

# Abnormal reciprocal inhibition between antagonist muscles in Parkinson's disease

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## Summary

Disynaptic Ia reciprocal inhibition acts, at the spinal level, by actively inhibiting antagonist motor neurons and reducing the inhibition of agonist motor neurons. The deactivation of this pathway in Parkinson's disease is still debated. Disynaptic reciprocal inhibition of H reflexes in the forearm flexor muscles was examined in 15 control subjects and 16 treated parkinsonian patients at rest and at the onset of a voluntary wrist flexion. Two patients were reassessed 18 h after withdrawal of antiparkinsonian medication. At rest, the level of Ia reciprocal inhibition between the wrist antagonist muscles was not significantly different between patients and controls. In contrast, clear abnormalities of this inhibition were revealed by voluntary

movements in the patients. In normal subjects, at the onset of a wrist flexion, Ia reciprocal inhibition showed a large decrease, and we argue that this decrease is supraspinal in origin. On the less affected sides of the patients the descending modulation was still present but lower than in controls; on the more affected sides this modulation had vanished almost completely. These movement-induced abnormalities of disynaptic Ia reciprocal inhibition were closely associated with Parkinson's disease but were probably not dependent on L-dopa. They could play a role in the disturbances of precise voluntary movements observed in Parkinson's disease.

**Keywords:** Parkinson's disease; reciprocal inhibition; cortical command; H reflex; L-dopa

**Abbreviations:** ECR = extensor carpi radialis; FCR = flexor carpi radialis;  $M_{\max}$  = maximum motor response; MT = motor threshold; MVC = maximum voluntary contraction; UPDRS = unified Parkinson's disease rating scale

## Introduction

The motor function of the basal ganglia is still a matter of debate. It has been suggested that the basal ganglia could select the desired motor pattern generator and inhibit competing motor pattern generators (Mink, 1996). Little is known of the ways through which the output of the basal ganglia exerts this selection at the spinal level. Some spinal pathways, such as presynaptic inhibition and disynaptic reciprocal Ia inhibition, are good candidates as they contribute to the isolation of the appropriate motor neuronal pool either by focusing excitatory drives (peripheral and/or descending in origin) and/or by inhibiting the other pools. Studies in humans have confirmed that supraspinal drives to interneurons interposed in these pathways are crucial (Day *et al.*, 1983, 1984; Hultborn *et al.*, 1987; Nielsen *et al.*, 1995).

Some arguments suggest that reciprocal inhibition is impaired in Parkinson's disease: during strong elbow movements EMG patterns have shown co-contraction of antagonist muscles in parkinsonian patients (Ohye *et al.*, 1965), and monkeys with MPTP (1-methyl-4-phenyl-1,2,3,6-

tetrahydropyridine) parkinsonism have slow movements with co-contraction of agonist and antagonist muscles (Benazzouz *et al.*, 1992). No obvious abnormality of the segmental control of disynaptic Ia reciprocal inhibition has been found in patients with parkinsonian symptoms, and it has been claimed that, at rest, reciprocal Ia inhibition was not modified (Nakashima *et al.*, 1994; Tsai *et al.*, 1997), was decreased (Lelli *et al.*, 1991) or was even increased (Delwaide *et al.*, 1993). In contrast, experiments performed during voluntary movements in the lower (Hayashi *et al.*, 1988) or upper (Nakashima *et al.*, 1994) limb suggest that movement-induced central drive to spinal interneurons is inappropriate in Parkinson's disease. Methods used in these studies did not permit the identification of all the different spinal pathways contributing to active inhibition of antagonist motor neurons during a contraction (disynaptic reciprocal inhibition, 'long-latency' reciprocal inhibition, presynaptic inhibition, recurrent inhibition). The aim of this study was to selectively analyse disynaptic reciprocal inhibition and its central

modulation during voluntary movement in parkinsonian patients. Parkinsonian symptoms often start at the hand and wrist level as difficulty in writing, so we chose to study reciprocal inhibition between wrist flexors and extensors.

## Methods

### Subjects

Sixteen patients with Parkinson's disease (aged 48–71 years; mean  $\pm$  SEM =  $60 \pm 2$ ) and 15 healthy control subjects (35–66 years; mean  $\pm$  SEM =  $51 \pm 2$ ) were enrolled in the study. They gave informed consent to the experimental procedure, which was approved by the local ethics committee.

Only patients with moderately severe Parkinson's disease were included. Patients and controls were also selected according to the possibility of recording a suitable H reflex in their wrist flexors [18 patients had agreed to participate in this study but in two of them it was impossible to evoke a flexor carpi radialis (FCR) H reflex].

The diagnosis of Parkinson's disease was established on the basis of: (i) akinetorigid symptoms of progressive onset; (ii) an improvement of  $>50\%$  in parkinsonian disability with antiparkinsonian treatment; (iii) absence of dementia; (iv) absence of signs or symptoms suggesting other degenerative syndromes; and (v) absence of chronic administration of neuroleptic drugs.

