co-administered with L-DOPA/benserazide (125/50 mg per animal) for 14 consecutive days (drug injection once per day). Two days before the start of the chronic study, the animals were administered a placebo treatment as control. A single injection of L-DOPA/benserazide (100/25 mg) was administered alone for comparison the day preceding the onset of the protocol (day 0).

2.3. Evaluation of the response

2.3.1. Parkinsonian syndrome

The parkinsonism following MPTP exposure and its relief following the administration of L-DOPA/benserazide alone or in combination with (−)-OSU6162 were rated, for a maximal disability score of 16 in the following way: (a) Posture: normal = 0, flexed intermittent = 1, flexed constant = 2, crouched = 3; (b) Mobility: normal = 0, mild reduction = 1, moderate reduction = 2, severe reduction = 3; (c) Climbing: present = 0, absent = 1; d) Gait: normal = 0, slow = 1, very slow = 2, very slow with freezing = 3; (e) Grooming: present = 0, absent = 1; (f) Vocalization: present = 0, absent = 1; g) Social interaction: present = 0, absent = 1; h) Tremor: absent = 0, mild action tremor = 1, moderate action tremor = 2, resting tremor = 3. A score was given every 30 min reflecting observations of the preceding half-hour.

2.3.2. The severity of dyskinesias

The severity of dyskinesias was rated, by two experienced observers (A.H.T., E.B.), every 30 min for the face, neck, trunk, arms and legs in the following way: None = 0; Mild = 1; Moderate = 2; Severe = 3. The difference between mild, moderate, and severe dyskinesias for a given body segment is based on the assessment of the amplitude of the abnormal movements and the frequency (whether they are occasional, intermittent or constant); each body segment being scored separately based on assessment of observation in the preceding 30 mn. The dyskinetic score obtained was the sum of the scores for all body segments for a maximal score of 21 points. Stereotypies or licking were not considered as dyskinesias.

2.3.3. Locomotor activity

Locomotion of all monkeys was monitored using an electronic motility monitoring system fixed on each cage (Datascience, St. Paul, MN). Signals were accumulated by a computer that provided a mobility count every 5 min.

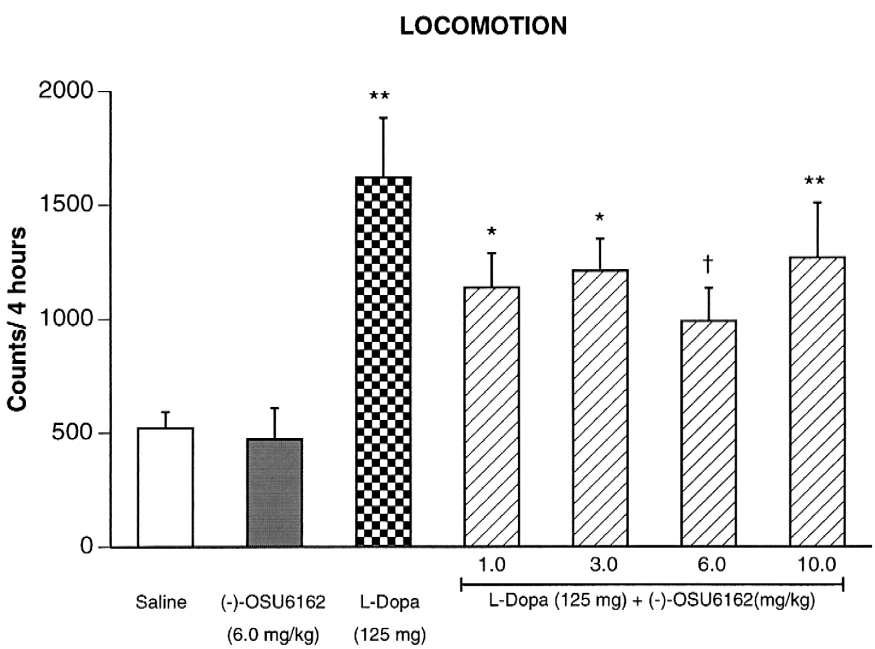

Fig. 1. The total mobility counts recorded individually during 4 h following a given treatment were averaged for all monkeys and compared using an analysis of variance (ANOVA) for repeated measures followed by a Fisher's PLSD test. Counts ± S.E.M. ($^{*}P < 0.05$ and $^{**}P < 0.01$ vs. saline; †$P < 0.05$ vs L-DOPA).

