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Pedunculopontine nucleus deep brain stimulation changes spinal cord excitability in Parkinson's disease patients

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Abstract Bilateral peduncolopontine nucleus (PPN) and subthalamic nucleus (STN) deep brain stimulation (DBS) was performed in six-advanced Parkinson's disease (PD) patients. We report the effect of both PPN-DBS (25 Hz) and STN-DBS (185 Hz) on patient spinal reflex excitability by utilizing the soleus-Hoffman reflex (HR) threshold. Compared to controls (n = 9), patients showed an increase of HR-threshold, which was scarcely affected by levodopa, but significantly reduced by DBS. In particular, we found that PPN-DBS alone, or plus STN-DBS induced a complete recovery of HR-threshold up to control values. The HR-threshold changes, although do not allow to investigate the contribution of specific intraspinal pathways, suggest that PPN may play a key-role in modulating spinal excitability in PD possibly by improving the basal ganglia-brainstem descending system activity.

Keywords Hoffman Roflex · Pedunculopontine nucleus · Deep brain stimulation · Spinal cord excitability

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Introduction

Peduncolopontine nucleus (PPN) deep brain stimulation (DBS) was recently proved as an effective treatment option for severe Parkinson's disease (PD) (Mazzone et al. 2005; Plaha and Gill 2005; Stefani et al. 2007). Our clinical follow-up on six PD patients undergoing bilateral PPN-DBS and Subthalamic nucleus (STN)-DBS, showed that PPN-DBS may exert an additive effect on Parkinsonian axial motor signs when associated to STN-DBS as well as to l-dopa (Stefani et al. 2007). Since PPN projects to the pontomedullary reticular formation and, thus, to the spinal cord (Mena-Segovia et al. 2004; Pahapill and Lozano 2000), it is reasonable that, in severe PD patients, PPN-DBS may not only contribute to modulate basal-ganglia functional activity, but also influences descending pathways (Mazzone et al. 2005; Stefani et al. 2007). Accordingly, preliminary electrophysiological findings carried out in four of these six PD patients reported a PPN-DBS—mediated effects on the descending reticulo-spinal control (Tisch et al. 2007). To test further this hypothesis, we investigated the influence of chronic PPN-DBS on spinal reflex excitability using the soleus-Hoffman reflex (HR) threshold. Moreover, the effect of low-frequency PPN-DBS was compared to STN-DBS and to l-dopa.

Methods

We studied six patients affected by severe, akinetic-rigid, non-tremulous form of PD, without peripheral nervous system lesions, bilaterally implanted in both STN and PPN. PD patients demographic and clinical features are those previously reported (Stefani et al. 2007) and they are summarized in Table 1, including the unified Parkinson

disease rating scale-motor section (minimum 0 maximum 108; UPDRS-III) used for clinical assessments. DBS surgical procedures are detailed elsewhere. Post-operative TC-magnetic resonance imaging checked for the precise placement of quadripolar electrodes (DBS 3389, Medtronic, Minneapolis). After surgery, chronic stimulation producing the best clinical status, without side effects, was determined as following monopolar stimulation through contact 1 or 2 negative, 185 Hz, 90 μs pulse width, 1.5–2.4 V for STN; bipolar stimulation contact 0 negative versus contact 1 positive, 25 Hz, 60 μs pulse width, 1.5–2.0 V for PPN.

Nine age-matched healthy volunteers (63.4 ± 2.9 years) were studied as age-matched control group.

All participants gave written informed consent to the study; the Local Ethical Committee approved study protocol.

Study protocol

A week pre-surgery, HR was recorded after an overnight therapy withdrawal, and then 1-h after a fasting administration of an oral carbidopa/l-dopa dose (50/200 mg).

Although the clinical assessment of these advanced PD patients selected for surgery included supra-maximal l-dopa tests, here we utilized a 200 mg l-dopa test instead of supra-maximal doses, in order to obtain a clear clinical improvement (however, >50%, see Table 1), but avoiding the risk of dyskinesia, which may hamper HR recordings.

