Psychopharmacology (1990) 102:21–27

Psychopharmacology

Characterisation of dyskinesias induced by L-dopa in MPTP-treated squirrel monkeys

S. Boyce, N.M.J. Rupniak, M.J. Steventon, and S.D. Iversen

Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Harlow, Essex, CM20 2QR, UK

Received September 6, 1989 / Final version March 8, 1990

Abstract. Intermittent treatment with L-dopa over a 2-year period induced abnormal involuntary movements in MPTP-treated squirrel monkeys. Dyskinesias included a choreic and dystonic component. Dose-response curves for chorea and dystonia revealed that the same dose of L-dopa (30 mg/kg) induced the highest score for both dyskinesias; however, the severity was much greater for chorea. Choreic movements were always most prevalent at the time of peak effect, whereas dystonia was apparent at the time of peak effect and at "end-of-dose", and was occasionally observed spontaneously. Our findings indicate that squirrel monkeys treated with MPTP develop L-dopa-induced dyskinesias which closely resemble those observed in Parkinson's disease. This species provides a valuable animal model to develop improved therapeutic agents.

Key words: L-dopa – Chorea – Dystonia – Parkinson's disease – Squirrel monkey

Dyskinesias are a debilitating neurological complication associated with long-term use of L-dopa in Parkinson's disease, affecting some 60–80% of patients (Marsden et al. 1982). Drug-induced dyskinesias include a bewildering spectrum of abnormal involuntary movements such as tics, stereotypy, chorea, athetosis, hemiballismus and dystonia. These may be categorised according to appearance and clinical pharmacology.

Choreiform movements (random, chaotic alternating flexion/extensions and twisting of the limbs and trunk) are the most common dyskinesia coinciding with the time of peak antiparkinsonian effect of L-dopa (Markham 1974). Like neuroleptic-induced tardive dyskinesias, chorea induced by L-dopa may be suppressed acutely by neuroleptic drugs (Klawans and Weiner 1974) and by cholinomimetic agents such as physostigmine (Tarsy et al. 1974), suggesting that chorea may be characterised as a dopamine excess, acetylcholine deficiency syndrome. In some patients, particularly those with early onset of the disease, dystonia (repeated brief or sustained abnormal posturing) is a prominent feature which may follow a more complicated and less predictable time course than chorea, for example becoming most prevalent as plasma dopa levels are rising or falling (Barbeau 1975; Muenter et al. 1977). Unlike chorea, dystonia has been characterised as a dopamine deficiency, acetylcholine *excess* disorder (see Stahl et al. 1982 for review).

Differences in the apparent pathophysiology of chorea and dystonia suggest that the antiparkinsonian effects of L-dopa might be separable from at least certain types of dyskinesia. A detailed understanding of the mechanisms which underlie chorea and dystonia could have important implications for future development of antiparkinsonian drugs, and of antidyskinetic agents which do not interfere with the antiparkinsonian activity of dopamine agonists.

At present there are no convincing models of chorea or dystonia in which to develop such drugs using rodents. In contrast, abnormal movements which bear a close similarity to both acute and tardive dyskinesias induced by neuroleptic drugs have been observed in several Old and New World species (see Rupniak et al. 1986 for review). The recent use of the neurotoxin MPTP to induce parkinsonism in monkeys has enabled development of an animal model of L-dopa-induced dyskinesias in Old World primates (Bedard et al. 1986; Clarke et al. 1987). Parkinsonism has also been induced in New World species such as marmosets (Jenner et al. 1986) and squirrel monkeys (Langston et al. 1984; Rupniak et al. 1989). These species offer certain advantages over the larger Old World primates because they can be more readily accommodated in captivity and can be handled more easily, facilitating procedures such as oral dosing. However, there are as yet no reports of parkinsonian marmosets or squirrel monkeys developing dyskinesias in response to L-dopa. We now report the development of L-dopa-induced dyskinesias in MPTP-treated squirrel monkeys and characterise in detail the type, time-course and dose-

Offprint requests to: S. Boyce

relationship of chorea and dystonia in order to validate this animal model as bearing a close similarity to the disease in man.

Methods

Subjects. Seven adult male squirrel monkeys (*Saimiri sciureus:* 850–1150 g) were housed in groups of three to seven under standard laboratory conditions of temperature (24 ± 1° C) and lighting (12 h light/dark cycle: lights on 7 A.M. to 7 P.M.). Animals received their last feed at 5 P.M. on the day previous to the experiment. Food was not available during behavioural observations.

Induction of parkinsonism using MPTP. Animals were rendered parkinsonian using the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as described previously by Rupniak et al. (1989). Briefly, animals received a total of between 6 and 44.5 mg MPTP in single doses of 2 mg IP at weekly intervals (see Table 1 for animals' previous drug history). The dose was titrated for each individual animal so as to produce a stable parkinsonian syndrome consisting of three of the four cardinal features of the disease: tremor, akinesia, bradykinesia or rigidity. These symptoms were rated for presence or absence and were not graded. These animals had previously served as subjects for a study involving the selective D_2 agonist (+)-PHNO and had received intermittent exposure to L-dopa during the 2 years prior to the present study (Table 1). Some remission from the acute effects of MPTP had taken place, but animals remained hypokinetic and bradykinetic by comparison with normal animals (equivalent to stages I–II on the Hoehn and Yahr rating scale; Hoehn and Yahr 1967). All animals had developed L-dopa-induced dyskinesias.

