

Subthalamic nucleus stimulation reverses spinal motoneuron activity in parkinsonian patients

Sylvie Raoul,¹ Vincent Roualdes,¹ Céline Deligny,² Dominique Leduc,³ Jean-Charles Lamy,⁴ Alexandra Lackmy-Vallée,⁵ Jean-Paul N'Guyen,¹ Philippe Damier² and Rose Katz^{5,6}

1 CHU Nantes, Neurosurgery Department, Hôpital G. et R. Laennec, 44093 Nantes, France

2 CHU Nantes, Neurology department, Hôpital G. et R. Laennec, 44093 Nantes, France

3 Faculté des Sciences, Physics department, Hôpital G. et R. Laennec, 44093 Nantes, France

4 CeSeM CNRS UMR 8194 /Paris Descartes University, Paris, France

5 Er 6 UPMC; Paris Univ 06, Physical Medicine & Rehabilitation Department, La Salpêtrière Hospital, 75651 Paris cedex 13, France

6 APHP; Physical Medicine & Rehabilitation Department, La Salpêtrière Hospital, 75651 Paris cedex 13, France

Correspondence to: Rose Katz,

Er 6 UPMC; Paris Univ 06,

Physical Medicine and Rehabilitation Department,

La Salpêtrière Hospital,

75651 Paris cedex 13, France

E-mail: rose.katz@upmc.fr

Although a cardinal symptom of Parkinsonian disease, up to now, rigidity has been investigated much less than spasticity in hemiplegic patients. Many pathophysiological mechanisms may at least theoretically contribute to Parkinsonian rigidity, from altered viscoelastic muscle properties to inability of parkinsonian patients to relax. However, as demonstrated many years ago, motoneuron responses to muscle afferent volleys are involved in rigidity since afferent volleys are suppressed after dorsal root section. To our knowledge, homosynaptic depression (i.e. the fact that motoneuron responses to Ia afferent volleys exhibit a frequency-related depression) has not been studied in parkinsonian disease, despite the fact that in spastic patients, changes in homosynaptic depression are significantly correlated at wrist and ankle levels with the severity of spasticity. Thus, in the present series of experiments, we investigated in parkinsonian patients with chronic implantation of both subthalamic motor nuclei, the amount of homosynaptic depression at wrist and ankle levels on and off deep brain stimulation. Off deep brain stimulation, the frequency-related depression disappeared, the patients became rigid and the amount of homosynaptic depression was significantly correlated with the severity of rigidity. On deep brain stimulation, the frequency-related depression was restored and the rigidity suppressed, suggesting that homosynaptic depression is one of the mechanisms underlying rigidity in Parkinson's disease. Moreover, the unexpected finding that changes in the rigidity score and the amount of homosynaptic depression are time-locked to the onset of deep brain stimulation leads us to reconsider the mechanisms underlying changes in homosynaptic depression.

Keywords: Parkinson; deep brain stimulation; rigidity; spinal motoneuron bistability; homosynaptic depression

Introduction

Rigidity is one of the three cardinal symptoms of Parkinson's disease and is characterized in flexor and extensor muscles by a

sustained increase in resistance throughout the full range of motion not influenced by the speed of the stretch. Studies of transmission within spinal pathways in Parkinson's disease rigidity are not so numerous and have provided controversial results as

well as non-congruent findings between upper and lower limbs. To sum up, the study of presynaptic Ia inhibition (Pierrot-Deseilligny and Burke, 2005) and of reciprocal inhibition between antagonistic muscles (Bathien and Rondot 1977; Obeso *et al.*, 1985; Lelli *et al.*, 1991; Nakashima *et al.*, 1994; Tsai *et al.*, 1997; Meunier *et al.*, 2000) have provided conflicting results. Ib inhibition has been found decreased in lower extremities of patients with Parkinson's disease and correlated with the severity of rigidity (Delwaide *et al.*, 1991), whereas long-latency reflexes and group II spinal reflex excitation have been found to be enhanced in both lower and upper limbs (Lee and Tatton 1975, 1978; Berardelli *et al.*, 1983; Rothwell *et al.*, 1983; Cody *et al.*, 1986; Bergui *et al.*, 1992; Simonetta-Moreau *et al.*, 2002; Marchand-Pauvert *et al.*, 2011). Moreover, in the case of long-latency reflexes, results obtained at rest and during natural movements seem to be different (Dietz *et al.*, 1988). On the whole, these inconsistent findings may be due to the heterogeneity of the symptoms among the different samples of patients or to the fact that other pathways than those studied are involved in the development of rigidity.