Between 3 and 6 months after surgery, once the steady-state best clinical response to DBS was reached, the effects on HR excitability of the following stimulation conditions were investigated in a double-blind randomised sequence: OFF-DBS, bilateral STN-DBS, bilateral PPN-DBS, and bilateral STN + PPN-DBS. During the 4-day protocol, DBS configuration was changed for the following stimulation modality at 6.00 p.m. to record the HR the next morning (9.00 a.m.) after an overnight therapy withdrawal. On the basis of the international standards (Preston and Shapiro 2005), the soleus-HR was recorded at rest, in the more symptomatic side of PD patients and in the right side of controls while an audio-visual feed-back of EMG background activity continuously monitored the lower limb muscular relaxation throughout all recordings. The tibial nerve was stimulated in the popliteal fossa (cathode proximal; rectangular pulses every 10 s) using long stimulus duration (0.5 ms). The stimulus intensity was progressively increased to evoke a reliable HR of 50 μV (HR-threshold), which was considered as the first response to the lowest stimulus intensity (Kushnir et al. 2000, 2001, 2002)[e1]. Then the intensity was progressively increased to evoke an M-response of 50 μV (M-response-threshold) to measure the threshold ratio ($H/M_{T\text{-}ratio}$, Kushnir et al. 2000, 2001, 2002)[e2]. Thereafter, the stimulus intensity was increased until producing the maximal HR and the maximal M-response to measure the amplitude ratio ($H/M_{A\text{-}ratio}$). Blocks of 20 trials were recorded, (filtering bandwidth 2–2,000 Hz; 5-kHz sampling frequency).

Statistical analysis included the Mann–Whitney *U* test to separately compare HR-threshold, M-response-threshold, $H/M_{T\text{-}ratio}$ and $H/M_{A\text{-}ratio}$ between controls and PD patients. The within PD patient group analysis included a non-parametric Friedman ANOVA, coupled with the Wilcoxon's matched pairs test.

Results

Pre-surgery, PD patients showed a significant increase of HR-threshold, which was higher than that for M-response, and therefore, an increase of $H/M_{T\text{-}ratio}$, in comparison to control subjects. The acute l-dopa test was scarcely effective on HR-threshold, whilst it induced a remarkable

Table 1 Demographic and clinical features (mean ± SD) of PD patients' participant the study

PD patients $n = 6$			
Age (years)	Disease duration (years)	l-dopa therapy duration (years)	Equivalent l-dopa daily dose (mg)
64.5 ± 3.2	12.1 ± 3.0	10.1 ± 3.6	1091.6 ± 227.3

UPDRS-III: total score (items 18–31):minimum 0 maximum108; axial signs sub-score (items 27–30): minimum 0 maximal 16

Morning-OFF		Best-ON		Pre l-dopa test (200/50 mg)		Post l-dopa test (200/50 mg)	
Total score	Axial signs sub-score	Total score	Axial signs sub-score	Total score	Axial signs sub-score	Total score	Axial signs sub-score
74.1 ± 4.6	11.9 ± 1.9	37.5 ± 4.9	7.8 ± 1.7	76.8 ± 3.5	12.2 ± 1.7	36.2 ± 4.2	8.2 ± 1.9

In lower part are reported the clinical scores rated by means of the Unified Parkinson disease rating scale-motor section (UPDRS-III) in OFF and ON conditions (Stefani et al. 2007) and before and after the l-dopa/carbidopa 200/50 mg acute test performed in the morning after an overnight therapy withdrawn