All patients were treated (L-dopa,  $n = 15$ , mean dose  $\pm$  SEM =  $347 \pm 44$  mg; bromocriptine,  $n = 6$ , mean dose =  $19 \pm 5$  mg; lisuride,  $n = 1$ , dose = 12 mg). They were evaluated clinically by the same neurologist and a unified Parkinson's disease rating score (UPDRS) was obtained at the time when the effect of antiparkinsonian treatment was maximal (ON condition), at the end of the electrophysiological tests. From the items of the UPDRS score (part III), for each patient's arm, we calculated a rigidity score and a subscore of akinesia (finger-taps + hand movements + rapid alternating movements of hands). A subscore for axial signs was also calculated by adding the corresponding items (gait, posture, postural stability, speech, ability to stand up). Data for the 16 patients are summarized in Table 1. At this time, parkinsonian signs were strictly unilateral in 11 patients, asymmetrical in 4 and bilateral in 1; patients were at Hoehn and Yahr stages I–II and had a UPDRS score of  $8 \pm 1$  (mean  $\pm$  SEM).

Two patients (Ta and La) (Table 1) were reassessed 18 h after withdrawal of all antiparkinsonian therapy, at the period of maximal parkinsonian disability (OFF condition).

### General experimental arrangement

Subjects were seated comfortably in an armchair, in front of a screen. Their forearm was pronated and supported by an armrest. The EMG was recorded from surface electrodes placed over the bellies of the wrist flexor and extensor muscles. Subjects could continuously watch the EMG

activities of their forearm flexor and extensor muscles on an oscilloscope. Signals from the electrodes over the flexor muscles were mainly from the FCR muscle and those from the electrodes over the extensor muscles were mainly from the extensor carpi radialis (ECR).

The method used to study reciprocal inhibition between the wrist flexors and extensors was that first introduced by Day and colleagues (Day *et al.*, 1984). The FCR H reflex was elicited by electrical stimulation of the median nerve in the antecubital fossa. The intensity of stimulation (shocks of 1 ms duration every 5 s) was adjusted in order to elicit approximately half-maximal H reflexes in the wrist flexor muscles. In this condition the size of the H reflex was between 5 and 15% of the  $M_{\max}$  (maximum motor response of wrist flexor muscles) in two-thirds of the patients and in almost all normal subjects. In one-third of the patients and in two controls, reflexes were very small, with sizes below 5% of  $M_{\max}$ .

A stimulation of the radial nerve in the spiral groove was used to activate extensor-coupled Ia interneurons and evoke a disynaptic inhibition of FCR motor neurons (Fig. 1)

In one patient and one control, it was possible to record a suitable ECR H reflex at rest. Activation of flexor-coupled Ia interneurons and the consequent disynaptic inhibition of ECR motor neurons was obtained by stimulating the median nerve at low intensity [lower than the FCR H reflex threshold, i.e. 0.6–0.7 motor threshold (MT)].

### Experimental protocol

The first step was to determine the earliest interval at which radial nerve stimulation (1 ms duration shocks), set at the threshold for the ECR M response (1 MT), induced significant inhibition of the FCR H reflex. This time interval was usually 0 ms, although it could vary by  $\pm 1$  ms in some subjects. This same interval was then used throughout the experiment. At such an interval, radial-induced inhibition reflects disynaptic inhibition of flexor motor neurons transmitted by spinal Ia inhibitory interneurons (Day *et al.*, 1983).

To avoid the excitation of heteronymous Renshaw cells (see Discussion), the intensity of radial nerve stimulation was decreased to 0.8 MT, an intensity at which neither M nor H responses were recorded in the ECR EMG. Inhibition obtained at this low intensity was compared at rest and during a wrist flexion.

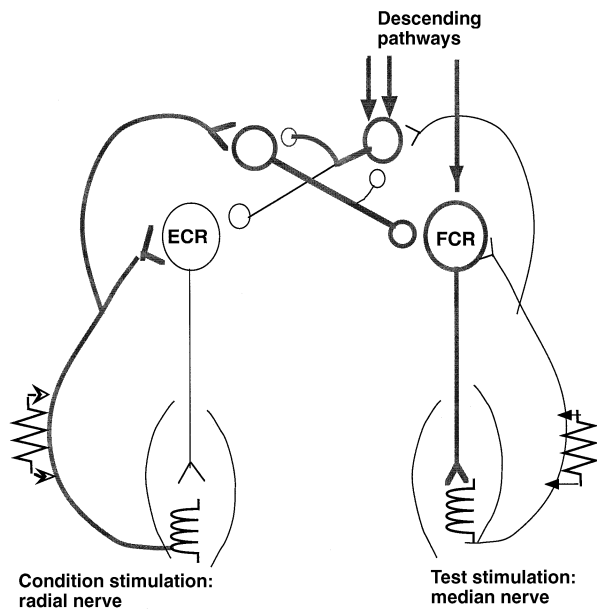
### Onset of movement

Eleven patients were tested bilaterally. Three were tested only on the more affected side (patients Ja, Le and Cu) (Table 1). Two were tested only on the less affected side (patients Ou and Al) (Table 1), one because of a substantial resting tremor on his more affected side and the other because it was impossible to record a suitable H reflex on his more affected arm. Normal subjects (12 right-handed, three left-handed) were tested on their dominant side.

