Movement Disorders
Vol. 18, No. 12, 2003, pp. 1436–1441

Chronic Treatment With Small Doses of Cabergoline Prevents Dopa-Induced Dyskinesias in Parkinsonian Monkeys

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Abstract: Levodopa continues to be the most effective agent for the symptomatic treatment of Parkinson's disease (PD). But over time, initial benefits decline in efficacy because of a rise in adverse effects such as dyskinesias. The pathophysiology of levodopa-induced dyskinesias (LID) is not completely understood, but it appears to result from deficient regulation by dopamine of corticostriatal glutamatergic inputs leading to a cascade of neurochemical changes in the striatum and the output pathways. In the present study, we examined if the addition of small doses of cabergoline (a long-acting D_2 receptor agonist) to levodopa could prevent LID. The major hypothesis is that sustained activation of postsynaptic D_2 receptors on medium spiny neurons even by small doses of cabergoline could prevent or reduce LID. The minor hypothesis, and the more controversial of the two, is that the long-acting stimulation by small doses of cabergoline could diminish the release of glutamate by the corticostriatal pathway and prevent LID. Eight MPTP-treated monkeys with a long-standing and stable parkinsonian syndrome and having never received dopaminergic agents were used. Two groups of four were treated for 1 month with levodopa/benserazide administered orally (100 mg/25 mg). The second group received in addition a threshold dose of cabergoline (dose ranging from 0.015 to 0.035 mg/kg, SC). During the treatment, we observed LID in the levodopa group but not in the group receiving levodopa+cabergoline. Furthermore, the combination produced a comparable antiparkinsonian effect in terms of quality but prolonged the duration (by 1 to 2 hours) and increased the locomotion (mean for 2 weeks $\cong$ 104%). Our data suggest that a small dose of a long-acting D_2 agonist combined with high doses of levodopa could be preventive of LID in patients with PD and could be an alternative to using antiglutamatergic agents for this purpose. © 2003 Movement Disorder Society

Key words: Parkinson's disease; Levodopa-induced dyskinesias; cabergoline; D_2 receptor; MPTP-treated monkeys

Parkinson's disease (PD) results from degeneration of the dopamine-containing cells of the substantia nigra pars compacta.[1] Treatment with levodopa, the precursor of dopamine (DA), initially provides stable symptomatic relief.[2–4] However, various adverse effects are observed with long-term levodopa treatment, including the uncontrolled involuntary movements of levodopa-induced dyskinesias (LID).[5–9]

Dyskinesias affect up to 80% of levodopa-treated patients and are characterized by chorea and dystonia. These dyskinesias eventually may become as debilitating as PD itself.[10] The dopamine system is thought to be tonically active. Oscillations in levodopa concentration in the brain (caused by diminished capacity of levodopa presynaptic storage as a result of progressive degeneration of nigrostriatal terminals) are believed to be partly responsible for LID.[11–13] The pulsatile effect of this treatment has an important impact on corticostriatal inputs. Normally, the glutamatergic pathway is excitatory on striatal neurons, but the short duration of the action of levodopa causes a deficient regulation of corticostriatal inputs, leading to a cascade of neurochemical changes in the striatum and the output pathways. Furthermore, at the neural level, this imbalance has repercussions on the equilibrium between the direct and indirect striatal efferent pathways.[14–16] In fact, both long-term exposure to exogenous dopaminergic agents and disease progression can cause a preferential shift in favor of the indirect

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Received 23 September 2002; Revised 20 May 2003; Accepted 30 June 2003
DOI 10.1002/mds.10589

pathway.[17–20] This pathway is known to be inhibited by levodopa through dopamine D_2 receptors. D_2 receptors are located presynaptically on corticostriatal axons regulating glutamate release (D_2-short) [21–30] and are located postsynaptically on striatal neurons regulating excitability (D_2-long).