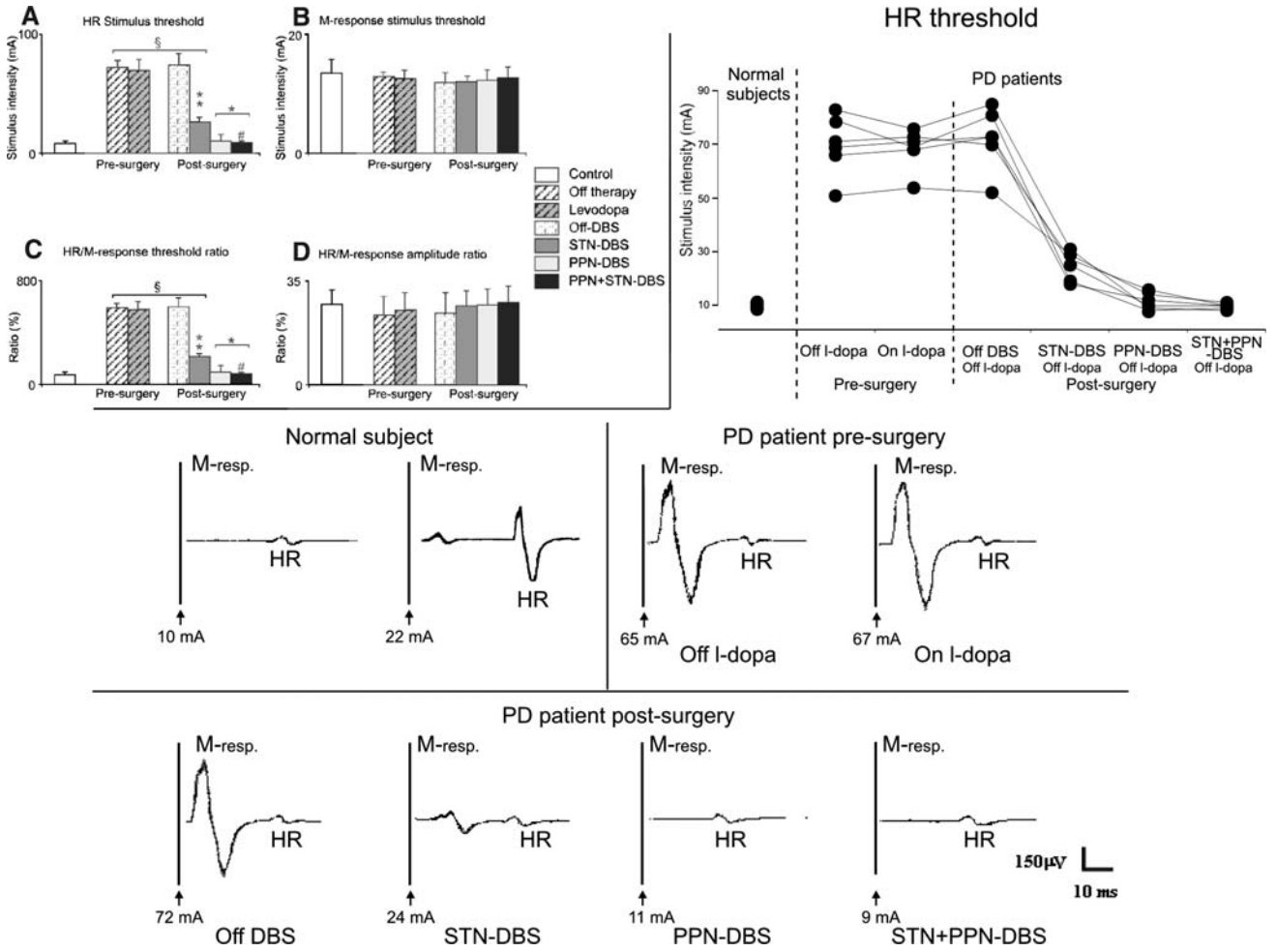

Fig. 1 *Upper left part* the histograms show mean and SD of the studied electrophysiological values in normal subjects and PD patients in the different testing conditions. In *panel A* and *B*, the *Y*-axis represents the stimulus intensity required to evoke a reliable HR of 50 μV (HR-threshold) and a M-response of 50 μV (M-response-threshold). *Between group analysis* in *panel A* § indicates the significant difference of HR-threshold between normal subjects and patients ($p < 0.01$; Mann–Whitney *U* test); in *panel C* § shows the significant difference of $H/M_{T\text{-ratio}}$ between normal subjects and patients ($p < 0.01$; Mann–Whitney *U* test). *Within PD group analysis* (Friedman ANOVA: $\chi^2 = 15.36$; $p < 0.001$ for HR-threshold and $\chi^2 = 13.40$; $p < 0.005$ for H/MT-ratio). * indicates the significant reduction of HR-threshold (*panel A*) and H/MT-ratio (*panel C*) in comparison to OFF-DBS (** $p < 0.01$ and * $p < 0.05$, Wilcoxon's pairs test); # indicates the significant reduction of HR-threshold and H/MT-ratio in comparison to STN-DBS ($p < 0.05$, Wilcoxon's pairs test). *Upper right part* the plot shows the individual stimulus intensity (mA) required to evoke the HR-threshold in controls ($n = 9$) and PD patients ($n = 6$) in the different testing conditions. *Lower part* superimposed raw traces showing the HR-threshold in a representative healthy subject and in a representative PD patient studied in different testing conditions (of course, traces devoid of a clear-cut HR—as under ≤40 mA—were not even shown). Note that the great stimulus intensity required to evoke the HR in the PD patient remains unchanged under l-dopa (>60 mA) but it is consistently reduced during DBS. In particular, low stimulus intensity, comparable to control value, (11 vs. 9 mA) are again capable to evoke a clear HR only during PPN-DBS and PPN-DBS plus STN-DBS

clinical benefit, as testified by the >50% of clinical amelioration at the UPDRS-III (see Table 1).

In OFF-DBS, PD patients showed no change in HR-threshold and $H/M_{T\text{-ratio}}$ in comparison to pre-surgery. However, PPN-DBS and PPN + STN-DBS produced a significant recovery of both HR-threshold and $H/M_{T\text{-ratio}}$ up to restore normal values (Fig. 1). STN-DBS also induced a significant reduction of both HR-threshold and $H/M_{T\text{-ratio}}$, when compared to OFF-DBS, but without a complete recovery of control values. During PPN + STN-DBS, both HR-threshold and $H/M_{T\text{-ratio}}$ were significantly lower than during STN-DBS (Fig. 1).