Indeed, it is well known that repetitive activation of afferent fibres strongly decreases the size of monosynaptic reflexes (Eccles and Rall, 1951; Lloyd and Wilson, 1957). This depression, termed homosynaptic depression, occurs without concomitant changes in membrane potentials or conductance (Hultborn and Nielsen, 1998) and is likely due to changes in a readily releasable transmitter operating within presynaptic terminals (Lev-Tov and Pinco, 1992). In hemiplegic patients, homosynaptic depression is strongly impaired (Aymard *et al.*, 2000) and this impairment is significantly correlated with the severity of spasticity, both in the lower and upper limbs (Lamy *et al.*, 2009). To our knowledge, possible changes of homosynaptic depression have never been explored in Parkinson's disease. Therefore, the purpose of this series of experiments was to determine if homosynaptic depression is impaired in Parkinson's disease and plays a role in the development of rigidity. To that end, we explored, in a sample of patients with advanced Parkinson's disease with chronic bilateral

subthalamic nucleus stimulation, the rigidity score and the amount of homosynaptic depression on and off deep brain stimulation, since high-frequency electrical stimulation of the subthalamic nucleus through implanted electrodes (Limousin *et al.*, 1995; 1998) has been proposed to decrease the hyperexcitability of the subthalamic nucleus and has been shown to improve rigidity and akinesia in advanced stages of Parkinson's disease (Krack *et al.*, 2003; Deuschl *et al.*, 2006; Benabid *et al.*, 2009; Moro *et al.*, 2010).

Subjects and methods

Subjects

Experiments were performed in nine patients with advanced Parkinson's disease (four females and five males, aged from 44 to 65 years, mean value 54.3 ± 2.4 years; Table 1), treated with chronic bilateral subthalamic nucleus deep brain stimulation associated with L-DOPA treatment. Standard clinical criteria have been used for the diagnosis of Parkinson's disease (Gelb *et al.*, 1999). Surgical inclusion criteria were: (i) idiopathic Parkinson's disease; (ii) Hoehn-Yahr stage IV or V; (iii) severe motor disability; and (iv) no dementia or psychiatric abnormalities. All patients exhibited rigidity and akinesia but no or little tremor and a clear-cut positive effect of deep brain stimulation. The severity of rigidity was assessed using the Unified Parkinson's Disease Rating Scale rigidity score. The Unified Parkinson's Disease Rating Scale has four parts, namely: I, Mentation, behaviour and mood; II, Activities of Daily Living; III, Motor Examination; and IV, Complications of therapy. All items have five response options with uniform anchors of 0 = normal, 1 = slight, 2 = mild, 3 = moderate and 4 = severe. In part III, rigidity is judged on passive movements of major joints with patients relaxed in a sitting position (Fahn and Elton, 1987).

The rigidity scores of the patients are presented in Table 1. Nine age-matched healthy subjects (six females and three males, aged from 44–64 years, mean value 54.6 ± 2.2 years; Table 2) were also enrolled in this study in order to allow quantitative comparison between patients with Parkinson's disease and healthy subjects. All of them gave their written informed consent before participation. The study was

Table 1 Homosynaptic depression in patients with Parkinson's disease

Patient	Age	Rigidity OFF/OFF	Rigidity ON/ON	HD SOL OFF/OFF	HD SOL ON/ON	HD FCR OFF/OFF	HD FCR ON/ON
1	54	3F4	1 + F2	1.13	0.95	0.75	0.53
2	61	1F2	1F1	0.38	0.93	1.02	0.97
3	65	2F3 +	0F1	1.13	0.24		0.85
4	44	2F3	0F0	1.21	0.39	1.09	0.64
5	59	1F2	0F0	0.68	0.53		0.72
6	49	2 + F4	0F0	0.83	0.99	0.89	0.70
7	54	2F3	0F0	1.56	0.73	1.26	0.81
8	51	1F2	0F0		0.50	1.39	1.15
9	52	2F3	0F0	0.80	0.49	1.26	0.72
Mean \pm SEM	54.33 (2.15)			0.97 (0.13)	0.64 (0.09)	1.09 (0.09)	0.79 (0.06)

HD sol OFF/OFF = homosynaptic depression of soleus H-reflex OFF L-DOPA and off stimulation; HD Sol ON/ON = homosynaptic depression of soleus H-reflex ON L-DOPA and on stimulation; HD FCR OFF/OFF = homosynaptic depression of flexor carpi radialis H-reflex OFF L-DOPA and off stimulation; HD FCR ON/ON = homosynaptic depression of flexor carpi radialis H-reflex ON L-DOPA and on stimulation. Rigidity OFF/OFF = rigidity without subthalamic nucleus stimulation and without L-DOPA and ON/ON = rigidity with subthalamic nucleus stimulation and with L-DOPA. The rigidity score was obtained from Unified Parkinsons Disease Rating Scale part III and expressed such that 4F4 means maximum rigidity and 0F0 means minimum rigidity.

Table 2 Homosynaptic depression in normal subjects

Subject	Age	HD SOL	HD FCR
1	54	0.21	0.60
2	44	0.76	0.53
3	61	0.66	0.63
4	53	0.62	0.53
5	50	0.57	0.55
6	62	0.73	0.37
7	54	0.65	0.43
8	50	0.45	0.66
9	64	0.66	0.47
Mean \pm SEM	54.67 (2.18)	0.59 (0.06)	0.53 (0.03)

HD sol = homosynaptic depression of soleus H-reflex; HD FCR = homosynaptic depression of flexor carpi radialis H-reflex.

performed in accordance with the ethical codes of the World Medical Association (Declaration of Helsinki) and was approved by the local ethics committees (CPP Ile de France 6-Pitié-Salpêtrière and CHU Nantes Hospital). All patients exhibit severe idiopathic Parkinson's disease with motor fluctuations, dopamine responsive symptoms, normal cognition or minimal impairment, depression or mood disorders adequately controlled with medication (clozapine), no known peripheral neuropathy and little or no tremor in OFF medication condition. The mean duration of Parkinson's disease was 7 years (range 3–10 years).