It has been reported that continuous exposure to dopamine D_2 agonists does not produce such marked sensitization.[31–34] Stimulation of postsynaptic D_2 receptors is obviously an important target, because long-acting D_2 agonists, such as cabergoline (1-[(6-allylergolin-8β-yl) carbonyl]-1-[3- (dimethylamino) propyl]-3-ethyl-urea), an ergoline derivative with potent, selective, and long-lasting dopamine D_2 receptor agonistic activity, are able to stabilize the shorter dopaminergic stimulation of levodopa.[35–38]

Our experience with cabergoline in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–treated monkeys demonstrated that high doses (0.25 mg/kg, s.c.) induce hyperactivity for 24 hours and cause nocturnal sleep disturbances.[37] These high doses can even induce transient dyskinesias in parkinsonian drug–naïve primates.[33] In all our experiments with cabergoline, the route used was always subcutaneous.

We explored two hypotheses. The major hypothesis is that sustained activation of postsynaptic D_2 receptors on medium spiny neurons even by small doses of cabergoline could prevent or reduce LID.[39–42] The chronic intermittent stimulation by levodopa of dopaminergic receptors activates specific signalling cascades in striatal dopaminoceptive medium spiny neurons. Levodopa's short-acting action eventually results in long-term potentiation of the synaptic efficacy of glutamate receptors of the *N*-methyl-D-aspartate subtype on these GABAergic efferents, and the consequence is their increasing sensitivity to excitation by cortical glutamatergic projections.[35–37] The minor and controversial hypothesis is that cabergoline, even in small doses, could prevent LID by regulating corticostriatal glutamatergic afferents. Small doses of a D_2 agonist would be expected to affect predominantly presynaptic receptors, which have a lower threshold.[43]

MATERIALS AND METHODS

Animals and Pretreatments

The experimental procedures were performed in accordance with the standards of the Canadian Council on Animal Care, in eight drug-naive female cynomolgus (*Macaca fascicularis*) monkeys weighing between 3.95 and 4.22 kg. They were housed separately in individual observation cages equipped with electronic locomotor activity monitoring systems (Datascience, St. Paul, MN) in a temperature-controlled room and exposed to 12-hour light/dark cycles (lights on from 6:00 AM to 6:00 PM). They were fed once daily at the end of the afternoon (certified primate chow and fruit), and water was provided ad libitum (the monkeys were in the fasting state during the experimental observations). All animals were initially treated with the neurotoxin MPTP (Sigma–Aldrich, Oakville, ON, Canada) dissolved in sterile water and injected subcutaneously for the first time in 3 mg/dose. The following week, each animal received MPTP by means of an Alzet minipump (0.5 mg/day) during a month when sustained parkinsonian features appeared. The animals were scored several times a week with a disability scale (described herein) in which the normal state extends from 0 to 2 and maximum disability is 16 points.

Experimental Treatments

When a bilateral parkinsonian syndrome had stabilized (i.e., unchanged disability score of 8 or more over the course of 1 month), the monkeys were divided in two groups: four monkeys were assigned to the control group, which received levodopa alone (levodopa/benserazide (100/25 mg) administered orally (Prolopa; Hoffman–LaRoche, Mississauga, ON), while four other monkeys were treated with a combination of oral levodopa and a threshold dose cabergoline administered subcutaneously. When the threshold doses of cabergoline were found for all monkeys, the experimentation started. The threshold dose of cabergoline was defined as the minimum dose producing a small stimulatory effect but not the antiparkinsonian effect. However, these changes were not sufficient to modify the antiparkinsonian score obtained with the disability scale. These perceptible changes were also analysed with an electronic locomotor activity monitoring system used in all experiments with MPTP monkeys (see the following).

Cabergoline (Adria laboratories, Columbus, OH) was dissolved in 0.9% sterile saline (1 ml) acidified with 2% phosphoric acid (30 μl) and administered at doses ranging from 0.015 to 0.035 mg/kg. Drugs were injected in the morning (at 9:30 AM) for 4 weeks, and spontaneous behaviors were observed until the end of levodopa/benserazide actions effects or 4 hours after the cabergoline administration.