Behavioural assessment. Animals were transferred to individual cages (0.6 × 0.5 × 0.75 m) and allowed a 15 min habituation period. Immediately following administration of L-dopa, animals were scored by two observers continuously by direct observation every 5 min for 3 h for dyskinesias and locomotor activity. Dyskinesias were classified as chorea or dystonia affecting the arms and legs. Chorea was defined as a random and chaotic alternating flexion/extension of the limbs. Occasionally choreic movements appeared repetitive and more closely resembled stereotypy. Dystonia involved brief or sustained (< 5 s) repetitive abnormal posturing caused by extension *or* flexion of the limbs. Criteria for assessing these behaviours were based on discussions with Professor C.D. Marsden (Institute of Neurology, London) who kindly examined video tape excerpts of the animals. Unless otherwise stated, behaviours were rated on a 0–4 scale (based on the AIMS clinical rating scale; Guy 1976) as follows: 0 = absent; 1 = occasional/mild; 2 = intermittent/moderate; 3 = frequent/marked; 4 = continuous/severe. Locomotor activity was scored as follows: −1 = hypoactive/sedated; 0 = absent; 1 = intermittent; 2 = continuous; 3 = hyperactive/hyper-reactive to external stimulae.

Table 1. Relationship between total previous exposure to MPTP or L-dopa and threshold dose of L-dopa to induce severe dyskinesias (score 3 or 4) in parkinsonian squirrel monkeys

Animal ID	Total dose of MPTP (mg)	Total dose of L-dopa (mg/kg)	Total number of days of L-dopa treatment (days)	Threshold dose of L-dopa for induction of dyskinesias (mg/kg)	
				Chorea	Dystonia
Artois	6	70	7	15	> 40
Skol	8	1338	80	15	> 40
Harp	30	1383	61	10	> 40
Schlitz	31	1048	59	15	20
4X	31	950	37	10	10
Kaliber	36	1422	90	10	10
Krug	45	1498	78	> 40	15

Drug administration. Drugs were administered to concious animals by oral gavage in a volume of 2 ml/kg according to a randomised Latin square design. Carbidopa was given as 1 h pretreatment to L-dopa in a fixed dose ratio of 1 : 2 mg/kg to inhibit peripheral decarboxylation. L-Dopa was administered at six doses in the range 5–40 mg/kg. Drugs were sonicated in suspension with 0.5% methyl cellulose (w/v) immediately before use.

Statistical analysis. Scores were summed over the 3 h observation period to give a maximum possible value of 144. Data were subjected to one-way analysis of variance with repeated measures. In cases where resulting F values were associated with a probability of less than 5% groups were compared with vehicle treatment using a two-tailed Dunnett's multiple comparison t-test. Differences in dyskinesia scores for the arms and legs were tested using paired Students t tests. Wilcoxon matched pairs ranked-sign tests were used to compare difference in locomotor activity scores between L-dopa (30 mg/kg) and vehicle treatment at each time point.

Results

Induction of parkinsonism

Administration of MPTP rendered all animals parkinsonian, although individual susceptibility varied considerably (Table 1). During the acute phase, animals exhibited marked akinesia, bradykinesia, freezing, hunched posture, and action tremor, sometimes accompanied by adipsia and aphasia during the first 48 h after MPTP treatment. Although the animals had undergone some spontaneous recovery from the effects of MPTP, akinesia and bradykinesia were still present 2 years after the last treatment.

Effects of L-dopa on behaviour

Stimulation of locomotor activity. Administration of L-dopa (5–40 mg/kg PO) caused a dose-dependent increase in summed locomotor activity scores over 3 h compared with vehicle treatment (Fig. 1a; $F_{6,36} = 7.65$, $P < 0.01$; one-way analysis of variance with repeated measures). There were marked differences in the response of different animals ($F_{6,36} = 12.38$, $P < 0.01$). The dose-response curve was steep such that low doses of L-dopa (5, 10 and 15 mg/kg) induced progressively greater increases in locomotor activity, reaching a peak at 15 mg/kg which was not exceeded by administration of higher doses (20, 30 and 40 mg/kg).

Examination of the time course for stimulation of locomotor activity by 30 mg/kg L-dopa revealed an onset approximately 15 min after treatment (Fig. 1b). At this dose of L-dopa locomotor activity showed biphasic peaks, the first after 45–95 min followed by a later peak between 140 and 150 min (Fig. 1b). The apparent reduction in activity between 95 and 135 min coincided with the emergence of climbing behaviour (see below).