Surgical procedure

Patients were placed in a stereotactic frame under local anaesthesia. Stereotactic MRI was performed just before the surgery and subthalamic nucleus targets were defined. A burr hole was performed and two to five microelectrodes were inserted to the subthalamic nucleus. Microrecordings were performed to localize the subthalamic nucleus and the substantia nigra. The subthalamic neurons have a characteristic pattern of discharge with high-frequency firing and sensitivity to passive mobilization. Clinical testing was performed to assess clinical benefits of the subthalamic nucleus stimulation, i.e. the disappearance of rigidity and the improvement of akinesia without side effects. If the electrode was lateral to the subthalamic nucleus hemispasm can occur, too anterior and some vegetative signs appear, and too medial oculomotor troubles are observed. When rigidity score was minimum (OF0 Table 1) with no side effect, a Medtronic 3389 electrode was inserted in the dorsolateral part of the subthalamic nucleus and fixed to the skull. The procedure took 3–6 h. Patients were awake, without medication and experiencing Parkinson's disease symptoms at their worst. Two days later, two stimulators were implanted under general anaesthesia. Stimulating parameters were optimized and medical treatment of L-DOPA was reduced.

General experimental arrangement

The subjects were comfortably seated in an armchair (Fig. 1A). For the experiments performed on the arm, the shoulder was slightly adducted (60°), the elbow semi-flexed (100°) with the forearm pronated and supported by the arm of the chair. For the experiments performed on the leg, the hip was semi-flexed (120°), the knee slightly flexed (160°), the ankle at 110° plantar flexion and the foot set on a foot plate.

Recordings were performed at rest on the dominant side of healthy subjects and in the more rigid side of patients with Parkinson's disease. Five patients and five healthy controls were tested on the right side and four patients and four controls on the left side.

H-reflexes

Soleus and flexor carpi radialis H-reflexes were recorded from pairs or non-polarizable electrodes (0.8 cm² silver plates, 1.5 cm apart secured to the skin over the corresponding muscle bellies). EMG signals were amplified (\times 1000–5000), filtered (0.1–1 kHz) and digitalized at 1–2 kHz. The reflexes were measured as peak-to-peak amplitude of the non-rectified EMG response (Figs 1B, 2B and C) and data were stored on a computer for subsequent off-line analysis.

To evoke an H-reflex in the flexor carpi radialis muscle, percutaneous electrical stimulation of the median nerve was delivered through bipolar electrodes applied 2 cm below the elbow on the medial side of the arm. A marked increase of the amplitude of the H-reflex during wrist flexion but not during pronation or finger flexion was used as a criterion indicating that the H-reflex originated mainly from the flexor carpi radialis.

Percutaneous electrical stimulation of the posterior tibial nerve was used to elicit an H-reflex in the soleus muscle. The posterior tibial nerve was stimulated through electrodes placed at the popliteal fossa.

Method of assessing homosynaptic depression and experimental procedure

As illustrated in Fig. 2A, decreasing the time interval between two consecutive stimuli results in a marked decrease of the H-reflex amplitude. The depression of H-reflexes is dramatic at short interval (1–2 s between two consecutive stimuli) with a rapid recovery up to 8 s although at least 15 s are required to completely extinguish this depression (Crone and Nielsen, 1989; Hultborn and Nielsen, 1998; Aymard *et al.*, 2000). In this study, H-reflex size evoked at 0.25–0.33 Hz was initially adjusted at maximal H-reflex response/2. Then, the amplitude of H-reflex was studied at low (0.125 Hz, i.e. 8 s between two consecutive stimuli) and high (0.5 Hz, i.e. 2 s between two consecutive stimuli) stimulus rate. The ratio of the H-reflex amplitude at high stimulus rate to the reflex amplitude at low stimulus rate (high/low ratio) was calculated and used to statistically compare the results between patients with Parkinson's disease and healthy subjects: the greater the high/low ratio, the smaller the homosynaptic depression (Aymard *et al.*, 2000; Lamy *et al.*, 2009). Special care was taken over recording sessions to ensure that the target muscle was as relaxed as possible since homosynaptic depression is decreased during voluntary contractions of the test muscle (Rothwell *et al.*, 1986; Burke *et al.*, 1989; Hultborn and Nielsen, 1998).

H-reflexes in patients were tested in the four following conditions: (i) without any treatment: (without L-DOPA, off deep brain stimulation = 'OFF-OFF'); (ii) without L-DOPA treatment and on deep brain stimulation ('OFF-ON'); (iii) with L-DOPA treatment and off deep brain stimulation ('ON-OFF'); (iv) with both treatments ('ON-ON').