Evaluation of the Response

The parkinsonian syndrome after exposure and the relief of parkinsonism after the administration of levodopa/benserazide or cabergoline were evaluated by ex-

TABLE 1. *Disability scale for MPTP monkeys*

	Score			
	0	1	2	3
Posture	Normal	Flexed intermittent	Flexed constant	Crouched
Locomotor activity	Normal	Mild reduction	Moderate reduction	Severe reduction
Gait	Normal	Slow	Very slow	Very slow with freezing
Tremor	Absent	Mild action tremor	Moderate action tremor	Resting tremor
Climbing	Present ($\geq$ 3)	Absent		
Grooming	Present ($\geq$ 2)	Absent		
Vocalization	Present ($\geq$ 2)	Absent		
Social interaction	Present ($\geq$ 2)	Absent		

perienced nonblinded observer with the scale shown in Table 1. A score was given every 30 minutes reflecting observations of the preceding half hour. The maximum disability score is 16.

The severity of dyskinesias was also scored every 30 minutes for the face, neck, trunk, arms, and legs: 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 was scored separately based on assessment of observation in the preceding half hour. The dyskinetic score obtained was the sum of the scores for all body segments, for a maximum score of 21 points. Dyskinesias were mainly choreic in nature, but dystonia was also seen. Stereotypies or licking were not considered as dyskinesias.

Locomotor activity of all monkeys was monitored with the use of an electronic locomotor activity monitoring system fixed on each cage (Dataquest IV; Datascience). With the use of radiowave frequency, a probe implanted subcutaneously in the back of each animal transmits the signal to a receiver attached to the cage, which is connected to a computer. Each animal's locomotor activity was cumulated every 5 minutes continuously.

Statistical Analysis

The peak locomotor activity counts/1 hour were averaged for all monkeys and compared with an analysis of variance for repeated measures followed by a Dunnett's *t* test. The minimum parkinsonian score and the maximum dyskinetic score, obtained during an observed effect with levodopa alone or during a 4-hour observation period during the peak effect with cabergoline combined to levodopa (usually in the morning), were used for the analysis. The intragroup comparisons were analysed with a nonparametric Friedman's test followed by a multiple comparisons test. The groups were compared with a Mann–Whitney test.

RESULTS

Effects of Levodopa Treatment Alone

The levodopa group's parkinsonian score was reduced by half under the effect of levodopa (Fig. 1). Dyskinesias appeared gradually and increased over the weeks of treatment in the group receiving levodopa alone (score increasing from 0.2 up to 5.0) (Fig. 2).

Effects of Threshold Doses of Cabergoline on Locomotor Activity

Effects of threshold doses of cabergoline on locomotor activity in each monkey were detected as a minimal increase of the parameters of the parkinsonian evaluation

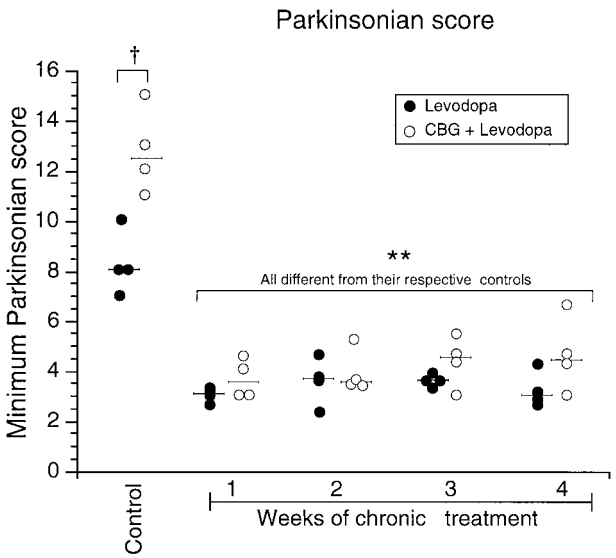

FIG. 1. Effect of levodopa alone or combined to cabergoline (CBG) on minimum parkinsonian score in MPTP-treated monkeys during the 4 weeks of treatment. Each bar represents mean ± SEM. $^{**}P < 0.01$ vs. respective control. † $P < 0.05$ levodopa + CBG vs. levodopa alone.

scale such as climbing, posture, gait, etc., compared to the baseline (data not shown), but these changes were not sufficient to modify the antiparkinsonian score obtained by means of this disability scale (see *Materials and Methods*, "Evaluation of the Response" section).