**Table 1** Clinical data of 16 parkinsonian patients

Patient	Sex	Age (years)	Affected side	Akinesia right arm	Akinesia left arm	Axial signs	Rigidity right arm	Rigidity left arm	Duration of evolution (years)	Duration of treatment (years)
No	F	48	L	1.5	3	1.5	0	0	7	5
Ma	F	58	R	2.5	0	0.5	1	0	8	8
Ou	M	68	R	2.5	0	1	0.5	0	3	2
Ja	M	57	L	2	5	2	0	1	4	3
Ta	F	58	R	1.5	0.5	1	1	0	2	1
La	M	52	R	2	2.5	1	1	1	4	2
De	M	61	R	2.5	0	2	0	0	6	5
Mo	M	66	R	4	0	0	1	0	6	2
Le	M	55	R	4	0	1.5	1	0	7	5
Cu	F	72	R	1	0.5	1	0	0	8	4
Ce	F	71	R	2	0	0	0	0	4	2
Be	M	65	L	0	1	0	0	0	4	2
Fo	F	51	L	0	4	4	0	2	3	2
Bl	F	50	L	0	1	0	0	0	9	2
Al	M	69	L	0	4.5	1	0	1	4	3
Go	M	62	R	5	0	2	1	0	4	2

Akinesia and rigidity scores were calculated for the upper limb from the UPRDS III subscores (see Methods).



**Fig. 1** Schematic diagram showing the generally accepted organization of the Ia reciprocal inhibitory pathways at the level of wrist muscles in man. Synapses are represented by bars if excitatory and by circles if inhibitory. Thick black lines represent the connections activated during our experiments.

Subjects were instructed to respond to an auditory and visual (i.e. the start of the sweep on the oscilloscope) GO signal by rapidly flexing their wrist (keeping the fingers extended). In a pretest session, subjects had been trained to perform phasic, isolated wrist flexion of 500 ms duration and of mild strength [between 10 and 20% of the maximum voluntary contraction (MVC)] and to relax their forearm muscles fully between each voluntary movement.

Five patients and five control subjects were reinvestigated with the hand attached to a torque-meter. The torque was displayed on an oscilloscope and subjects were instructed to

perform a ramp and hold (500 ms for each phase) isometric wrist flexion of 10–15% of their MVC, following a line drawn on the oscilloscope.

The voluntary EMG activity was recorded, amplified, rectified and connected to a triggering circuit. The first voluntary EMG potential triggered conditioning and test stimuli. At the onset of a wrist flexion the test FCR H reflex was strongly facilitated in all control subjects and patients. As the amount of reciprocal inhibition (expressed as a percentage of the unconditioned reflex) increases when the amplitude of the unconditioned H reflex is decreased (Fuhr and Hallett, 1993), the test stimulus intensity was adjusted (decreased) carefully during movement so that the control H reflex was the same size as at rest. The amount of change in the unconditioned H reflex size at the onset of a wrist flexion was evaluated more precisely in six normal subjects and six patients.

**Tonic contraction**

In five control subjects and the more affected sides of five patients, reciprocal inhibition was also assessed during a tonic voluntary wrist flexion of 10–15% of MVC. As the unconditioned H reflex was only slightly, if at all, facilitated during such a contraction, adjustment of the test stimulus intensity was not necessary.

Three sequences at rest and three during phasic or tonic movements were alternated. Twenty unconditioned (median nerve stimulation alone) and 20 conditioned reflexes (median plus radial nerve stimulations) were presented randomly every 5 s in each sequence. When a cyclic tremor activity appeared during the experiments or when relaxation was not good enough between each movement, the corresponding files were disregarded.

### Phasic contraction with a background of tonic activity

Control experiments were performed in five healthy subjects: subjects were asked to maintain a very weak background tonic activity in wrist flexor muscles (one or a few motor units) and to perform a phasic wrist flexion while listening to the GO signal. Three sequences during background tonic activity and three with a superimposed phasic movement were alternated.

To ensure the stability of the conditioning stimulation during movement, the threshold for the ECR M response was checked after every second series of stimulations. In addition, in some subjects an ECR M response, evoked by a radial nerve stimulation at 1.2 MT, was also recorded and measured during the same sequences as when reciprocal inhibition was assessed, using three configurations: median nerve stimulation; median and radial (0.8 MT) nerve stimulations; and radial nerve (1.2 MT) stimulation.

### Measurements and statistics

The mean size and standard error of the mean of the 60 unconditioned and the 60 conditioned H reflexes were calculated for the reflexes obtained during the control situation or during movement. Reciprocal inhibition was expressed as the ratio of conditioned to unconditioned H reflex sizes. Movement-induced modulation of reciprocal inhibition was calculated as the difference between the values at which reciprocal inhibition reduced the H reflex at rest and during movement (reciprocal inhibition during rest minus reciprocal inhibition during movement) (Iles, 1996); a negative value indicates a decrease in reciprocal inhibition during movement. As the extent of the reciprocal inhibition at rest varied among subjects, the movement-induced decrease in reciprocal inhibition was expressed as a percentage of reciprocal inhibition at rest (100 – reciprocal inhibition at rest), so that this normalized variation could vary between 0 (no change) and 100% (complete depression).

Intragroup comparisons were done with the Wilcoxon *T* test. Reciprocal inhibition at rest and movement-induced modulation and its normalized value were compared between the more and less affected sides of the patients and the dominant sides of the controls, using variance analysis (ANOVA) and then a multiple comparisons post test (Bonferroni–Dunn). When patients had been tested only on their more affected side (tonic contractions), comparison with control subjects were done using the Mann–Whitney *U* test. Correlations between the electrophysiological data and the clinical items were evaluated using Spearman's correlation analysis.