The time interval between surgical procedure and experiments was 3 months, i.e. when the deep brain stimulation parameters were optimized (L-DOPA treatment was reduced and possible side effects of the electrodes were avoided). In OFF L-DOPA conditions, the L-DOPA was stopped 12 h before the experiments. In 'off' subthalamic nucleus conditions, the stimulator was turned off about 10 min before the experiment: the rigidity score was assessed, and experiments started as soon

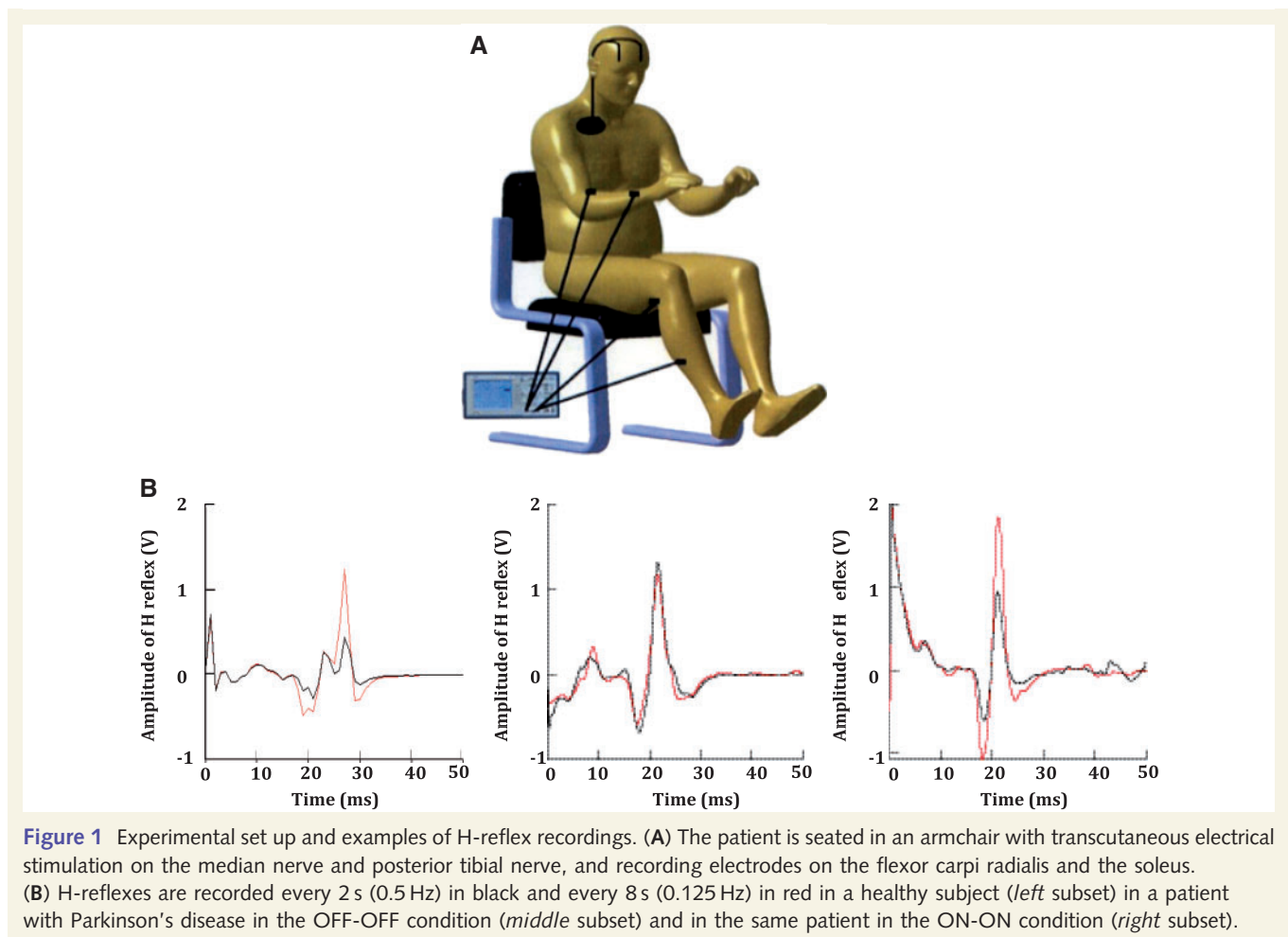


Figure 1 Experimental set up and examples of H-reflex recordings. (A) The patient is seated in an armchair with transcutaneous electrical stimulation on the median nerve and posterior tibial nerve, and recording electrodes on the flexor carpi radialis and the soleus. (B) H-reflexes are recorded every 2 s (0.5 Hz) in black and every 8 s (0.125 Hz) in red in a healthy subject (*left* subset) in a patient with Parkinson's disease in the OFF-OFF condition (*middle* subset) and in the same patient in the ON-ON condition (*right* subset).

as patients recovered their baseline rigidity score. OFF-OFF and OFF-ON experiments were performed in the morning. In 'on' subthalamic nucleus conditions, the experiments were performed as soon as the stimulator was turned on. Then, patients received their first oral dose of L-DOPA of the day. Their second intake of L-DOPA was taken 2 or 3 h later. ON-OFF and ON-ON experiments were then performed starting 20 min after this second intake of L-DOPA, i.e. when the effect of the medication was maximal.

