Overactivity of cervical premotor neurons in Parkinson's disease

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Abstract

***Objectives*—Cortical command to upper limb motor neurons is transmitted, in humans, not only through the monosynaptic corticomotor neuronal pathway, but also through cervical premotor neurons. Whether activity in this non-monosynaptic corticospinal pathway is modified in Parkinson's disease was explored.**

***Methods*—Ongoing EMG activity recorded in wrist extensors during tonic extension of the wrist is suppressed by a volley evoked by stimulating the superficial radial nerve. It has been shown that this cutaneous induced suppression is due to inhibition of transmission of the cortical command at a premotor neuronal level. By comparing the cutaneous induced EMG depression between 45 de novo parkinsonian patients and 23 age matched controls it has been possible to appreciate if and to what extent the "non-monosynaptic" part of the cortical command is modified in these patients.**

***Results*—At the early stage of the illness the EMG depression, reflecting the "non-monosynaptic" part of the cortical command, was bilaterally increased despite very asymmetric clinical status. When the duration of the disease was more than 36 months, EMG depression returned to its control level. No correlation was found between the amount of the EMG depression and parkinsonian symptoms before and after levodopa treatment.**

***Conclusion*—Increase of the relative "non-monosynaptic" part of the cortical command could reflect a compensatory motor mechanism elaborated upstream from the motor cortex**

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Keywords: Parkinson's disease; cervical premotor neurons; cortical command-EMG

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It has recently been suggested that in humans there may be a substantial disynaptic corticospinal excitation of motor neurons of some, but not all (see discussion), arm muscles which acts in parallel with the monosynaptic component.[1] The relevant premotor neurons are located in the cervical cord[2] and figure 1 shows their connections. Besides their corticospinal excitation[3] they receive monosynaptic excitation and disynaptic inhibition from peripheral afferents.[4 5] In particular they receive powerful inhibition from cutaneous afferents[6] and this inhibition has been used to show that, in normal subjects, a significant portion of the descending command for tonic wrist extension is mediated through this premotor neuronal relay.[7 8] Experiments using transcranial electrical[9 10] or magnetic[11 12] stimulation have shown that corticospinal projections are not abnormal in patients with Parkinson's disease, and that the source of the abnormal command received by motor neurons lies "upstream" from the motor cortex.[9 10] The present investigation was undertaken to explore whether this abnormal command results in an abnormal activity of cervical premotor neurons in patients with Parkinson's disease.

Methods

PATIENTS

Forty five patients with diagnoses of de novo Parkinson's disease[13] agreed to participate in the study. Mean (SEM) age of the patients was 59.5 (1.5) years; mean (SEM) duration of disease 27.6 (3.7) months; mean (SEM) age at onset of Parkinson's disease 56.8 (1.5); Hoehn and Yahr stages I-II. Their results were compared with those from 23 neurologically healthy age matched control subjects (mean age (SEM) 58 (3) years). They gave informed consent to the experimental procedure which had been approved by the appropriate ethics committee.The diagnosis of Parkinson's disease was established on the basis of: (1) akinetorigid symptoms of progressive onset; (2) absence of symptoms or signs suggesting other degenerative syndromes, such as supranuclear palsy, cerebellar, pyramidal, pseudobulbar signs or apraxia; (3) absence of dementia as defined by a mini mental state examination score above 27[14]; (4) absence of chronic administration of neuroleptic drugs; (5) normal CT or MRI. Patients with a substantial resting tremor were rejected.Eleven patients were reassessed electrophysiologically after levodopa treatment: mean (SEM) duration of treatment 3.9 (1.6) months (range 3 to 6 months), mean daily dose of levodopa 360 mg (range 150–750 mg), percentage of improvement with levodopa 60 (range 30–100)% on UPDRS scores. Associated treatments were 15 mg/day bromocriptine in two patients and 0.6 mg/day lisuride in another. Parkinson motor disability was assessed semiquantitatively, using items from the modified third section of the UPDRS rating scale,[15] each item being rated 1 to 4 with a maximal score of 108. The baseline score (BS) was obtained before any antiparkinsonian treatment, the treated score (TS) at the time of maximal clinical improvement. The percentage of improvement[16] was