## Results

### Inhibition from wrist extensors to wrist flexors at rest

In all subjects, stimulating the radial nerve at 1 MT evoked, at rest, a significant inhibition of the FCR H reflex. When

**Table 2** Mean value ( $\pm$  SEM) of the conditioned FCR H reflex at rest and during movement expressed as a percentage of the control FCR H reflex size

	Patients ( <i>n</i> = 16)		Controls ( <i>n</i> = 15)
	Less affected side	More affected side	
Depth of reciprocal inhibition at rest and at onset of wrist flexion			
Rest (radial 0.8 MT)	64.5 $\pm$ 2%	65.1 $\pm$ 2%	63.9 $\pm$ 2%
Onset of flexion (radial 0.8 MT)	76.2 $\pm$ 5%	67 $\pm$ 4%	83.3 $\pm$ 3%
Movement-induced modulation	-31.5 $\pm$ 13%	-4.8 $\pm$ 10%	-58 $\pm$ 9%
		Patients ( <i>n</i> = 5) More affected side	Controls ( <i>n</i> = 5)
Depth of reciprocal inhibition at rest and during a tonic wrist flexion			
Rest (radial 0.8 MT)		64.8 $\pm$ 4%	58.6 $\pm$ 2%
Tonic flexion (radial 0.8 MT)		69.9 $\pm$ 6%	81.2 $\pm$ 5%
Movement-induced modulation		-18.2 $\pm$ 9%	-56 $\pm$ 10%

Movement-induced modulation is normalized and expressed as a percentage of inhibition at rest.

the intensity of the radial stimulation was decreased to 0.8 MT (see Methods), inhibition was still present in all subjects. The extent of inhibition differed greatly among the subjects: the conditioned H reflex varied from 49 to 80% of its control size. The mean value of the conditioned reflex was 63.9  $\pm$  2% (mean  $\pm$  SEM) in controls and was not significantly different in patients on either their less or their more affected side (64.5  $\pm$  2 and 65.1  $\pm$  2%, respectively; ANOVA; *F* = 0.02, *P* = 0.98) (Table 2).

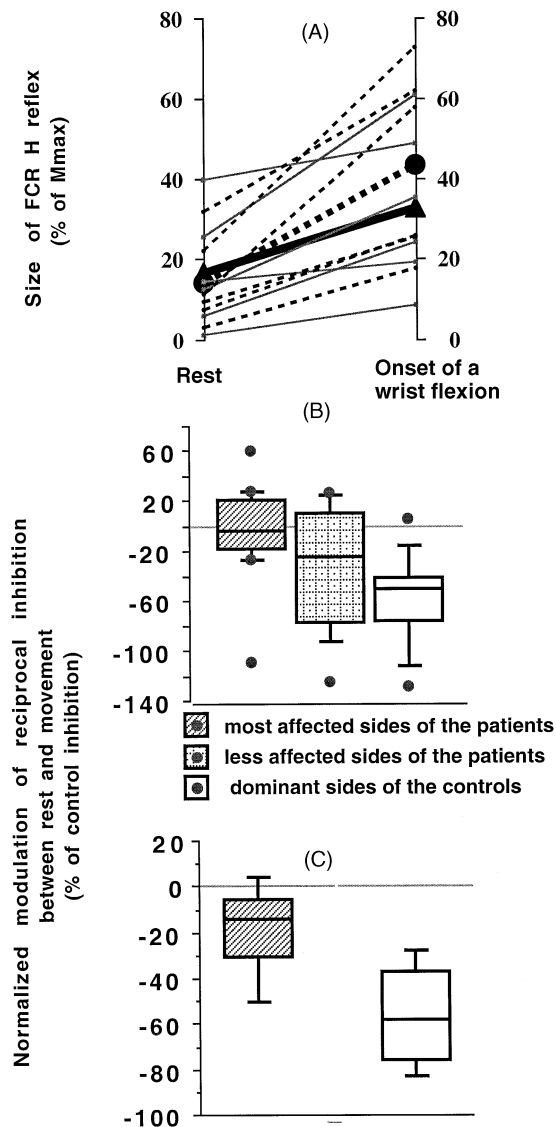
### Movement-induced modulation of the FCR H reflex

In all patients and controls, the FCR H reflex was strongly facilitated at the onset of a voluntary wrist flexion. Figure 2A shows that the amount of this movement-induced facilitation of the unconditioned H reflex (assessed in six controls and six patients) was very similar (ANOVA repeated measures; between-group effect, *P* = 0.7; interaction between group and effect of the movement, *P* = 0.14), whereas movement-induced facilitation was highly significant (*P* = 0.0002).