Two runs of 20 stimulations were performed at 0.5 Hz and 0.125 Hz in the upper and lower limbs in each condition. Before each run, we checked that the H-reflex amplitude evoked at 0.33 Hz remained unchanged. Figs 1B, 2B and C illustrate examples of H-reflexes evoked in healthy subjects and in patients with Parkinson's disease in the OFF-OFF and ON-ON conditions at low and high stimulus rate.

Statistical analysis

The reflex responses were measured as peak-to-peak amplitude on the non-rectified response. For each run, the mean value of the amplitude was determined with its standard error of the mean (SEM). To examine the relationship between homosynaptic depression and Unified Parkinson's Disease Rating Scale rigidity score, Spearman's correlation coefficient was used. To compare the ratio of homosynaptic depression evoked at 0.5 Hz and at 0.125 Hz, two non-parametric tests were

used (Mann-Whitney and Wilcoxon) due to the small number of patients enrolled.

Results

Maximal H-reflex response/maximal motor response ratios

Usually, H-reflex experiments are performed with a stimulus rate of 0.2–0.3 Hz (Pierrot-Deseilligny and Burke, 2005). Therefore, to allow comparison with previous studies of maximal H-reflex response/maximal motor response in Parkinson's disease (Angel and Hoffmann 1963; Dietrichson 1973; Obeso *et al.*, 1985; Lelli *et al.*, 1991; Nakashima *et al.*, 1994; Meunier *et al.*, 2000; Kushnir *et al.*, 2001; Sabbahi *et al.*, 2002), we used a similar stimulus rate to determine maximal H-reflex response/maximal motor response ratio in our sample of patients with Parkinson's disease and healthy subjects. In patients with Parkinson's disease, maximal H-reflex response/maximal motor response ratio mean values were roughly similar whatever the conditions, and ranged from 27% to 31% for soleus H-reflexes, and from 14–17% for flexor carpi radialis H-reflexes. Maximal H-reflex

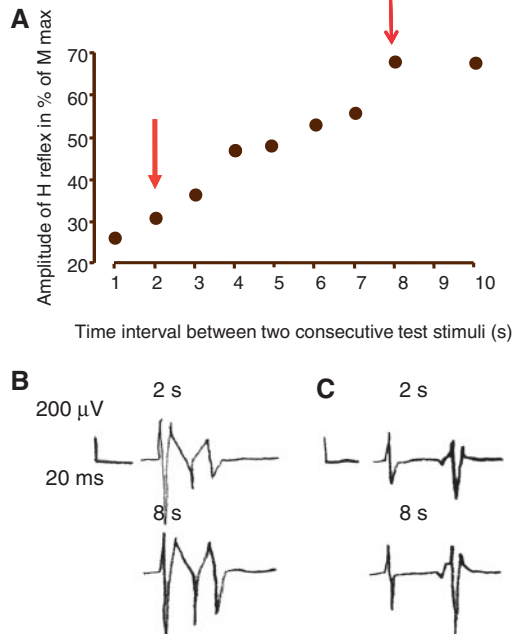


Figure 2 Homosynaptic depression in healthy subjects. (A) The amplitude of flexor carpi radialis H-reflex (expressed in percentage of flexor carpi radialis maximal motor response) is plotted against the time interval between two consecutive stimulations of the median nerve in one representative subject. Each symbol represents the mean of 20 reflexes. (B) Examples of flexor carpi radialis H-reflex recordings obtained for a time interval between two consecutive stimulations of 2 s (left arrow in A) and of 8 s (right arrow in A). (C) Examples of soleus H-reflex recordings obtained in one representative subject for a time interval between two consecutive posterior tibial nerve stimulations of 2 s and of 8 s. M max = maximal motor response.

response/maximal motor response ratio mean values were strongly depressed in patients with Parkinson's disease, since in healthy subjects, the soleus maximal H-reflex response/maximal motor response ratio mean value was 53% and the flexor carpi radialis maximal H-reflex response/maximal motor response ratio mean value was 30%.

Homosynaptic depression

Individual values obtained in healthy subjects and patients with Parkinson's disease are displayed in Tables 1 and 2. As stated in the 'Subjects and methods' section, homosynaptic depression is expressed as: H-reflex amplitude at 0.5 Hz/H-reflex amplitude at 0.125 Hz. The greater the ratio, the lower the homosynaptic depression. Results obtained at wrist and ankle levels were congruent as illustrated in Fig. 3. The high/low ratio was minimum in healthy subjects: 0.59 at soleus level and 0.53 at flexor carpi radialis level. In patients with Parkinson's disease, the high/low ratio was maximum (i.e. the homosynaptic depression was minimum and in fact, totally suppressed) in absence of treatment (OFF-OFF

condition): 0.97 at soleus level and 1.09 at flexor carpi radialis level. In contrast, in ON-ON situation, the high/low ratio was strongly reduced (i.e. the homosynaptic depression reappeared and was maximum): 0.64 at soleus level and 0.79 at flexor carpi radialis level. The high/low ratios mean values in OFF-ON and ON-OFF conditions ranged between ON-ON and OFF-OFF conditions.