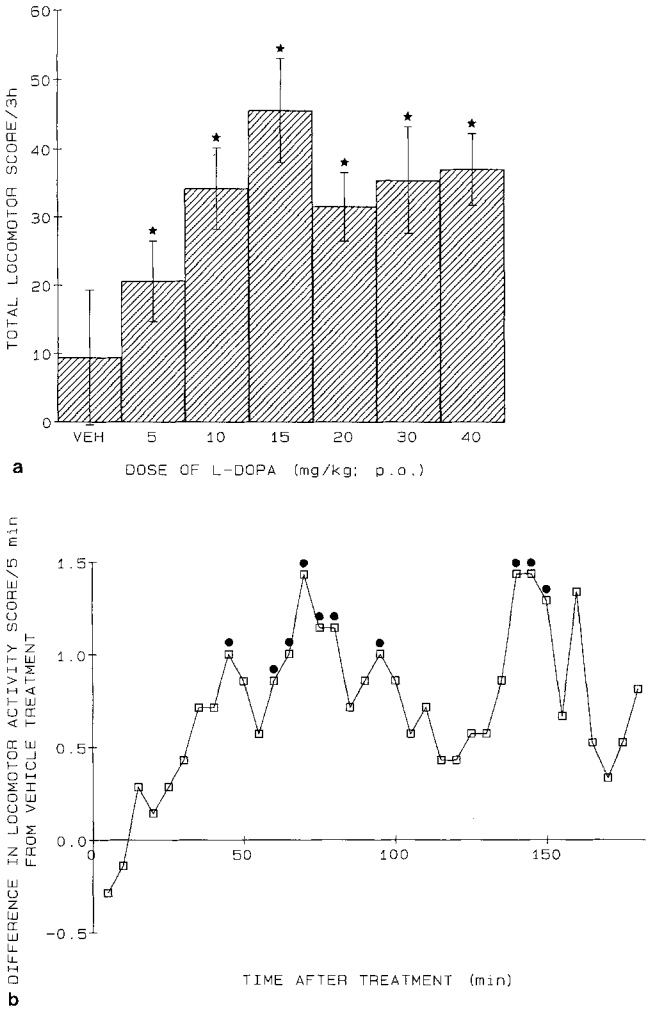

Fig. 1a, b. Locomotor activity induced by L-dopa. **a** Dose-response curve for activity obtained over 3 h following oral administration of L-dopa (5–40 mg/kg) and **b** time-course data using 30 mg/kg L-dopa in MPTP-treated squirrel monkeys. Values are expressed as the mean obtained from seven animals. SEMs are presented on dose-response curves alone for clarity. Data were subjected to one-way analysis of variance with repeated measures followed by Dunnett's test: ANOVA for drug effect $F_{6,36} = 7.65$, $P < 0.05$; for subjects $F_{6,36} = 12.38$, $P < 0.05$. * $P < 0.05$ compared to vehicle treatment, Dunnett's multiple comparison test. ● $P < 0.05$ compared to vehicle treatment at each time point, Wilcoxon matched-pair ranked-sign test. -□- L-dopa 30 mg/kg p.o.