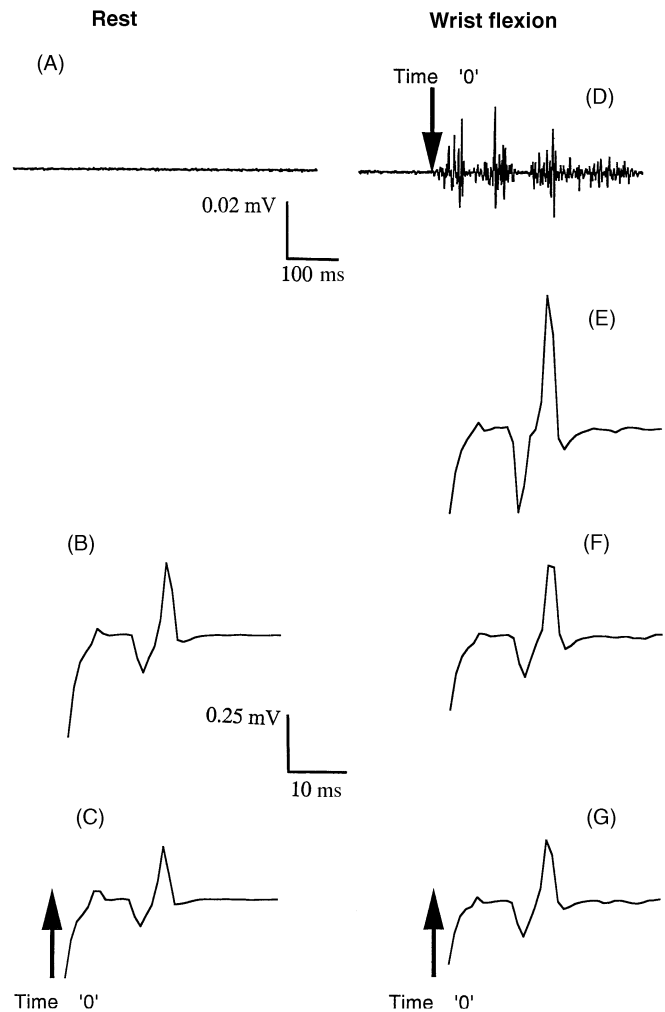
### Movement-induced modulation of reciprocal inhibition from wrist extensors to wrist flexors

#### Phasic contraction

Figure 3 shows the averaged reflexes of a single representative patient (patient Ta) (Table 1). The data from all patients and controls are summarized in Table 2 and illustrated in Fig. 2B.



**Fig. 2** (A) Effect of a phasic wrist flexion on the size of the unconditioned FCR H reflex. The left side of the graph indicates the size of the FCR H reflex at rest expressed as a percentage of  $M_{max}$ ; the right side is the corresponding size of the reflex at the onset of a phasic wrist flexion. Each thin line represents data from one subject (continuous lines represent patients; interrupted lines represent controls). Thick lines represent the mean values in the control group (filled circles) and in the patient group (filled triangles). (B and C) Box plots indicating median (centre bar in box) and centiles [bars with (bottom to top) 10th, 25th, 50th, 75th and 90th centiles] of the normalized modulation of Ia reciprocal inhibition from wrist extensors to wrist flexors. Values below the 10th and above the 90th centiles are represented by the black dots. (B) Modulation at the onset of a phasic wrist flexion. Three groups are compared (left to right): more affected side of the parkinsonian patients; less affected side of the patients; dominant side of the controls. (C) Modulation during a tonic wrist flexion. Two groups are compared: the left part shows the more affected side of the parkinsonian patients and the right part shows the dominant side of the control subjects.



**Fig. 3** Movement-induced modulation of disynaptic Ia reciprocal inhibition from wrist extensors to flexors at the onset of a phasic wrist flexion. Raw data for subject Ta. On the left are recordings during the rest condition with (A) electromyographic recordings of FCR EMG activity, (B) control H reflex and (C) conditioned H reflex (87% of its control size). On the right are recordings during a phasic wrist flexion with (D) electromyographic recordings of FCR EMG activity (time 0 represents the onset of EMG activity and is taken as the origin in the recordings E, F and G); (E) FCR H reflex at the onset of the flexion before adjusting the test stimulus intensity (267% of its size at rest); (F) FCR H reflex after decreasing the test stimulus intensity (137% of its control value); and (G) conditioned H reflex (83% of its control size). Each trace (B, C, E, F and G) represents the mean of 60 trials.

Radial-induced inhibition was consistently decreased at the onset of a wrist flexion in control subjects. The mean size of the conditioned reflexes became  $83.3 \pm 3\%$  at the onset of a phasic wrist flexion versus  $63.9 \pm 2\%$  at rest ( $P = 0.0008$ , Wilcoxon test). This decrease was observed in all except one subject. In patients, some movement-induced modulation was still observed on their less affected side, where the conditioned reflex size became  $76.2 \pm 5\%$  at the onset of the flexion versus  $64.5 \pm 2\%$  at rest ( $P = 0.05$ , Wilcoxon test). On the more affected side, modulation almost

totally disappeared, and the conditioned reflex size did not change between rest ( $65.1 \pm 2\%$ ) and movement ( $67 \pm 4\%$ ) ( $P = 0.9$ , Wilcoxon test). In six patients (No, Ou, La, Mo, Ce, Bl) (Table 1), not only was reciprocal inhibition not decreased during movement but it even showed an increase.

The medians and centiles of normalized values of the movement-induced modulation are shown in Fig. 2B for the three groups of control subjects, patients on the less affected side and patients on the more affected side. The normalized value of the movement-induced modulation was significantly less in patients than in controls (ANOVA for the three groups;  $F = 7.77$ ,  $P = 0.0014$ ). The most striking difference was between the more affected side of the patients and the control subjects (patients,  $-4.8 \pm 10$ ; controls,  $-58 \pm 8.7\%$ ; Bonferroni–Dunn,  $P = 0.0003$ ). There was a tendency towards a decrease in modulation on the less affected side of the patients ( $-31.5 \pm 13$  versus  $-58 \pm 8.7\%$ ; Bonferroni–Dunn,  $P = 0.0494$ ). Nevertheless, there was no statistically significant difference between the more and the less affected sides of the patients (Bonferroni–Dunn,  $P = 0.1$ ).