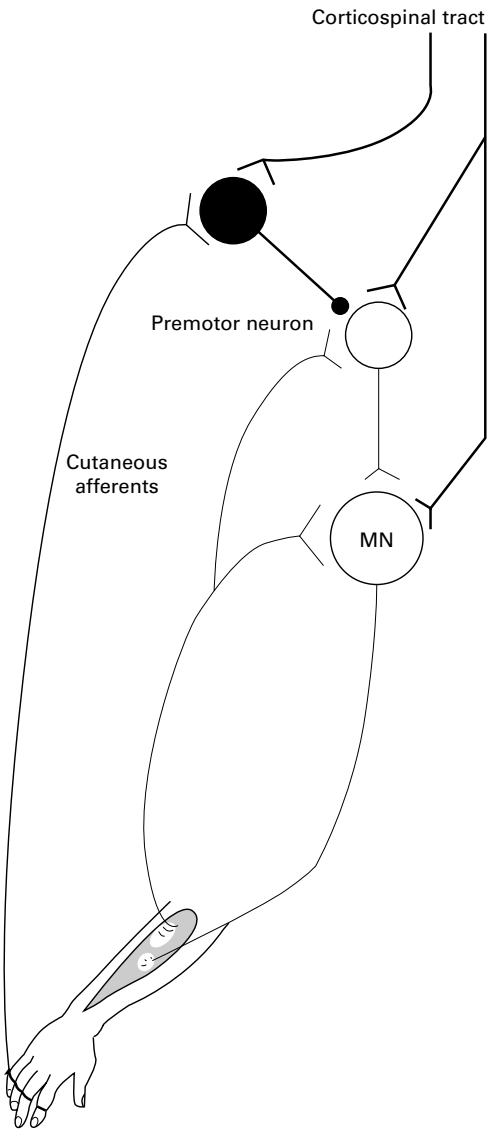

Figure 1 Schematic diagram showing the inhibition by cutaneous afferents in the superficial radial nerve (originating from the dorsal side of the hand) of premotor neurons mediating cortical excitation to motor neurons (the monosynaptic corticomotor neuron component is also sketched). Synapses are represented by bars if excitatory and by black circles if inhibitory. (Modified from Pierrot-Deseilligny, 1996.[1])

calculated as (BS–TS) / BS. For each patient we calculated for the right and the left upper limbs: a rigidity score, and a subscore of akinesia (finger taps+hand movements+rapid alternating movements of hands), and of tremor (tremor at rest+postural tremor) and an axial score (gait+posture+postural stability+ ability to stand up+speech). The two first scores (rigidity and akinesia) were the most relevant to the task that the patients had to perform during the experiments. Table 1, column 1, presents the mean (SEM) of the clinical scores.

TECHNIQUE

Principle

The technique used was developed by Burke and colleagues.[7] It is briefly summarised here.To appreciate the respective part of the voluntary EMG due to the activation of monosynaptic and of disynaptic corticomotor neuronal pathways, premotor neurons were inhibited by a cutaneous volley. The deeper the cutaneous induced inhibition of the EMG the larger the premotor neuronal mediated part. We used the fact that cutaneous afferents from the dorsal side of the hand elicit a pure inhibition of premotor neurons projecting to triceps and wrist extensor motor neurons (fig 1).

Experiments

Subjects were comfortably seated in a reclining armchair in front of a screen where they could watch their wrist muscle EMG activity. Forearms and hands were supported by arm rests, elbows flexed at 120°. An EMG was recorded bilaterally by surface electrodes 2 cm apart secured to the skin over wrist extensor muscles (ECR); EMG activity was continuously monitored. Subjects were asked to perform a bilateral symmetric tonic voluntary wrist extension so as to maintain the position against gravity, keeping the fingers flexed. Between each of the three recording sessions it was carefully ascertained that the subject was able to fully relax the forearm muscles. An EMG baseline level was then calculated and had to be similar on each side. In some patients a cyclic tremor in EMG activity appeared during the experiments. The corresponding files were rejected. The superficial radial nerve was stimulated at the wrist through bipolar surface electrodes on both sides. Stimuli were trains of three shocks (300 Hz, 6 ms) each of 1 ms duration at twice the threshold for perception (2×PT). In some complementary experiments 1 ms single shocks were also used. EMG activity was filtered (100 Hz-1 kHz), full wave rectified, and averaged against the superficial radial nerve stimulus for 20–50 ms using a sampling rate of 1kHz. In most of the cases, 50 control trials (without cutaneous stimulation) and 50 trials with ipsilateral superficial radial stimulation were randomly alternated (2 Hz) in a sequence for each side. Three sequences were then replicated. Because it could be difficult for the more severely affected patients to maintain the contraction during a 100 trial sequence, or