As illustrated in Fig. 3, the rigidity score strikingly paralleled the amount of homosynaptic depression. At soleus level (Fig. 3A–C), the rigidity score was minimum in ON-ON condition, maximum in OFF-OFF condition with intermediate scores in ON-OFF and OFF-ON conditions. However, in OFF-ON condition (last column Fig. 3A), the rigidity score was much closer to ON-ON condition than to ON-OFF condition. Similarly, homosynaptic depression (Fig. 3C) was almost equivalent between healthy subjects and patients in ON-ON condition, whereas it has completely vanished in the OFF-OFF condition with intermediate values for ON-OFF and OFF-ON conditions. Analogous results were obtained in the upper limb (Fig. 3B–D). However, in all conditions, the rigidity score was greater in the upper than in the lower limb. A significant correlation was found between the decrease of homosynaptic depression and the severity of rigidity ($r = 0.53$; $P < 0.0002$). Moreover, it should be stressed that changes in both the rigidity score and the amount of homosynaptic depression were time-locked to the onset of the deep brain stimulation: as soon as the stimulation turned on, the changes appeared.

Discussion

In the present series of experiments, we have explored rigidity score and homosynaptic depression in four different conditions: (i) without any treatment (OFF-OFF); (ii) with both L-DOPA and subthalamic nucleus stimulation (ON-ON); (iii) with L-DOPA alone (ON-OFF); and (iv) with subthalamic nucleus stimulation alone (OFF-ON). The main finding is that changes induced by subthalamic nucleus stimulation in the rigidity score and in the amount of homosynaptic depression closely parallel each other. Before discussing the potential clinical interest of this finding, some points must be taken into account.

Methodological considerations

Healthy control subjects and patients with Parkinson's disease were carefully age-matched (Tables 1 and 2) to avoid possible ageing effects. Although the effects of ageing have not been systematically studied in healthy subjects, a reduction of the number of group I afferents and a decrease of their conduction velocity have been suggested (Pierrot-Deseilligny and Burke, 2005). The fact that the ages were similar in the two populations allows us to discard this possible bias. Homosynaptic depression is attenuated during voluntary contractions in healthy subjects, probably due to enhanced Ia afferent firing during voluntary contractions (Rothwell *et al.*, 1986). It can be thus hypothesized that during tremor, a similar reduction of homosynaptic depression may occur. To avoid this possible bias, only patients with no or little tremor were