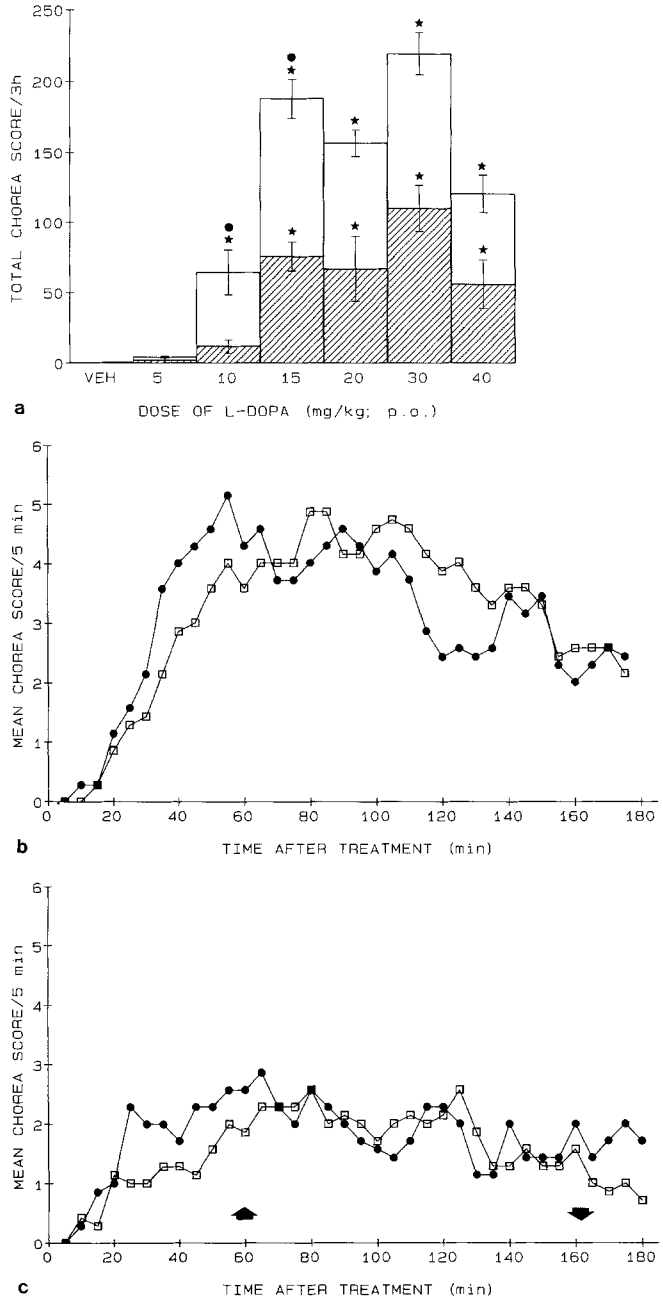

Fig. 2a–c. Chorea induced by L-dopa **a** Dose-response curves for chorea in the arms and legs of MPTP-treated squirrel monkeys following oral administration of L-dopa (5–40 mg/kg), and time course data using **b** 30 mg/kg and **c** 40 mg/kg L-dopa. Values are expressed as the mean obtained from seven animals. SEMs are presented on the dose-response curves alone for clarity. Data were subjected to one-way analysis of variance with repeated measures followed by Dunnett's or Student's *t*-tests. ANOVA: legs – drug effect $F_{6,36} = 14.94$, $P < 0.05$, subjects $F_{6,36} = 2.48$, $P < 0.05$; arms – drug effect $F_{6,36} = 16.40$, $P < 0.05$, subjects $F_{6,36} = 5.40$, $P < 0.05$. * $P < 0.05$ compared to vehicle treatment, Dunnett's multiple comparison test. ● $P < 0.05$ compared to equivalent dose in the arms, paired Student's *t*-test. *Arrows* denote the emergence of a compulsive "climbing" response. **a** □ Leg; ▨ arm. **b + c** -□- Arm; -●- leg

L-Dopa-induced dyskinesias: chorea. Treatment with L-dopa induced both chorea and dystonia. Choreiform movements were never observed spontaneously in untreated parkinsonian monkeys or following treatment with carbidopa alone. The severity of chorea was related to the dose of L-dopa; the dose-response curve was steep and bell-shaped (Fig. 2a). Administration of 5 mg/kg L-dopa, a dose causing a modest increase in locomotor activity, did not induce chorea in any animal over the 3 h observation period. Treatment with 10 mg/kg L-dopa induced mild intermittent choreiform movements in the limbs. With higher doses (15, 20 and 30 mg/kg) choreiform movements became severe and virtually continuous and consisted, in the legs, of chaotic alternating flexions and extensions of the hip, knee and ankle, with eversion and inversion of the foot, and abduction and adduction of the hip (Fig. 2a). Similar choreiform movements were observed in the arms of all animals. Occasionally, the ab-

normal movements were so dramatic and severe as to force the animals into involuntary hand-stands, causing a marked loss of balance. L-Dopa-induced chorea typically affected both the arms and legs to a similar extent, although choreiform movements were more prevalent in the legs than the arms using doses of 10 and 15 mg/kg (Fig. 2a).

The time-course for L-dopa-induced chorea at 30 mg/kg revealed that chorea was severe (mean peak score = 5.2; maximum possible score = 8) and of rapid onset (20–30 min; Fig. 2b). Chorea reached a peak after 40–50 min was maintained around this level continuously for some 60 min. Choreiform movements were still present 3 h after drug administration, although milder and less frequent. Time course profiles were similar for lower doses of L-dopa (for example, 15 mg/kg: onset = 20–30 min, peak effect between 60 and 140 min, mean peak score = 5.2) but of shorter duration. Surprisingly, chorea induced by the highest dose of L-dopa (40 mg/kg) was *less* severe than that induced by 30 mg/kg (Fig. 2a). Administration of 40 mg/kg L-dopa initially induced severe choreiform movements in some animals; at the time of peak effect, chorea was blocked by the emergence of a marked compulsive "climbing" response (lasting from 60 to 160 min; Fig. 2c). Apparent rigidity was observed in the hands and feet during climbing. As climbing diminished, some animals again displayed choreiform movements in the limbs.

Dystonia. L-Dopa-induced dystonias were not as severe or frequent as chorea (maximum observed mean score for chorea = 5.2; maximum mean score for dystonia = 2.0). The dose-response curve for dystonia was less steep than for chorea, and clearly dose related (Fig. 3a). Unlike chorea, dystonic-like postures were occasionally observed in all animals in the untreated state. Dystonic postures were repeated periodically, typically affecting a particular limb and usually maintained for less than 5 s. L-Dopa-induced dystonia increased both in severity and frequency with increasing dose, such that at its most severe dystonia was present for approximately 50% of the observation period. Dystonia in the leg was characterised by either a brief or sustained flexion of the hip and knee with plantar-flexion of the ankle and eversion of the foot, accompanied by abduction of the hip, or extension of the hip and knee, with plantar-flexion of the ankle. Dystonia affected the legs almost exclusively: only one animal developed dystonia in the arms (Fig. 3a). Unlike chorea, dystonias were not only observed at the time of peak effect of L-dopa, as assessed by stimulation of locomotor activity, but were also present in some individuals as the effect of L-dopa was diminishing (Fig. 3b).