Table 1 Clinical data from 45 parkinsonian patients (mean values (SEM))

				Duration of disease					
	All patients (n=45)	*Affected side*	*Less affected side*	*⩽ 36 months (n=37)*	*Affected side*	*Less affected side*	*> 36 months (n=8)*	*Affected side*	*Less affected side*
Duration of the disease (months)	27.6 (3.7)			18.4(2)			69 (9)		
UPDRS	17.1 (1.1)			16.1(1)			21.5(3.4)		
Akinesia		5.2(0.3)	1 (0.2)		4.9(0.3)	0.9(0.2)		6.7(0.5)	1.8 (0.7)
Rigidity		1.6(0.1)	0.3 (0.08)		1.5(0.1)	0.2(0.08)		1.8(0.2)	0.6 (0.2)
Tremor		1 (0.2)	0.13(0.06)		1 (0.1)	0.1(0.05)		1.2(0.7)	0.25(0.2)

to do it without the occurrence of a tremor, we sometimes had to replicate six sequences of twice 25 trials.

Measurements and statistics
The averaged EMG area was measured, from the baseline level, for the period from 32 ms after the cutaneous stimulation (at a central delay of 4 ms after the arrival at spinal level of the cutaneous volley evoked by the last shock of the train) to 42 ms when using a train of three shocks, and from 26 ms (central delay 4 ms) to 36 ms when using a single shock. It was compared to the control averaged EMG area at corresponding delays. Poststimulus averages of EMG activity were expressed as a percentage of background EMG activity.

Statistical analysis
The experiments were designed to consider two comparisons: between patients and normal subjects and within individual patients.

Intraindividual comparisons
Variance analysis (Scheffé's test) was used to show if, in each subject, the cutaneously induced EMG depression was significant at each side. A paired Student's *t* test was used for the comparison between the cutaneously induced depression of the EMG between the affected and the non-affected or less affected side both before and after levodopa therapy. The correlation between the amount of the cutaneously induced depression of the EMG and the clinical status or the duration of disease was evaluated using Spearman's correlation analysis. Clinical scores before and after treatment were compared by a Wilcoxon signed rank test.

Comparison between parkinsonian patients and normal subjects
Mean values of the poststimulus averaged EMG activity, obtained on the affected and on the less affected sides of the patients, were compared with the values obtained in controls by a Mann-Whitney *U* test. Twenty two patients were more affected on the right side and 23 on the left side, so comparisons were done with mean values of 11 right and 12 left control EMGs. This and the fact that there was the same proportion of right handed, left handed, and ambidextrous subjects in the two populations minimised the effects of handedness[1] on the cutaneous induced depression of the EMG.

Table 2 Mean (SEM) values of the poststimulus averaged EMG (% of background EMG)

	Patients		*Controls*	
	Affected side	*Unaffected or less affected side*	*Corresponding side*	*Corresponding side*
All patients (n=45)	79.9 (1.8)	78.5 (2.3)**	86.5 (2.5)	87.1 (2.4)
Duration of the disease ⩽ 36 months (n=37)	78.4 (2)**	77.9 (2.5)**		
Duration of the disease > 36 months (n=8)	87.1 (1.7)	78.5 (5.6)		

* p = 0.05; ** p ⩽ 0.03.