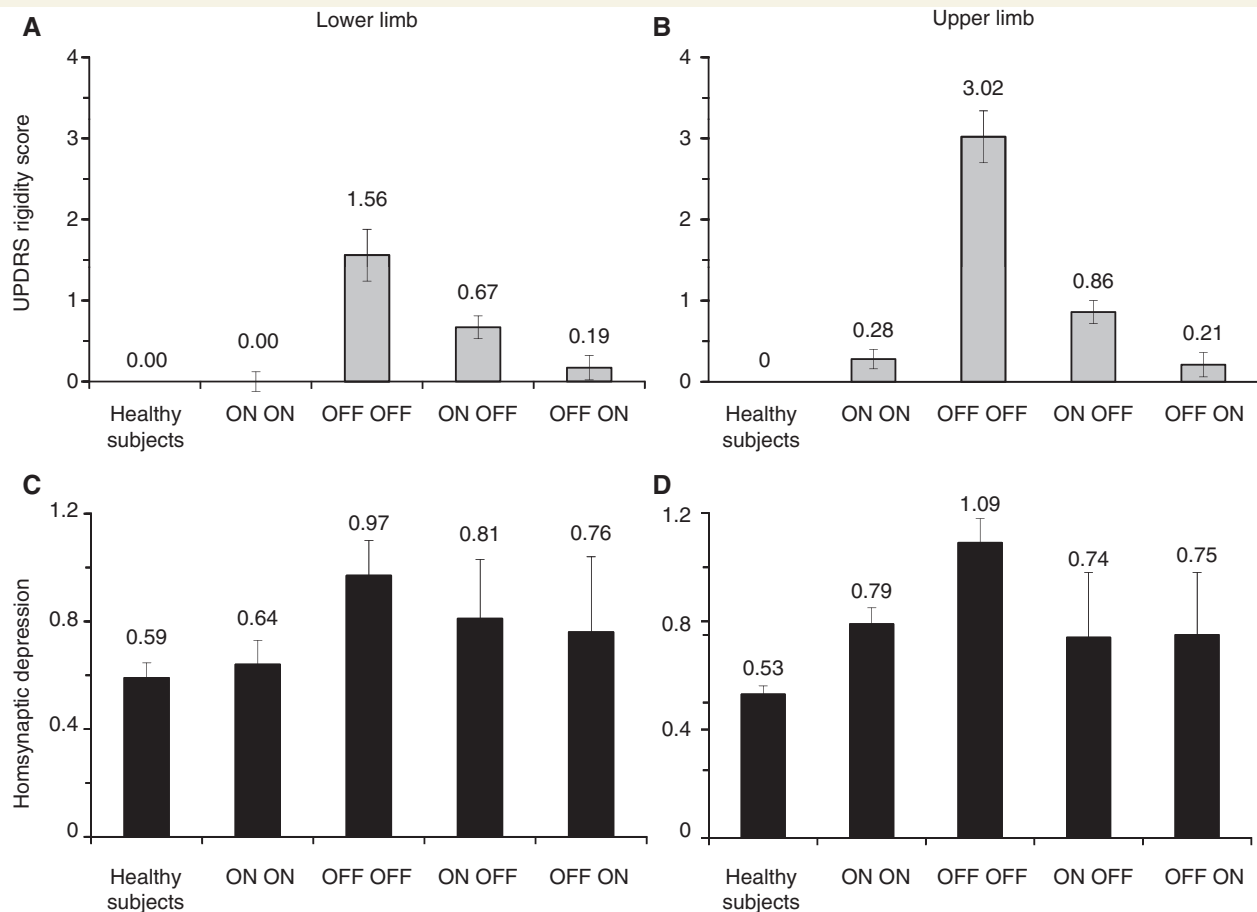


Figure 3 Homosynaptic depression and rigidity score. Each column represents the mean and SEM of the rigidity score (A, B) and of homosynaptic depression (C, D). The higher the rigidity score, the more rigid the patients. Homosynaptic depression is expressed as the amplitude ratio of the H-reflex evoked at 0.5 Hz/amplitude of the H-reflex evoked at 0.125 Hz. The lower the ratio the greater the homosynaptic depression. In each subset A–D, the left column represents the mean value obtained in healthy subject and the other columns represent the mean value obtained in patients with Parkinson’s disease in the four conditions. UPDRS = Unified Parkinson’s Disease Rating Scale.

enrolled and we carefully verified that patients were at rest during all the recordings.

Effects of subthalamic nucleus stimulation versus L-DOPA treatment

The reduction of the rigidity score and the restoration of homosynaptic depression were maximum with both treatments (i.e. ON-ON condition) even though the rigidity score was close between ON-ON and OFF-ON conditions. This suggests a cumulative effect of L-DOPA and subthalamic nucleus stimulation. A more pronounced effect of both treatments has also been reported by Maurer *et al.* (2003) in their study of the effects of subthalamic nucleus stimulation on postural control in Parkinson’s disease leading to the conclusion that the combination of both treatments led to a synergic summation of the effects. The connections between the subthalamic nucleus and the pedunculo-pontine nucleus (see below) are probably more sensitive to

electrical stimulation and may recruit more GABAergic and cholinergic neurons that the indirect chemical stimulation by L-DOPA. Another explanation may be that other pathways of activation of the spinal cord, which are silent in normal situation, are activated only if the subthalamic nucleus is strongly activated.

Physiological mechanisms underlying changes in homosynaptic depression

In the present study, we report for the first time that in patients with advanced Parkinson’s disease, the severity of rigidity is significantly correlated with the decrease of homosynaptic depression. Moreover, in absence of treatment, homosynaptic depression is completely suppressed and the rigidity is maximum. Although not definite proof, these results strongly suggest that decreased homosynaptic depression plays a role in the development of rigidity in Parkinson’s disease as it has recently been

shown for the development of spasticity in patients with stroke (Lamy *et al.*, 2009).

Studies performed both in spastic patients (Schindler-Ivens and Shield, 2000) and in spinal lesioned rats (Thompson *et al.*, 1992; Skinner *et al.*, 1996) indicate that changes in homosynaptic depression do not occur immediately after the lesion, suggesting that such changes may be related to the disuse of the Ia fibre- α motoneuron synapses brought about by the impaired motor command. Thus, an intriguing finding of our series of experiments is that phasic changes of subthalamic nucleus excitability (via the ON-OFF state of the high-frequency subthalamic nucleus continuous electrical stimulation) result in phasic changes of homosynaptic depression at cervical and lumbar levels, suggesting that homosynaptic depression, i.e. the behaviour of Ia afferent- α motoneuron synapses, may be subjected to descending influences originating from the brainstem.

What are the possible descending pathways and mechanisms responsible for this brainstem descending control onto the behaviour of group Ia afferent- α motoneuron synapses? The subthalamic nucleus facilitates the globus pallidus internus and the substantia nigra pars reticula (deLong, 1990; Levy *et al.*, 1997), which have inhibitory projections to the pedunculopontine nucleus (Shink *et al.*, 1997; Takakusaki *et al.*, 2003; Nandi *et al.*, 2008). The pedunculopontine nucleus projects onto the ponto-medullary reticular formation, the former having bilateral projections onto the spinal cord (Pahapil and Lozano, 2000; Takakusaki *et al.*, 2003). High-frequency subthalamic nucleus stimulation is known to result in a 'lesioning-like effect' and thus to reduce the over-active subthalamic nucleus drive to its target. It is likely that subthalamic nucleus stimulation induces changes in descending drive onto spinal neurons allowing for controlling gait and muscle tone (Chen and Lemon, 2004; Pierantozzi *et al.*, 2008) and restoring autogenic inhibition at soleus level (Pötter *et al.*, 2004), corticospinal facilitation at soleus level (Pötter-Nerger *et al.*, 2008) or group II spinal excitation at wrist level (Marchand-Pauvert *et al.*, 2011).

What are the possible pathophysiological mechanisms underlying changes in homosynaptic depression?