Other behaviours. At high doses of L-dopa (20, 30 and 40 mg/kg), animals exhibited compulsive "climbing" behaviour which appeared to interfere with other activities; this was particularly marked following 40 mg/kg L-dopa. At the time of peak drug effect, animals often hung motionless continuously in a fixed "climbing" position at the top of the cage for up to 80 min with apparent rigidity in the hands and feet. Occasionally, animals

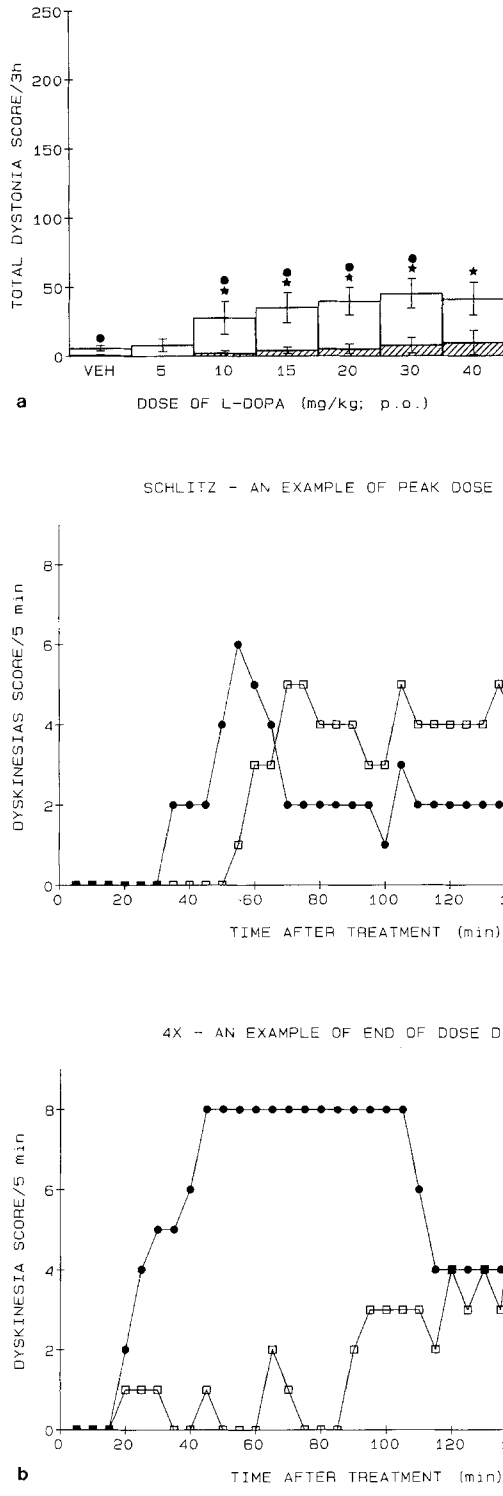

Fig. 3a, b. Dystonia induced by L-dopa **a** Dose-response curves for dystonia in the arms and legs of MPTP-treated squirrel monkeys following oral administration of L-dopa (5–40 mg/kg) and **b** time-course data using 30 mg/kg L-dopa (chorea; dystonia). Values are expressed as the mean obtained from seven animals. SEMs are presented on the dose-response curves alone for clarity. Data were subjected to one-way analysis of variance with repeated measures followed by Dunnett's or Student's *t*-tests. ANOVA: □ legs – drug effect $F_{6,36} = 3.42$, $P < 0.01$, subjects $F_{6,36} = 6.93$, $P < 0.01$; ▨ arms – drug effect $F_{6,36} = 0.79$, $P > 0.05$; subjects $F_{6,36} = 1.85$, $P > 0.05$. * $P < 0.01$ compared to vehicle treatment, Dunnett's multiple comparison test. ● $P < 0.05$ compared to equivalent dose in the arms, paired Student's *t*-test -●- chorea; -□- dystonia

appeared to be in a "psychotic trance" with a fixed vacant stare and unresponsive to external stimulae.

Discussion

In Old World primates, parkinsonism induced by MPTP has been argued to closely resemble idiopathic Parkinson's disease in man with respect to neuropathology, symptomatology and dyskinetic response to chronic L-dopa therapy (Crossman et al. 1987). Until now, there have been no reports of New World primates exhibiting dyskinesias in response to L-dopa. In the present study we have characterised L-dopa-induced dyskinesias in MPTP-treated squirrel monkeys in order to enable a detailed comparison with the effects of L-dopa in man. Our findings indicate a close similarity between the time-course and type of dyskinesia induced by L-dopa in MPTP-treated squirrel monkeys and those observed in Parkinson's disease. This model therefore provides a valuable opportunity to develop new antiparkinsonian and antidyskinetic drugs.