Results
In patients, cutaneously induced depression of the EMG was more pronounced than in controls on both sides (Mann-Whitney *U* test, affected side p=0.06, less affected side p=0.03) (table 2 and fig 2). Poststimulus averaged EMG values were symmetric in controls and in patients despite the patients' pronounced asymmetric clinical status (table 1). Study of correlations between duration of illness and amount of the EMG depression clearly disclosed that patients could be divided into two groups corresponding to the degree of severity of the disease (table 2): when duration of illness was ⩽36 months (group A, n=37) a symmetric significant increase of the EMG depression occurred in patients (Mann-Whitney *U* test, affected side p=0.02, less affected side p=0.03). When duration of illness was longer than 36 months (group B, n=8) poststimulus averaged EMG values were asymmetric. Nevertheless the side to side difference did not reach significance, probably on account of the small sample size (Wilcoxon test, p=0.1). The mean EMG value obtained on the less affected side in group B did not differ from that obtained in group A, whereas the value obtained on the more affected side was similar to that obtained in controls (table 2). In group A, on the affected side, no correlation (Spearman's test) was found between the amount of the EMG depression and the following items: age of the patients (r=−0.03); severity of parkinsonism (UPDRS r=−0.4); akinesia (r=−0.3); rigidity (r=- 0.1); and axial signs (r=0.2). Similar results were obtained for the less affected side (age r=0.06; UPDRS r=0.1; akinesia r=0.08; rigidity r=0.2; and axial signs r=0.2). The mean (SEM) improvement after levodopa treatment was 60 (SEM 7)%. Treatment improved akinesia, rigidity, and axial signs (Wilcoxon signed rank test: akinesia p=0.003; rigidity p=0.007; and axial signs p=0.005), but did not modify the amount of the EMG depression (paired Student's *t* test, affected side p=0.5; less affected side p=0.7). To see if the difference between controls and parkinsonian patients could be due to a modification of the transmission in cutaneous inhibitory pathways (see discussion) we compared, in six subjects, the effect on the EMG activity of a superficial radial nerve stimulation with either a single shock or a train of three shocks. When using a single shock cutaneously induced inhibition was small (94.7 (SEM 2.4)%; 94.8 (SEM 2.5)% of background EMG on the affected and less affected sides respectively); but was more pronounced when using a train of three shocks (79.4 (SEM 2.7)% and 83.8 (SEM 4.9)% respectively). Difference in the amount of EMG depression obtained with one or three shocks was significant (Wilcoxon signed rank test p=0.03 for each side) and in the same order of magnitude as in controls (single shock 95.8%, train 85%).

Discussion
PATHWAY OF CUTANEOUS INDUCED INHIBITION
Cutaneous induced inhibition of ongoing voluntary EMG activity recorded in wrist extensors during tonic contraction against