It is well known that Parkinson's disease patients move more slowly than normal subjects (Hallett *et al.*, 1977), and the slope of the force at the onset of movement could be less steep in patients than in control subjects. To rule out the possibility that modifications of the mechanical characteristics of the voluntary wrist flexion account for the lack of modulation observed in patients, the slope of the force and the force at the end of the ramp were matched exactly in five patients and five controls using a torque-meter (see Methods). In this condition, means of the movement-induced modulation of reciprocal inhibition remained very different in the controls ( $-92 \pm 21\%$ ) and on the more affected side of the patients ( $-31.9 \pm 14\%$ ) ( $P = 0.07$ , Mann–Whitney  $U$  test).

### *Tonic contraction*

Studies of the H-reflex recovery cycle (Sax *et al.*, 1977) suggest that the level of segmental excitability is higher at rest in Parkinson's disease patients than in control subjects, making comparison between the rest state in patients and controls difficult. To investigate such a shift in excitability, the amount of reciprocal inhibition was compared (i) between rest and a tonic voluntary wrist flexion, and (ii) between a tonic voluntary wrist flexion and the onset of a superimposed phasic voluntary wrist flexion.

During a tonic wrist flexion (Table 2 and Fig. 2C), the amount of reciprocal inhibition clearly did not exhibit such a large decrease in the five patients studied as in the five matched controls. The mean value of the normalized modulation of reciprocal inhibition during tonic contraction was  $-56 \pm 10\%$  in controls and  $-18.2 \pm 9\%$  in patients ( $P = 0.028$ , Mann–Whitney  $U$  test).

The amount of reciprocal inhibition was assessed in five healthy subjects, in the same experimental session, using four conditions: rest; onset of a voluntary wrist phasic flexion

(15% of MVC); weak voluntary tonic contraction (few motor units); and the onset of a wrist voluntary phasic flexion (15% of MVC) superimposed on the background tonic activity. Movement-induced modulation of reciprocal inhibition (normalized value) was the same whether the phasic movement was performed by a previously completely relaxed muscle or by a muscle previously activated in a background contraction ( $-59.7 \pm 7$  and  $-50.6 \pm 6\%$ , respectively;  $P = 0.68$ , Wilcoxon test).

### *Effect of withdrawal of L-dopa therapy*

To appreciate how L-dopa therapy may interfere with the loss of an adapted modulation of reciprocal inhibition, two patients were reassessed, on their more affected side, at their maximal parkinsonian disability 18 h after withdrawal from medication (patients Ta and La) (Table 1). There was no difference either in reciprocal inhibition at rest or in the normalized modulation of Ia reciprocal inhibition during the ON and the OFF periods. For patient Ta, inhibition at rest was 52% during the OFF period versus 58% during the ON period, and its modulation during movement was  $-4.8\%$  during the ON period and  $-2.1\%$  during the OFF period. For patient La (one of the six patients in whom wrist flexion induced an increase in Ia reciprocal inhibition; see above), inhibition at rest was 66% during the OFF period versus 62% during the ON period, and its modulation during movement was 21% during the ON period and 27% during the OFF period.

### *Reciprocal inhibition from wrist extensors to wrist flexors.*

We were also able to study reciprocal inhibition from wrist flexors to wrist extensors in two subjects (one patient and one control) in whom it was possible to record an H reflex in the ECR by stimulating the radial nerve. Stimulation of the median nerve (0.7 MT) induced a significant inhibition of the ECR H reflex. This inhibition significantly decreased at the onset of a wrist extension in the control subject (the size of the conditioned H reflex was  $57 \pm 3\%$  at rest and  $81 \pm 5\%$  during wrist extension) but not in the patient ( $80 \pm 9\%$  at rest and  $70 \pm 5\%$  during movement).

### *Correlations with clinical signs*

Eleven patients were tested bilaterally; six of them had an asymmetrical modulation of Ia reciprocal inhibition and five had strictly unilateral clinical signs with a clinical score equal to 0 on the side on which movement-induced modulation was normal. In four patients, modulation of Ia reciprocal inhibition had disappeared bilaterally; two had a very symmetrical clinical status but the two others were scored at 0 on one side (patients Ce and Bl). In one patient the

modulation of reciprocal inhibition was in the normal range on both sides (patient De).

In the control subjects, no correlation (Spearman test) was found between age and the amount of inhibition at rest ( $\rho = 0.09$ ) or of movement-induced modulation ( $\rho = -0.09$ ). In the patients, movement-induced modulation did not correlate with duration of the illness ( $\rho = 0.4$ ), duration of the treatment ( $\rho = 0.2$ ), UPDRS score ( $\rho = -0.1$ ), akinesia score ( $\rho = -0.2$ ) or rigidity score ( $\rho = -0.2$ ), but correlated weakly with the axial signs score ( $\rho = 0.5$ ,  $P = 0.05$ ).

## Discussion

Disynaptic reciprocal inhibition from wrist extensors to flexors was assessed by the inhibition of the FCR H reflex evoked by radial nerve stimulation. This inhibition was found, at rest, in all subjects. At the onset of a wrist flexion, reciprocal inhibition was strongly decreased in control subjects, but this movement-induced modulation disappeared almost completely on the more affected side of the patients and was decreased on their less affected side.