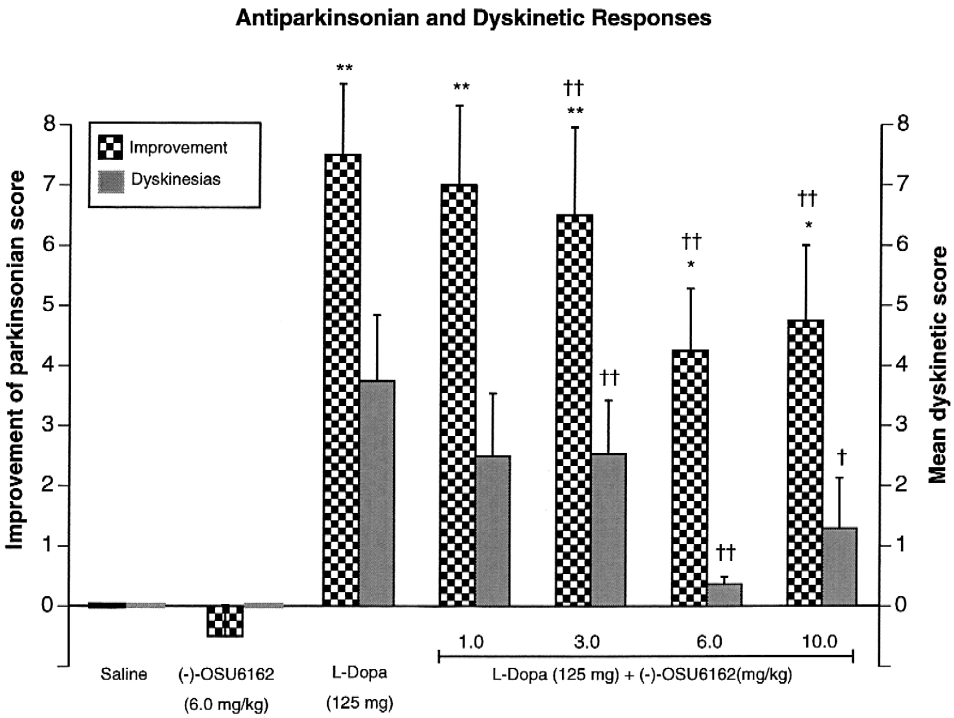

Fig. 2. Anti-parkinsonian and dyskinetic response after acute treatment with a given drug. The improvement in parkinsonian scores and the mean dyskinetic scores, respectively, obtained every 30 min. during an observed effect were averaged for each monkey. These averaged scores were then pooled for all monkeys and compared using the non-parametric Friedman's test. In cases where no behavioral effect was seen (as for saline injections), the scores obtained during a comparable interval of time were considered. Improvement in parkinsonian scores ± S.E.M. ($^{*}P < 0.05$ and $^{**}P < 0.01$ vs saline; ††$P < 0.01$ vs L-DOPA). Dyskinetic scores ± S.E.M. (†$P < 0.05$ and ††$P < 0.01$ vs L-DOPA).

2.4. Statistical analysis

The total mobility counts recorded individually during a 4 h period following a given treatment were averaged for all monkeys and compared using an analysis of variance (ANOVA) for repeated measures followed by a Fisher's LSD test (least significant differences). The mean parkinsonian scores and the mean dyskinetic scores obtained during each observation interval were averaged for all monkeys. These averaged scores were compared using a nonparametric Friedman's test.

3. Results

3.1. Locomotion

L-DOPA/benserazide produced an improvement in motor activity as indicated by the mobility counts which increased significantly as compared to the baseline level (saline treatment, Fig. 1). In contrast, (−)-OSU6162 administered alone at 6 mg/kg had no statistically significant effect on motor activity, as compared to the baseline value (Fig. 1).

Fig. 1 also shows that after co-administration of L-DOPA/benserazide with (−)-OSU6162 there was a significant stimulatory effect on locomotion when compared to saline treated animals, although the activity was slightly decreased as compared to L-DOPA/benserazide given alone. Nevertheless, at the dose of 6.0 mg/kg, (−)-OSU6162 reduced the L-DOPA-increase in locomotion.