Effects of Cabergoline and Levodopa Combination

The animals treated with the combination of levodopa and cabergoline had their parkinsonian score reduced by more than half; the antiparkinsonian response for this combination group was comparable to the levodopa alone group (Fig. 1). As shown on Figure 2, dyskinesias were not observed during the 4 weeks of treatment with the combination of levodopa and cabergoline. However, one of the animals started to show signs of end-dose dystonia during the fourth week. This finding explains the slight dyskinetic effect on the graph. Figure 2 illustrates the average response for each week of the animals that received the combination. Adding cabergoline even in small doses to levodopa prevented dyskinesias without modifying the antiparkinsonian effect, but it prolonged this effect by 1 to 2 hours. The mean duration of effect in the levodopa group was 4 hours compared with a duration in the combination group of 5.7 hours.

Locomotor Activity of the Levodopa Control Group Compared to the Group That Received Combination (Cabergoline–Levodopa)

The locomotor activity of the group receiving the combination of levodopa and cabergoline, increased over the weeks in comparison with the levodopa group that showed a stable lower locomotor activity (Fig. 3) despite displaying evident dyskinesias. For the last 2 weeks, locomotor activity in the combination group was significantly higher than the group receiving levodopa alone (mean for 2 weeks ≅ 104%).

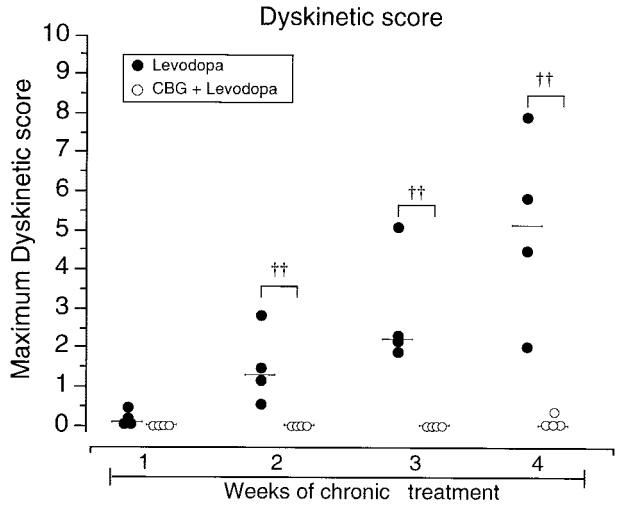

FIG. 2. Effect of levodopa alone or combined to cabergoline (CBG) on maximum dyskinetic score in MPTP-treated monkeys during the 4 weeks of treatment. Each bar represents mean ± SEM. ††$P < 0.01$ levodopa + CBG vs. levodopa alone.

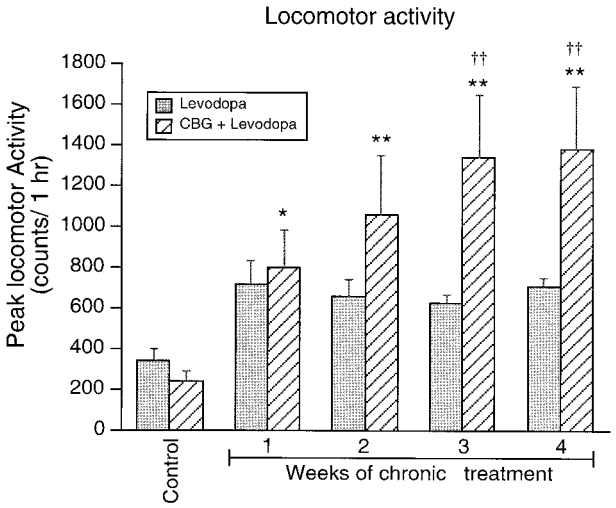

FIG. 3. Effect of levodopa alone or combined to cabergoline (CBG) on peak locomotor activity (counts/1 hour). Each bar represents mean ± SEM. *$P < 0.05$; **$P < 0.01$ vs. respective control. ††$P <$ 0.01 levodopa + CBG vs. levodopa alone.