We found no differences in M-response-threshold and $H/M_{A\text{-ratio}}$ between groups, and within the PD patient group, among the testing conditions. Nevertheless, a not significant trend to $H/M_{A\text{-ratio}}$ increase was observed during each DBS compared to OFF-DBS, probably due to the lowered HR-threshold that allowed to achieve a greater HR amplitude coupled to a lower M amplitude as a consequence of the low stimulus intensity (Fig. 1).

Discussion

In the present report we showed that the HR-threshold is markedly increased in advanced PD patients, even after a clinically effective l-dopa test (>50% clinical improvement at the UPDRS-III). Moreover, we found that PPN-DBS and, in a lesser extent STN-DBS is able to recover this electrophysiological abnormality.

Previous studies, carried out in l-dopa chronically treated stable PD patients, have already reported that HR may be elicited only at stimulus intensities greater than those required for the M-response (Kushnir et al. 2000, 2001, 2002)[e3]. In addition, Delwaide and colleagues (1991) described a clear relationship between l-dopa sensitive PD motor symptoms and changes of spinal cord excitability in PD. These authors, in fact, observed a reduction of short-latency autogenic inhibition correlated to rigidity (Delwaide et al. 1991), as well as a reduction of audiospinal reaction correlated to bradykinesia (Delwaide et al. 1993).

The presently reported scarce effect of l-dopa in improving HR-threshold seems at odds with these previous data, and the possibility of a sub-optimal l-dopa challenging dose has to be taken into account. However, the observation that the UPDRS-III clinical improvement due to l-dopa was greater than that obtained by PPN-DBS (Stefani et al. 2007), could suggest a different modulation of clinical motor signs, and HR-threshold changes, these latter possibly not so strictly dependent on l-dopa or on l-dopa sensitive motor symptoms. Yet, also Meunier and colleagues (2000) found movement-induced abnormalities of dysinaptic reciprocal inhibition in l-dopa treated PD patients, which were considered probably not depended on l-dopa, since they were clearly unaffected by the drug. The apparent incongruence among these studies may be related to the different electrophysiological tools used to investigate the HR, which may be influenced in a variable manner by l-dopa, since they explored different functional loops involved in spinal reflex activity.

We are aware that the evaluation of HR-threshold does not permit to identify unequivocally the putative anatomical pathways specifically involved in the reported HR changes, nevertheless the observation that HR-excitability completely regains control values only during PPN-DBS seems to suggest a possible, key-role for PPN in modulating spinal reflex activity. Previous studies documented that PPN receives inhibitory projections from basal ganglia and, in turn projects to the pontomedullary reticular structures (Munro-Davies et al. 1999; Pahapill and Lozano 2000). More recently it has been also suggested that in PD the descending inhibitory output from basal ganglia may be overactive reducing PPN excitation over pontomedullary reticular formation and reticulospinal nuclei, possibly contributing to gait and postural impairment in PD (Pahapill and Lozano 2000; Takakusaki et al. 2003). Considering these anatomical and functional evidences indicating PPN as one of the primary target for basal ganglia descending outputs and the reciprocal connection relating PPN to the reticular pontomedullary nuclei, it is possible that in PD the PPN-DBS may act on spinal cord excitability by improving the reticulospinal pathway transmission. This hypothesis is in accord with previous electrophysiological studies suggesting that abnormalities of spinal interneuron activity in PD may be due to a dysfunction in the descending reticulospinal tract and in the nucleus reticularis giganto-cellularis, directly influencing both Ia and Ib spinal interneurons (Delwaide et al. 1991, 2000, 2001).

Finally, also STN-DBS was able to modulate HR-threshold, although in a lesser extent than PPN-DBS. Since excitatory glutamatergic projections are directed from the STN towards both GPi/substantia nigra reticulate (SNr) and PPN, STN-DBS might cluster or even excite the PPN firing discharge, as demonstrated in PD SNr (Galati et al. 2006) and inferred in rodent PPN (Florio et al. 2007).

In conclusion, our data seem to suggest that, in PD, 25 Hz PPN-DBS, besides the proposed role within the basal ganglia circuitry, provides a distinctive influence on spinal reflex excitability. The exact correlation of these findings with gait improvement will be addresses as soon as a larger cohort and a more prolonged follow-up are available.

Given the simultaneous involvement of multiple segmental and supra-segmental pathways in controlling spinal activity, our present observations may represent the starting point for further studies investigating possible PPN-DBS-mediated effects on different intraspinal inhibitory mechanisms, as recently described for STN-DBS (Potter et al. 2004).

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