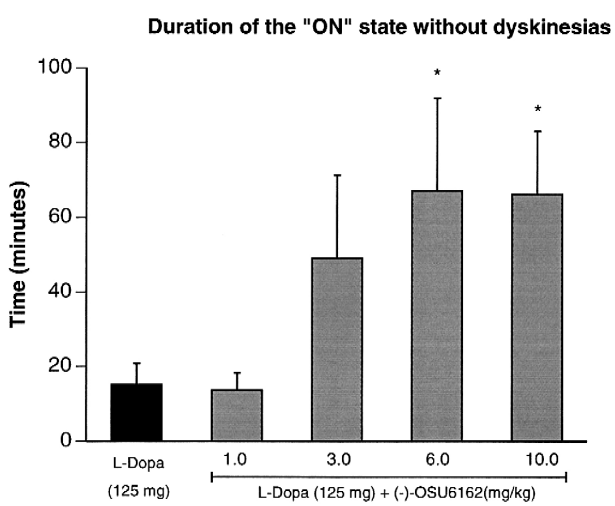

Fig. 3. Duration of the "ON" state without dyskinesias obtained individually following L-DOPA alone or in co-administration with (−)-OSU6162 were averaged for all monkeys and compared using an analysis of variance (ANOVA) for repeated measures followed by a Fisher's PLSD test. Duration ± S.E.M. ($^{*}P < 0.05$ vs L-DOPA).

Table 1
Delay before and duration of L-DOPA response with and without (−)-OSU6162

	Delay (min.) ± S.E.M.	Duration (min) ± S.E.M.
L-DOPA (125 mg)	14.00 ± 2.09	176.00 ± 7.29
L-DOPA + OSU (1.0 mg/kg)	35.00 ± 3.54[a]	163.75 ± 6.12
L-DOPA + OSU (3.0 mg/kg)	40.00 ± 7.18[a]	156.25 ± 10.77[b]
L-DOPA + OSU (6.0 mg/kg)	47.00 ± 6.00[a]	129.25 ± 4.61[a]
L-DOPA + OSU (10.0 mg/kg)	67.00 ± 3.67[a]	131.25 ± 4.00[a]

Delay before and total duration of L-DOPA response. The delay before and the duration of the on-state obtained individually following a given treatment were averaged for all monkeys and compared using an analysis of variance (ANOVA) followed by a Fisher's PLSD test. Delays ± S.E.M. and duration ± S.E.M.

[a] $P < 0.01$ vs. L-DOPA.

[b] $P < 0.05$ vs. L-DOPA.

3.2. Anti-parkinsonian and dyskinetic response

Fig. 2 illustrates the results of the improvements in parkinsonian score and the mean dyskinetic response for each drug treatment. The MPTP-treated primates used in this study presented a stable parkinsonian syndrome with an average baseline score of 11.6. The improvement was defined as the difference between the baseline score (parkinsonian score under saline) and parkinsonian score under a given treatment.

Administration of L-DOPA/benserazide improved the parkinsonism significantly as compared to the control (saline) (Fig. 2). On the other hand, s.c. injection of (−)-OSU6162 (alone at 6 mg/kg) had no significant effect on parkinsonism (Fig. 2). Co-administration of (−)-OSU6162 with L-DOPA/benserazide tended to decrease the improvement in parkinsonism but there was still a clear cut anti-parkinsonian effect when compared to control (Fig. 2).

L-DOPA/benserazide administered alone induced dyskinesias (Fig. 2). Dyskinesias were mainly choreic (quick and unpredictable involuntary movements) in nature but dystonia (slower twisting movement of a body segment) was also observed. These dyskinetic movements were seen mainly in low and upper limbs, some times in the neck or trunk and very rare in the face. Stereotypies, hypermobility, or licking were not considered as dyskinesias. The co-administration of (−)-OSU6162 with L-DOPA/benserazide was followed by a decrease in dyskinesias (mean dyskinetic scores; Fig. 2). The inhibition of dyskinesias was not related to sedation as locomotor activity levels were still high when compared to baseline (Fig. 1). In fact, there is a trend for an increase in the duration of the on-state of L-DOPA without dyskinesias (delay in the onset of dyskinesias) when (−)-OSU6162 is added to L-DOPA/benserazide (Fig. 3). Indeed, dyskinesias appeared after 15 min on average after the animals were turned "on" with L-DOPA/benserazide given alone. This on-state without dyskinesias was increased by 2.3- to 3.4-fold by the co-administration of (−)-OSU6162 at the doses of 3 and 10 mg/kg, respectively (Fig. 3).