### *Does the radial-induced inhibition of the FCR H reflex reflect disynaptic reciprocal inhibition from wrist extensors to wrist flexors?*

Congruent data in the literature support the view that the early part of the radial-evoked inhibition of the FCR H reflex is mediated by interneurons that present some of the main characteristics of those mediating the disynaptic Ia reciprocal inhibition in the cat spinal cord, where it has been investigated extensively (Jankowska and Roberts, 1972). Radial-evoked inhibition of the FCR H reflex (i) can be evoked with stimulus intensities activating group I afferents (0.7–0.8 MT) (Day *et al.*, 1983); (ii) has been shown to be postsynaptic in origin (Berardelli *et al.*, 1987); (iii) has a central delay that has been calculated to be ~0.95 ms longer than the central delay in the H reflex, which suggests disynaptic linkage (Day *et al.*, 1983); (iv) shows a mutual opposition linking wrist flexor- and wrist extensor-coupled interneurons (Baldissera *et al.*, 1987); and (v) involves fast-conducting corticospinal axons converging with group I afferents onto Ia interneurons, as shown by the use of cortical electrical or magnetic stimulation (Rothwell *et al.*, 1984; Mercuri *et al.*, 1997) (Fig. 1). However, at wrist level these reciprocal Ia interneurons do not receive inhibitory projections from Renshaw cells, which is contrary to what has been observed in the cat hindlimb (Hultborn *et al.*, 1971) and in human elbow muscles (Katz *et al.*, 1991; Aymard *et al.*, 1995).

As we studied the first millisecond of the radial-induced inhibition, activity in other oligosynaptic spinal pathways fed by radial afferents ['long-latency reciprocal inhibition' (Crone and Nielsen, 1989); Ib excitation (Cavallari *et al.*, 1985); cutaneous inhibition (Day *et al.*, 1984, Berardelli *et al.*,

1987); presynaptic inhibition (Berardelli *et al.*, 1987)] would not have interfered.

We therefore used a weak radial stimulation (0.8 MT) to prevent Renshaw cells from being activated by any conditioning motor discharge as, using EMG recordings, Aymard and colleagues have shown that, in wrist muscles, an antagonistic motor volley results in an early and long-lasting inhibition that is increased by injection of L-acetylcarnitine, suggesting Renshaw inhibition (Aymard *et al.*, 1997).

### *Supraspinal origin of movement-induced modulation of reciprocal inhibition*

The decrease in radial-induced inhibition of the FCR H reflex at the onset of a wrist flexion was observed at the very beginning of the voluntary EMG, when motor neuron excitability was not yet influenced by the contraction-induced afferent discharge. The simplest explanation for the decrease in reciprocal inhibition at the onset of an agonist contraction in control subjects is a decrease in the excitability of Ia reciprocal interneurons from extensors to flexors, which can be assumed to be supraspinal in origin. This is supported by the results obtained by Day and colleagues, in which, during the 60 ms preceding a willed wrist movement, reciprocal inhibition from extensors to flexors was decreased before a wrist flexion but was increased before a wrist extension (Day *et al.*, 1983). This is consistent with the idea that the descending command simultaneously activates the agonist  $\alpha$ -motor neurons and their 'corresponding' Ia interneurons and, at the same time, induces depression of the antagonist-coupled interneurons. If the descending facilitation is strong enough to make the agonist-coupled interneurons fire, the antagonist-coupled interneurons will be inhibited because of mutual inhibition between antagonist Ia interneurons (Fig. 1). Another possibility is that reciprocal interneurons are tonically inhibited by the brain and that, during an agonist contraction, this descending tonic inhibitory control is reinforced to agonist-coupled interneurons and reduced to antagonist-coupled ones (Nielsen and Kagamihara, 1992). Such tonic control has been described in anaesthetized baboons (Hongo *et al.*, 1984), but there has been no argument to suggest that it could exist in awake humans.

### *Reciprocal inhibition and Parkinson's disease*

Disynaptic reciprocal Ia inhibition has been studied previously in Parkinson's disease patients at rest. Despite the fact that a similar method was used (radial-induced FCR H reflex inhibition), the results are not homogeneous. In patients without any medication, Lelli and colleagues found decreased reciprocal inhibition (Lelli *et al.*, 1991), whereas Tsai and colleagues did not find any modifications (Tsai *et al.*, 1997). Nakashima and colleagues found that reciprocal inhibition was retained at rest in their 12 treated patients but described

abnormalities during tonic movements (Nakashima *et al.*, 1994). In our 16 patients, reciprocal inhibition at rest was the same as in the control subjects.

Although the amount of reciprocal inhibition from wrist extensors to wrist flexors was in the normal range, at rest, in Parkinson's disease patients, it was clearly less depressed than in controls, during wrist flexion. Control experiments (see Results) have ruled out the possibility that this discrepancy is due to some experimental bias: patients were unable to relax their forearm muscles fully or performed slower and weaker movements than the control subjects, or had abnormalities in the modulation of the H reflex *per se*. So the lack of depression of reciprocal inhibition in Parkinson's disease patients probably reflects a lack of inhibition to extensor-coupled Ia interneurons during wrist flexion movements. Taking into account the mutual inhibition between antagonist Ia interneurons (see above), this lesser inhibition of extensor-coupled Ia interneurons might be due to a lack of descending excitation of flexor-coupled Ia interneurons by the descending volley to flexor motor neurons. Under this assumption, there would be a lack of reciprocal inhibition to antagonist motor neurons during movement. It has already been suggested that, in Parkinson's disease patients, reciprocal inhibition to antagonist motor neurons is inadequate during movement. Indeed 'natural' reciprocal inhibition, i.e. decreasing size of the soleus H reflex during ankle dorsiflexion, was clearly decreased and was even replaced by facilitation in Parkinson's disease patients (Hayashi *et al.*, 1988). While activation of disynaptic reciprocal inhibitory pathways certainly participates in this natural inhibition, other pathways, such as long-latency reciprocal inhibition and presynaptic inhibition, may also play a role.