In agreement with clinical experience, dyskinesias were readily induced in all seven animals examined and were characterised predominantly by chorea and to a lesser extent dystonia. The induction of both chorea and dystonia was dose related, both reaching maximum scores at a dose of 30 mg/kg L-dopa, marginally higher than that required for optimal locomotor stimulation.

Examination of the time course for induction of chorea and dystonia revealed that choreiform movements were typically observed at the time of peak effect of L-dopa; in contrast, the occurrence of drug-induced dystonias was less predictable, with dystonic postures occurring at peak effect but also as the effect of L-dopa was diminishing. Moreover, dystonic postures were also observed in the untreated state, whilst choreiform movements were never seen spontaneously. Our observations closely resemble clinical findings that dystonia, especially prolonged abnormal postures and torsion spasms, often occurs early in the morning when plasma levels of L-dopa are low (Melamed 1979), or in a time-related diphasic pattern when levels of L-dopa are rising or falling (Muenter et al. 1977). Dystonic postures were only maintained for relatively short periods (< 5 s) in squirrel monkeys. However, the severity and frequency with which dystonic postures occurred increased with increasing dose of L-dopa, such that, in severe cases, dystonia could be present for up to 50% of the observation period. In man, drug-induced dystonia takes many forms and may be either brief or sustained.

As typically occurs in younger parkinsonian patients (Gerlach 1977) L-dopa-induced dyskinesias in MPTP-treated monkeys were mainly restricted to the extremities (particularly the legs), with little or no dyskinesia in the oro-facial region. In patients, dyskinesias particularly affect those limbs showing greatest parkinsonian symptoms, suggesting that the severity and location of the lesion are predisposing factors for dyskinesia (Mones et al. 1971; Gerlach 1977). Dystonia typically occurs much later in the course of L-dopa therapy (Lang 1985), presumably due to progression of the disease, suggesting a possible association with the severity of the lesion. Other evidence indicates that the induction of dyskinesia, particularly chorea, is correlated with the duration of L-dopa treatment, rather than the severity of the disease (Mouradian et al. 1989). Interestingly, in the present study we observed that the prevalance of dystonia, but not chorea, was lower in those animals that had received higher doses of MPTP. However, there appeared to be no relationship between the prevalance of chorea *or* dystonia and the cumulative dose or duration of L-dopa treatment prior to the experiment. It is not known whether prior administration of (+)-PHNO would have any effect on the development of dyskinesias. We found no correlation between the dose or duration of previous treatment with (+)-PHNO and the severity of dyskinesia.

The exact neural mechanisms involved in the genesis of dyskinesias by L-dopa and other drugs are not yet fully understood. However, there is growing evidence implicating stimulation of D_1 receptors in the mediation of chorea. Bedard and colleagues (Bedard et al. 1986; Falardeau et al. 1988) found that chronic treatment with the selective D_2 agonist bromocriptine, unlike L-dopa, did not induce dyskinesias in MPTP-treated macaques. Similarly, in parkinsonian patients, there was a reduced propensity for induction of chorea by bromocriptine (Lees and Stern 1983). Interestingly, the less selective D_2 agonist apomorphine has been claimed to *reduce* chorea induced by L-dopa in Parkinsonian patients (Duby et al. 1972) and in Huntington's disease (Corsini et al. 1978). It should be noted, however, that in other studies dyskinesias have been observed in parkinsonian patients treated with D_2 agonists (for example, see Grandas Perez et al. 1986). Interpretation of the role of D_1 and D_2 receptors in the induction of dyskinesias is complicated by possible pharmacodynamic receptor changes following chronic exposure to L-dopa therapy, and possibly the type of dyskinesia (chorea or dystonia). Recent studies in 6-hydroxydopamine lesioned rats have demonstrated a progressive exaggeration of D_1-mediated behaviours following repeated administration of the D_1 receptor agonist SKF 38393 (Criswell et al. 1989). Such priming or sensitization of D_1-mediated effects following chronic L-dopa therapy could presumably alter the subsequent tendency for other dopamine agonists to induce dyskinesias. Interestingly, priming of dyskinesias in primates treated chronically with neuroleptics has been reported (Neale et al. 1982) such that they may ultimately become permanent and irreversible (Kovacic and Domino 1982). In rodents, sensitization of D_1-mediated behaviours was extremely long lasting (at least 6 months) and was also induced by repeated anticholinergic treatment (Criswell et al. 1989). This mechanism might be of great importance in the generation of irreversible tardive dyskinesias by chronic neuroleptic treatment which may be aggravated by concomittant anticholinergic therapy.