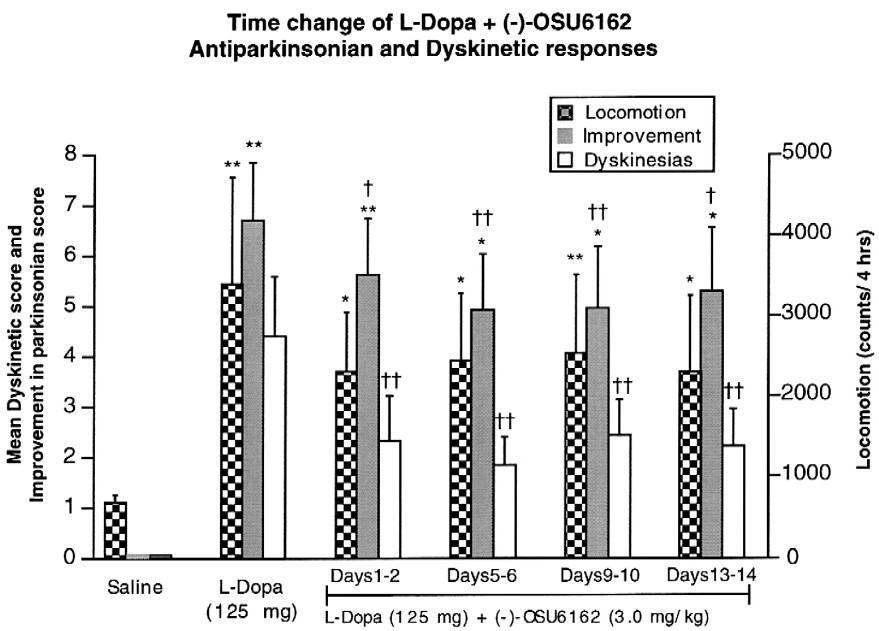

Fig. 4. Locomotion, anti-parkinsonian and dyskinetic responses during the chronic study. The total mobility counts recorded individually during 4 h following L-DOPA with or without (−)-OSU6162 were averaged for all monkeys and compared using ANOVA for repeated measures followed by a Fisher's PLSD test. Counts ± S.E.M. ($^{*}P < 0.05$ and $^{**}P < 0.01$ vs saline). The improvement in parkinsonian scores and the mean dyskinetic scores obtained every 30 min. during an observed effect were respectively averaged for all monkeys and compared using the non-parametric Friedman's test. Improvement in Parkinsonian scores ± S.E.M. ($^{*}P < 0.05$ and $^{**}P < 0.01$ vs saline; ††$P <$ 0.01 vs L-DOPA). Dyskinetic scores ± S.E.M. (††$P < 0.01$ vs L-DOPA).

3.3. Delay before and duration of L-DOPA response

The behavioral response to L-DOPA/benserazide given alone occurred 14 ± 2 min after oral administration and lasted 176 ± 7.3 min (Table 1). Co-administration of (−)-OSU6162 with L-DOPA/benserazide lengthened in a dose-dependent manner the delay for the onset of the anti-parkinsonian response by 10 to 50 min. Thus, the total duration of L-DOPA effects was slightly decreased. In addition, emesis was seen in one monkey treated with (−)-OSU6162 alone (6.0 mg/kg). When the two drugs were combined, mostly with the higher doses of (−)-OSU6162, three animals appeared nauseated and some retching was observed, particularly at the beginning of the effect. This response may explain the apparent delay in the onset of the anti-parkinsonian and locomotor-activating effects of L-DOPA/benserazide.

3.4. Repeated treatment for 2 weeks

In the second part of the study, a fixed dose (3.0 mg/kg) of (−)-OSU6162 was administered once daily together with L-DOPA/benserazide for 14 days. This co-administration resulted in a clear reduction of L-DOPA-induced dyskinesias and the effect was maintained until the end of the study. The anti-parkinsonian response to L-DOPA/benserazide was somewhat decreased by (−)-OSU6162 co-administration. However, it remained significantly higher than saline control animals during the entire 14-day treatment (Fig. 4).

4. Discussion

Our results indicate that the addition of (−)-OSU6162 significantly reduced L-DOPA-induced dyskinesias (Fig. 2) and tripled the duration of the on-state of L-DOPA without dyskinesias (Fig. 3). However, (−)-OSU6162 slightly decreased L-DOPA/benserazide's anti-parkinsonian action, although some autonomic effects at the onset of the treatment may have been a confounding factor. Our data support the results of Ekesbo et al. (1997) who showed that pretreatment with (−)-OSU6162 of MPTP-lesioned common marmosets relieved L-DOPA-induced dyskinesias. Moreover, our data show that the anti-dyskinetic effect of (−)-OSU6162 was maintained during 14 days and no tolerance to this effect was observed (Fig. 4).