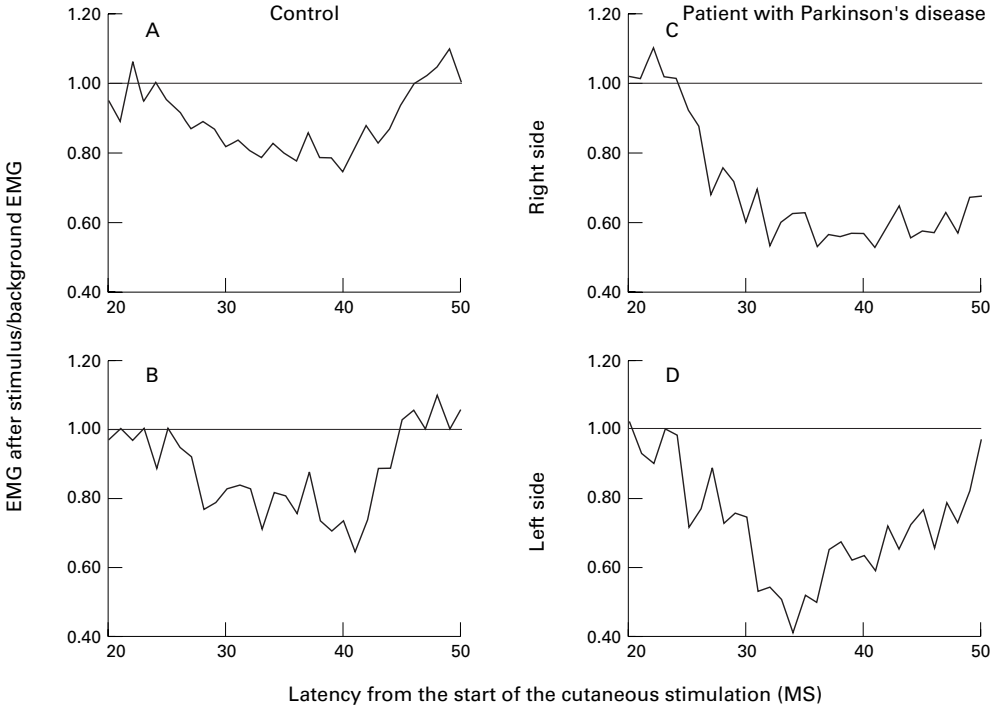

Figure 2 Comparison of the cutaneous induced inhibition of ECR EMG between a normal subject (45 years old) (A-B) and a hemiparkinsonian patient (C-D) whose right side was the more affected (48 years old, UPDRS=11; on the affected side: akinesia=6.5, rigidity=2, tremor=0, axial signs=0.5; on the non-affected side: akinesia, rigidity, tremor=0 ; duration of the disease=6 months). Note that, in the hemiparkinsonian patient, the cutaneous induced EMG depression, which is symmetric during its first 10 ms, is deeper than in the control.

gravity was significantly larger in a population of 45 patients with Parkinson's disease than in a population of 23 age matched control subjects. In normal subjects, stimulation of cutaneous afferents from the dorsal side of the hand, at intensities (2–3×PT) far below pain threshold, evokes a depression of ongoing ECR EMG activity, which occurs with a central delay of 3–6 ms. If this depression was due to an inhibition exerted directly on motor neurons (creating IPSPs in motor neurons), it would be expected that all motor neuron responses, whether evoked by cortical stimulation or by stimulation of homonymous Ia afferents (H reflex), are similarly reduced.[17] Direct inhibition of motor neurons was therefore eliminated by the finding that cutaneous stimulation significantly reduces the motor evoked potential (MEP) after transcranial magnetic stimulation but spares the H reflex.[7] Because, in addition, presynaptic inhibition of Ia fibres was shown to be unchanged,[7] this differential effect must reflect an inhibition of the transmission of descending excitation to motor neurons (a disfacilitation). The finding that the initial (1–2 ms) part of the MEP, reflecting the purely monosynaptic component of the cortical volley, is spared by cutaneous induced suppression provides further support for disfacilitation.[8] We suggest, therefore, that the greater reduction in ECR EMG found in patients with Parkinson's disease may reflect an increased cutaneous induced disfacilitation. An opposite change (decrease) in cutaneous induced inhibition has been described in intrinsic hand muscles of parkinsonian patients[18] which, contrary to the increased disfacilitation of ECR found here, was asymmetric in patients with hemiparkinsonism and was reversed by drug therapy. This implies that, contrary to what has been speculated,[7 19] the central pathways of the disfacilitation of the ECR and that of the I1 inhibition of hand muscles are different. This was also suggested by the fact that non-monosynaptic excitation mediated by cervical premotor neurons does not exist in hand muscles.[1] Cutaneous volleys activate inhibitory interneurons, which in turn inhibit premotor neurons (fig 1). Transmission in the inhibitory pathway may be facilitated by decreased presynaptic inhibition of cutaneous terminals, descending excitation of inhibitory interneurons, or both. The question then arises whether the greater reduction in EMG in patients with Parkinson's disease reflects a facilitation of the transmission in the inhibitory pathway or an overactivity of the premotor neurons resulting in an increase of the part of the descending command passing through this relay (the larger this part, the larger can be the cutaneous induced disfacilitation). Even though there is no direct evidence for either possibility, indirect arguments have been drawn from the comparison between the effects evoked by a single shock and by a train at the onset and at the offset of movement.[1] At the onset the weak inhibition evoked by a single volley was significantly increased by the use of a train (temporal facilitation at the level of inhibitory interneurons). By contrast, at the offset, the inhibition evoked by a single volley was strong but it was not significantly increased when using a train. This was interpreted as reflecting an increased descending excitatory drive on inhibitory interneurons: if the spatial facilitation between this increased descending input and the first

peripheral volley recruits most inhibitory interneurons, temporal summation due to the train can no longer manifest itself. The finding that in patients with Parkinson's disease the cutaneous depression of EMG evoked by a train of three shocks was significantly larger than that evoked by a single volley therefore goes against a facilitation of transmission in the cutaneous inhibitory pathway. Under these conditions, it is argued that the greater depression of EMG found in patients with Parkinson's disease might reflect an overactivity of the premotor neurons mediating the descending command.