The hypothesis argued below relies on findings originally described by Schwindt and Grill (1980) i.e. their discovery that a motoneuron could display self-sustained firing induced by persistent inward currents. Indeed, a motoneuron can exhibit two different kinds of firing patterns in response to a given synaptic current: (i) a state without persistent inward currents; and (ii) a state with persistent inward currents. The shift from one state to another i.e. the bistability of a motoneuron firing (Hounsgaard *et al.*, 1998), depends on neuromodulatory inputs originating from the brainstem via the raphe nucleus spinal projections (Hultborn *et al.*, 2004; Heckman *et al.*, 2009). To summarize the findings obtained in various animal preparations, a high level of neuromodulatory input at the spinal level favours the development of persistent inward currents in the motoneurons. Thus, an appealing

interpretation of our results is that when there is a hyperexcitability of the subthalamic nucleus, i.e. off deep brain stimulation, the neuromodulatory inputs to motoneurons are enhanced. In such conditions, persistent inward currents are present in motoneurons and the depressive effect of the repetitive activation of Ia fibres is overcome by the self-sustained firing of motoneurons. When subthalamic nucleus deep brain stimulation is activated, the subthalamic nucleus excitability decreased leading to a decrease in neuromodulatory inputs and therefore to a decrease or even to a suppression of persistent inward currents thus restoring the homosynaptic depression existing in healthy subjects. The phasic reversal of the amount of homosynaptic depression with the OFF-ON status of the deep brain stimulation strongly supports this hypothesis. However, although descending monoaminergic projections can powerfully modify the manner in which motoneurons respond to a given synaptic input, as demonstrated in the anaesthetized decerebrate animal preparation, the demonstration of the existence of self-sustained firing of motoneurons is obviously difficult in humans. Nevertheless, experiments performed with paired motor unit technique (Kiehn and Eken, 1997; Gorassini *et al.*, 1998, 2002a, b) or high-frequency stimulation of Ia afferents (Collins *et al.*, 2001, 2002; Nozaki *et al.*, 2003) favour the hypothesis of plateau-like behaviour in humans. Moreover, in patients with cramps, Baldissera *et al.* (1994) have reported plateau-like behaviour triggered by low-frequency Ia volleys. It may seem surprising to argue that homosynaptic depression abnormalities may be involved both in spasticity, rigidity or muscle cramps, since those clinical symptoms are obviously different. However, final path for motor control is the spinal motoneuron and whatever the mechanisms influencing the efficacy of the Ia fibre α -motoneuron synapse, it will affect the motoneuron discharge and thus the muscle contraction. In other words, the finding that homosynaptic depression is decreased does not necessarily imply that the mechanisms leading to this decrease are similar in different diseases.

An alternative explanation to interpret our results would be that the deep brain stimulation would reduce the 'natural' background discharge in Ia afferents and thus restore a significant level of homosynaptic depression, taking into account that rigidity itself can be considered as an involuntary contraction. This hypothesis relies on the fact that during voluntary contractions of healthy subjects, homosynaptic depression is reduced (Rothwell *et al.*, 1986; Burke *et al.*, 1989; Hultborn and Nielsen, 1998). The most likely explanation for such a decrease is that the Ia firing occurring during voluntary contractions generates a background homosynaptic depression that can only be marginally increased by additional Ia volleys. It may be therefore hypothesized that in the OFF-OFF condition, 'natural' Ia firing is greater than in the ON-ON condition and this would explain decreased homosynaptic depression in the OFF-OFF condition. However, the fact that maximal H-reflex response/maximal motor response values were similar in all conditions does not favour this hypothesis. Indeed, if the 'natural' Ia firing was larger in the OFF-OFF condition, it should result in an increase in the amplitude of the monosynaptic reflexes.

On the whole, although it may be argued that a neuronal circuit revealed in chronic patients may not be functional in healthy

subjects, the present results suggest for the first time in humans that neuromodulatory inputs originating from the brainstem influence the behaviour of spinal motoneurons and thus play a role in the control of muscle tone.

Clinical impact

It is well known by physicians that the follow-up of treatment using clinical assessments, although essential, is submitted to limits in reliability and in accuracy to detect small changes. This has led to the development of biomechanical and neurophysiological tools, which may be rather complex to use and time consuming. Homosynaptic depression is one of the simplest and shortest duration EMG tests, since it only relies on a sample of 40 H-reflexes evoked at two different frequencies. The only restriction is that the recordings must be performed at rest. Taking into account the strict parallelism between the changes in rigidity score and those of homosynaptic depression amount, it may be envisaged that amount of homosynaptic depression can be used as a marker for rigidity treatment assessment. Another clinical interest would be to search for non-invasive tools able to enhance homosynaptic depression. Indeed, if the reduction of homosynaptic depression plays a role in the development of rigidity, it may be hypothesized that restoring homosynaptic depression by any tool would reduce rigidity.

Clinical impact could also be to test homosynaptic depression before surgery. Indeed, in some patients who have not been included in this series of experiments because they responded only partially to the subthalamic nucleus stimulation with mild improvement of rigidity and freezing appearing after surgery, homosynaptic depression was not modified. Thus, homosynaptic depression may help to select candidates for deep brain stimulation.

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