Dopamine D_2 receptor mechanisms are implicated in the genesis of L-DOPA-induced dyskinesias (Crossman, 1990; Tedroff et al., 1997; Blanchet et al., 1995a). Our experience in MPTP-treated cynomolgus monkeys suggests that supersensitivity of D_2 receptor-mediated striatal outflow is sufficient for the induction of L-DOPA dyskinesias, with perhaps a synergistic contribution from dopamine D_1 receptors, and that repeated stimulation of short duration is important for the sensitization process (Blanchet et al., 1995a,b; Bédard et al., 1993). In fact, the administration of selective dopamine D_1 agonists to primed monkeys produces similar anti-parkinsonian effects but with fewer dyskinesias (Blanchet et al., 1993; Grondin et al., 1997). Thus, once primed, enhanced D_1 neural transmission might in fact contribute to reduce L-DOPA-induced dyskinesias. The high dyskinesiogenic potential of selective, short-acting, dopamine D_2 agonists and the favorable outcome on dyskinesias resulting from the continuous stimulation of dopamine D_2 receptors (leading to dopamine D_2 receptor down-regulation) are important clues suggesting the primary role of dopamine D_2 receptor-mediated mechanisms in the dyskinesia-priming process (Blanchet et al., 1995b; Grondin et al., 1996). There are also reports suggesting that dopamine D_2 receptors may play a primary role in the dyskinesia-priming process. In fact, short- and long-acting dopamine D_2 receptor-selective agonists are reported to have a high and low dyskinesia-potential, respectively (Blanchet et al., 1995b; Grondin et al., 1996).

In the present study, the anti-dyskinetic effect obtained with (−)-OSU6162 differed considerably from that obtained using classical dopamine D_2 receptor antagonists. In fact, such drugs that impede dopaminergic transmission improve dyskinesias at the cost of a return to parkinsonism (Grondin et al., 1999; Klawans and Weiner, 1974). Thus, blockade of dopamine D_2 receptors by raclopride was shown not to be advantageous in the treatment of L-DOPA-induced dyskinesias. In fact, raclopride reduced L-DOPA-induced dyskinesias but also caused a return to parkinsonism (Ekesbo et al., 1997). Raclopride also antagonizes dopamine effects in most paradigms and shows little state-dependent discrimination with dopamine-mediated behaviors (Orgren et al., 1986). It is interesting to note that with (−)-OSU6162 co-treatment there was no clear dose-dependent effect. This is indeed surprising and not easily explained according to standard pharmacology. One explanation may lie in the observations made by Ekesbo et al. (2000) in the primates with a unilateral 6-OHDA lesions of the substantia nigra. They observed that (−)-OSU6162 attenuated rotational behavior induced by apomorphine and the dopamine D_2 receptor agonist, quinpirole, but increased the rotational response to dopamine D_1 receptor agonists. This is highly unusual for a dopamine antagonist and was described as "state-dependent effect" of the molecule on dopamine D_1 and dopamine D_2 receptor agonist-induced behavior. In the present study, (−)-OSU6162 when combined with L-DOPA, may have exerted opposite effects on dopamine D_1 and dopamine D_2 receptors and the resulting motor response may have varied depending on the balance between the modulation of dopamine D_2 receptors (reduction of response) and dopamine D_1 receptors (increase of response). This could explain the unusual dose–response curves.

In support of its weak dopamine receptor antagonistic effects, (−)-OSU6162 given alone had little effect on motor behavior (Figs. 1 and 2). Moreover, when given

together with L-DOPA/benserazide, a significant anti-dyskinetic effect was seen. Hence, the dopamine antagonizing properties of (−)-OSU6162 are only seen in the dopamine overactive state and are lost in the case of decreased dopaminergic tone, as in MPTP-lesioned monkeys. Therefore, it is reasonable to assume that (−)-OSU6162 not only shows selectivity for the dopamine D_2 receptor type, but may also have a receptor state-dependent affinity. Furthermore, a more favorable balance of L-DOPA-induced dopamine D_1/D_2 receptor-mediated output from the striatum may also be a tentative explanation for the anti-dyskinetic effects of the compound. In addition to its comparatively weak dopamine D_2 receptor antagonist properties, (−)-OSU6162 increased contraversive circling behavior induced by a dopamine D_1 receptor agonist (Ekesbo et al., 2000; Tedroff et al., 1997). This positive modulation of the activity of striatal output neurons bearing dopamine D_1 receptors (direct pathway) could in part account for its anti-dyskinetic effects (Grondin et al., 1997). In conclusion, it is clearly possible to find a window or balance in which dyskinesias are decreased significantly with (−)-OSU6162 at the cost of an "acceptable" reduction or decrease of the anti-parkinsonian effect. This would make (−)-OSU6162 a clinically useful tool in advanced fluctuating Parkinson's disease patients.

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