POSSIBLE MECHANISM FOR OVERACTIVITY OF CERVICAL PREMOTOR NEURONS

The simplest explanation for this overactivity would be that it contributes, or is related to, parkinsonian motor disturbance(s). It has been proposed that motor neurons of rigid muscles receive an undue excitatory descending drive[20] which could account for the finding that at rest the amplitude of the F wave[21] and that of the response evoked by transcranial magnetic stimulation at suprathreshold intensities[11 21] are larger than normal. Part of this presumed enhanced supraspinal drive could be transmitted through the cervical premotor neurons, thus evoking their overactivity. Alternatively, the afferent discharge related to rigidity might produce an exaggerated excitatory input on these premotor neurons which can be excited by group I afferents from virtually all upper limb muscles.[2] In fact, several arguments strongly suggest that overactivity of premotor neurons is not directly related to motor disturbances: (*a*) there was no correlation between the amount of depression in EMG and the severity of symptoms; (*b*) accordingly, the increased inhibition was symmetric whereas the symptoms were clearly asymmetric; (*c*) inhibition returned to control levels in the more severe patients (evolution>36 months); (*d*) it was not modified by levodopa treatment, which improved the patients' clinical status. We therefore suggest that overactivity of cervical premotor neurons might reflect a compensatory mechanism aiming at palliating the defective execution of movements. If so, it is puzzling that this mechanism was no longer visible in the more affected side of the more advanced patients. We can only speculate that this compensatory mechanism originates from and/or is relayed in basal ganglia, so that it can no longer manifest itself when dopaminergic denervation increases. Another surprising finding is the existence in early patients of overactivity on their less affected side. In fact, bilateral lesions of the dopaminergic pathways exist at the early stage of Parkinson's disease,[22] and the presumed compensatory mechanisms could start with the first anatomical lesions. It has been shown that the responses evoked by transcranial magnetic stimulation in the active abductor pollicis brevis are smaller in patients with Parkinson's disease than normal.[11] This was interpreted as reflecting a decreased excitability of α motor neurons during contraction relative to normal (which implies a change in the input/output relation within the motor neuron pool). Under this assumption, the significance of overactivity of cervical premotor neurons might be to provide an extraexcitatory input to α motor neurons during contraction. However, conflicting results have been found with increased MEPs during contraction[21] and this decreased excitability of motor neurons of patients with Parkinson's disease needs to be confirmed. If this excitability is normal, a given contraction (here tonic wrist extension against gravity) must require the same amount of descending command as normal, and an increase in the premotor neuronal mediated command must mean a decrease in the monosynaptic corticospinal activation of motor neurons. So far there is no evidence for such a decrease in the monosynaptic activation of motor neurons in Parkinson's disease. Neither is there evidence against it, and the fact that corticomotor neuronal projections are normal[9–12] does not contradict this possibility as, during movement, a normal motor cortex transmits an abnormal command elaborated upstream from the corticospinal tract.[9 10] What could be the compensatory role of such a switch from monosynaptic to disynaptic transmission? We can only speculate that the strong inhibitory input[5 6] from muscle and cutaneous afferents to cervical premotor neurons could be useful in an attempt to palliate the difficulty of these patients to relax. The abnormal excitatory input to the cervical premotor neurons which is elaborated upstream from the motor cortex can be transmitted to motor neurons by the corticospinal tract or by other descending tracts. In effect, after corticospinal lesions it has been shown that the part of the residual command passing through the premotor neuron relay is increased in hemiplegic patients, suggesting that other descending (reticulospinal) tracts converge on these premotor neurons.[1]

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