These findings clearly implicate D_1 receptor stimulation in the genesis of dyskinesias by L-dopa. In contrast, the D_2 receptor appears essential for the mediation of antiparkinsonian activity as is demonstrated, for exam-

ple, by the therapeutic efficacy of the selective D_2 agonist (+)-PHNO (Stoessl et al. 1985). D_1 binding sites are particularly abundant in the medial segment of the globus pallidus (Graham and Crossman 1987; Richfield et al. 1987), an area implicated in the production of chorea (Robertson et al. 1988), and which is the major output station of the basal ganglia. L-Dopa-induced dyskinesia may, therefore, reflect an alteration in the output of the medial pallidal segment. Such a conclusion would seem justified, since ventrolateral thalamotomy for the relief of parkinsonian tremor and rigidity appears to protect against subsequent L-dopa-induced chorea (Cooper 1970; Tasker 1970). Interestingly, Parent and Smith (1987) have recently demonstrated a direct nigropallidal dopamine pathway in the squirrel monkey which is relatively spared following MPTP treatment (see Smith et al. 1989). This could provide a direct route for the production of chorea by L-dopa. The preferential localization of D_2 binding sites in the substantia nigra pars compacta, lateral pallidal segment, and striatum (Richfield et al. 1987) may provide a separate route for dopamine stimulation more closely linked to antiparkinsonian activity.

Finally, further clarification of the nature of the compulsive climbing behaviour we observed in monkeys treated with supratherapeutic doses of L-dopa is required. The response occurred at the time of peak effect and blocked all other activities, including dyskinesias and locomotor activity. Animals would typically climb to the top corner of the cage and hang motionless in a fixed position for up to 80 min. This behaviour could represent a "normal" motor stimulant response in this species, as might be clearly revealed if the animals were placed in a more natural environment. This would seem unlikely, since animals displayed an apparent rigidity in the hands and feet. An alternative and more likely explanation is that climbing represents a toxic effect of L-dopa. In the squirrel monkey, compulsive climbing might represent a psychosis-like stereotypy resembling the climbing behaviour induced by dopamine agonists in rodents (Protais et al. 1976). Examination of the effects of such supratherapeutic doses of L-dopa in man would be limited for ethical reasons, but one study suggests that climbing might represent the simian equivalent of "akinesia spastica" observed in parkinsonian patients following administration of extremely high doses of L-dopa (Muenter et al. 1977).

Acknowledgement. We wish to thank Professor C.D. Marsden for his helpful comments in describing L-dopa-induced dyskinesias in squirrel monkeys.

References

Barbeau A (1975) Diphasic dyskinesia during levodopa therapy. Lancet I:756

Bedard PJ, DiPaolo T, Falardeau P, Boucher R (1986) Chronic treatment with L-dopa, but not bromocriptine induces dyskinesia in MPTP-parkinsonian monkeys. Correlation with [^{3}H]-Spiperone binding. Brain Res 379:294–299

Clarke CE, Sambrook MA, Mitchell IJ, Crossman AR (1987) Levodopa-induced dyskinesia and response fluctuations in primates rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) J Neurol Sci 78:273–280

Cooper IS (1970) Clinical physiology of abnormal movements. In: Barbeau A, McDowell FH (eds) L-dopa and parkinsonism. FA Davis, Philadelphia, pp 170–179

Corsini GU, Onali PL, Masala C, Cianchetti C, Mangoni A, Gessa GL (1978) Apomorphine hydrochloride-induced improvement in Huntington's chorea. Arch Neurol 35:27–30

Criswell H, Mueller RA, Breese GR (1989) Priming of D_1-dopamine receptor responses: long-lasting behavioural supersensitivity to a D_1-dopamine agonist following repeated administration to neonatal 6-OHDA-lesioned rats. J Neurosci 9:125–133

Crossman AR, Clarke CE, Boyce S, Robertson RG, Sambrook MA (1987) MPTP-induced parkinsonism in the monkey: neurochemical pathology, complications of treatment and pathophysiological mechanisms. Can J Neurol Sci 14:428–435

Duby SE, Cotzias GC, Papavasiliou PS, Lawrence WH (1972) Injected apomorphine and orally administered levodopa in Parkinsonism. Arch Neurol 27:474–480

Falardeau P, Bouchard S, Bedard PJ, Boucher R, DiPaolo T (1988) Behavioural and biochemical effect of chronic treatment with D-1 and/or D-2 dopamine agonists in MPTP monkeys. Eur J Pharmacol 150:59–66

Gerlach J (1977) Relationship between tardive dyskinesia, L-dopa-induced hyperkinesia and parkinsonism. Psychopharmacology 51:259–263

Graham WC, Crossman AR (1987) Autoradiographic localization of dopamine D_1 binding sites in areas receiving striatal input. Eur J Pharmacol 142:479–481

Grandaz Perez FG, Jenner PG, Nomoto M, Stahl S, Quinn NP, Parkes JD, Critchley P, Marsden CD (1986) (+)-4-Propyl-9-hydroxynaphthoxazine in Parkinson's disease. Lancet I:906