### ***Does the loss of supraspinal modulation to reciprocal interneurons in Parkinson's disease depend on L-dopa?***

We have shown that movement-induced modulation of Ia reciprocal inhibition was significantly more disturbed on the more affected side of the patients than on the less affected side. This seems to suggest that the modifications of excitability of reciprocal interneurons correlate well with Parkinson's disease. Nevertheless, these modifications do not seem to be related to the loss of dopamine, as (i) all our patients except one were treated with L-dopa at the time of the experiment; (ii) in the two patients so investigated, the results were not modified after withdrawal of antiparkinsonian therapy; and (iii) there is a puzzling contrast between the minor disability of the patients (with good response to L-dopa) and the persistence of severe impairment (most often a loss) of supraspinal modulation to reciprocal Ia interneurons.

The only (weak) positive correlation found between clinical signs and abnormalities of reciprocal inhibition was for axial signs, and no correlation was found for akinesia or rigidity.

This could be due, in part, to the fact that clinical scores were in a narrow range (as the patients were studied at the time of maximal effect of treatment), which is not a good criterion to use in statistical correlation tests. However, it is worth noting that the axial signs are known to be less improved by L-dopa therapy than akinesia or rigidity.

If the loss of dopamine in the substantia nigra is not, *per se*, the relevant factor for the abnormalities described here, it could perhaps act through its modulating action on synapses using other transmitters.

### ***Possible origin of impaired descending control to reciprocal Ia interneurons***

In the cat hindlimb, disynaptic reciprocal inhibition is facilitated by volleys in the cortico-rubro- and vestibulo-spinal tracts (Lundberg and Voorhoeve, 1962; Grillner *et al.*, 1966; Hongo *et al.*, 1969). In man it has been shown that descending pathways either from the cortex (Rothwell *et al.*, 1984; Mercuri *et al.*, 1997) or from the brainstem (Iles and Pisini, 1992) and group I peripheral fibres converge onto interneurons mediating disynaptic Ia reciprocal inhibition. The output structure of the basal ganglia (globus pallidus-substantia nigra pars reticulata) sends the same message up to the cortex through the thalamus and down through the brainstem, and in particular through the pedunculopontine nucleus to the spinal cord (Jackson and Crossman, 1983; Perciavalle, 1987). The corticospinal and the reticulospinal drive to spinal interneurons could both be abnormal in Parkinson's disease patients. Although the output connections from the motor cortex are normal in Parkinson's disease (Dick *et al.*, 1984; Thompson *et al.*, 1986; Cantello *et al.*, 1991), it has been suggested that motor neurons could receive an abnormal corticospinal drive, as pyramidotomy improves parkinsonian rigidity (Putnam and Herz, 1950). In such conditions, the abnormality should lie upstream from the motor cortex, and this has been confirmed by the finding that intracortical inhibitory interneurons are underexcited in Parkinson's disease (Priori *et al.*, 1994; Ziemann *et al.*, 1996). Furthermore, it has been shown recently (Bertolasi *et al.*, 1998) that areas of the motor cortex controlling antagonist muscles could be organized in a similar way to reciprocal inhibition at the spinal level, as inputs from contracting agonist muscles not only excite areas controlling these muscles but also inhibit areas controlling the antagonists.

Indirect methods have suggested that functional changes in reticular nuclei may occur in Parkinson's disease. The auditory startle response is delayed in Parkinson's disease patients and does not improve after L-dopa treatment (Vidailhet *et al.*, 1992), and audiospinal facilitation has been found to be decreased bilaterally in Parkinson's disease, even in patients with unilateral symptoms (Delwaide *et al.*, 1993). The positive correlation found here between axial signs and neurophysiological data is consistent with the fact that reticulospinal pathways, in particular, project onto motor



neurons of the axial muscles involved in posture and locomotion. Pallidotomy improved the agonist/antagonist co-contraction observed in severe parkinsonian patients, whereas lack of reciprocal inhibition of antagonist muscles often remained after thalamotomy (Iacono *et al.*, 1995), which suggests that the interruption of the descending output from the globus pallidus to the mesencephalon is the effective mechanism. Greatly increased uptake of 2-deoxyglucose was found in the lateral pallidal segment in MPTP-parkinsonian monkeys (Mitchell *et al.*, 1989) and also in the pedunculo-pontine nucleus. Excessive output from globus pallidus–substantia nigra may lead to excessive GABAergic inhibition of the pedunculo pontine nucleus (Mitchell *et al.*, 1989).

Loss of adapted supraspinal excitation of agonist-coupled reciprocal interneurons during selective voluntary contraction in parkinsonian patients probably leads to insufficient inhibition of the antagonist motor neurons and to excessive inhibition of the agonist motor neurons when the antagonist muscle is stretched during the movement. Such a disorder of the agonist–antagonist activation pattern probably explains some of the difficulty that Parkinson's disease patients have in performing precise movements, but does not seem to be the neurophysiological correlate of rigidity or akinesia.

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