DISCUSSION

The present experiment shows that adding cabergoline even at a very low dose to levodopa does not affect the quality of the antiparkinsonian effect but prolongs this effect by 1 to 2 hours and increases the locomotor stimulation (a postsynaptic effect). However, this finding was not paralleled by an increased incidence of dyskinesias but rather the opposite. This result suggests that these two parameters can be dissociated and that it is possible to maximize the antiparkinsonian effect without necessarily causing or increasing dyskinesias. This beneficial effect could be explained by the fact that cabergoline is a long-acting D_2 agonist and by sustained activation of postsynaptic D_2 receptors is likely to stabilize the dopaminergic stimulation of levodopa, which is shorter, thus preventing LID. Other mechanisms could also be invoked.

Compared to other studies on cabergoline's potential to prevent LID, our experiment differs by the dosage. Here, only very small doses of agonist were combined with regular fixed high doses of levodopa, contrary to other studies that tested efficient doses of agonist alone supplemented if necessary with levodopa.[41,44–47]

On the other hand, it has been shown that inhibition of the glutamatergic corticostriatal pathway reduces the inci-

dence of dyskinesias associated with levodopa treatment in parkinsonian primates.[44] Presynaptic inhibition of glutamate release may involve the action of dopamine on voltage-gated calcium channels at the presynaptic terminal. D_2 receptors may be activated presynaptically to reduce calcium currents involved in the release of glutamate.[48,49] Indeed, D_2 receptors have been shown to decrease calcium currents in several systems.[50–53] Clear presynaptic effects have been observed using chronic depletion of DA in different animal models.[54] This observation is probably because after DA-depletion D_2 receptors become supersensitive. Similarly, the study by Cepeda and colleagues in 2001, demonstrated a presynaptic inhibitory role of D_2 receptors on glutamate release in mutant mice chronically deprived of D_2 receptors.[55] The presynaptic regulation of glutamate release by D_2 receptors is better appreciated after unilateral lesions of the substantia nigra that deplete the striatum of DA. One of the chronic effects of such lesions is to increase spontaneous synaptic activity and cell firing in striatal neurons.[56–58] This activity can be modulated by D_2 receptor agonists such as cabergoline, possibly by means of presynaptic mechanisms.[54] Our data do not demonstrate clearly that cabergoline could act preferentially on glutamatergic corticostriatal fibers at the threshold doses used. It is suggestive, however, of such an interpretation based on the finding that the presynaptic D_2 receptors have a lower threshold than the postsynaptic receptors of the corticostriatal pathway.[43] Thus, the dose used can be smaller and maybe could be more specific of these presynaptic D_2 receptors. The increase in locomotor activity suggests a postsynaptic effect but the small threshold doses of cabergoline used in this experiment could also be involved in the reduction of presynaptic glutamate release. Further studies will be necessary to resolve these questions. It is also important to note the absence of LID during this increase of locomotor activity. It is easier to move when dyskinesias are avoided, because these dyskinesias disturb the flow of locomotor activity.

Cabergoline represents a useful tool for the treatment of PD, because the stimulation of postsynaptic dopamine receptors by this dopamine receptor agonist increases locomotor activity of normal animals and reverses akinesia in MPTP monkeys.[45,59–62] Combined with levodopa therapy, in PD patients, cabergoline (2–10 mg/day) significantly decreases the number of *off* hours compared to placebo.[60] Moreover, early cabergoline treatment of de novo patients with PD delays the onset of motor complications.[63,64] Finally, the addition of a small doses of a long-acting DA D_2 agonist such as cabergoline may represent a relatively simple and safe method to prevent or reduce dyskinesia induction while maximizing the antiparkinsonian effect and could be an alternative to using antiglutamatergic agents.

Acknowledgment: This work was supported by a grant from the Medical Research Council of Canada.

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