Guy W (1976) Psychopharmacology Research Branch NIMH. Abnormal involuntary movement scale (AIMS). In: Guy W (ed) ECDEU Assessment manual for psychopharmacology, revised. DHEW, Rockville MD, pp 534–537

Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression, and mortality. Neurology 17:427–442

Jenner P, Rose S, Boyce S, Kelly E, Kilpatrick G, Rupniak NMJ, Briggs R, Marsden CD (1986) Induction of parkinsonism in the common marmoset by administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. In: Fahn S. (ed) Recent developments in Parkinson's disease. Raven Press, New York, pp 137–146

Klawans HL, Weiner WJ (1974) Attempted use of haloperidol in the treatment of L-dopa-induced dyskinesias. J Neurol Neurosurg Psychiatry 37:427–430

Kovacic B, Domino EF (1982) A monkey model of tardive dyskinesia (TD): evidence that reversible TD may turn into irreversible TD. J Clin Psychopharmacol 2:305–307

Lang AE (1985) Dopamine agonists in the treatment of dystonia. Clin Neuropharmacol 8:38–57

Langston JW, Forno LS, Rebert CS, Irwin I (1984) Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the squirrel monkey. Brain Res 292:390–394

Lees AJ, Stern GM (1983) Sustained bromocriptine therapy in previously untreated patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 44:1020–1023

Markham CH (1974) The choreoathetoid movement disorder induced by levodopa. Clin Pharmacol Ther 12:340–343

Marsden CD, Parkes JD, Quinn N (1982) Fluctuations of disability in Parkinson's disease – clinical aspects. In: Marsden CD, Fahn S (eds) Movement disorders. Butterworths, London, pp 96–122

Melamed E (1979) Early-morning dystonia. A late side effect of long-term levodopa therapy in Parkinson's disease. Arch Neurol 36:308–310

Mones RJ, Elizan TS, Siegel GJ (1971) Analysis of L-dopa induced dyskinesia in 61 patients with parkinsonism. J Neurol Neurosurg Psychiatry 34:668–673

Mouradian MM, Heuser IJE, Baronti F, Fabbrini G, Juncos JL, Chase TN (1989) Pathogenesis of dyskinesias in Parkinson's disease. Ann Neurol 25:523–526

Muenter MD, Sharpless TS, Tyce GM, Darley FL (1977) Patterns of dystonia ("I–D–I" and "D–I–D") in response to L-dopa therapy for Parkinson's disease. Mayo Clin Proc 52:163–174

Neale R, Gerhardt S, Fallon S, Liebman JM (1982) Progressive changes in the acute dyskinetic syndrome as a function of repeated elicitation in squirrel monkeys. Psychopharmacology 77:223–228

Parent A, Smith Y (1987) Differental dopaminergic innervation of the two pallidal segments in the squirrel monkey *(Saimiri sciureus)*. Brain Res 426:397–400

Protais P, Constentin J, Schwartz JC (1976) Climbing behaviour induced by apomorphine in mice: a simple test for the study of dopamine receptors in striatum. Psychopharmacology 60: 1–6

Richfield EK, Young AB, Penney JB (1987) Comparative distribution of dopamine D–1 and D–2 receptors in the basal ganglia of turtles, pigeons, rats, cats and monkeys. J Comp Neurol 262:446–463

Robertson RG, Farmery SNM, Sambrook MA, Crossman AR (1989) Dyskinesia in the primate following injection of an excitatory amino acid antagonist into the medial segment of the globus pallidus. Brain Res 476:317–322

Rupniak NMJ, Jenner P, Marsden CD (1986) Acute dystonia induced by neuroleptic drugs. Psychopharmacology 88:403–419

Rupniak NMJ, Tye SJ, Jenning CA, Loper AE, Bondi JV, Hichens M, Hand E, Iversen SD, Stahl SM (1989) Antiparkinsonian efficacy of a novel transdermal delivery system for (+)-PHNO in MPTP-treated squirrel monkeys. Neurology 38:329–335

Smith Y, Lavoie B, Dumas J, Parent A (1989) Evidence for a distinct nigropallidal dopaminergic projection in the squirrel monkey. Brain Res 482:381–386

Stahl SM, Davis KL, Berger PA (1982) The neuropharmacology of tardive dyskinesia, spontaneous dyskinesia, and other dystonias. J Clin Psychopharmacol 2:321–328

Stoessl AJ, Mak E, Calne DB (1985) (+)-4-Propyl-9-hydroxynaphthoxazine (PHNO), a new dopaminomimetic, in treatment of parkinsonism. Lancet II:1330–1331

Tarsy D, Leopold N, Sax DS (1974) Physostigmine in choreiform movement disorders. Neurology 24:28–33

Tasker RR (1970) Significance and etiology of induced abnormal movements: physiological implications. In: Barbeau A, McDowell FH (eds) L-dopa and parkinsonism. FA Davis, Philadelphia, pp 159–163