SHORT REPORT

Effects of subthalamic nucleus stimulation and levodopa on the autonomic nervous system in Parkinson's disease

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J Neurol Neurosurg Psychiatry 2007;**78**:742–745. doi: 10.1136/jnnp.2006.103739

Dysfunctions of the autonomic nervous system (ANS) are common in Parkinson's disease (PD). Regarding motor disability, deep brain stimulation of the subthalamic nucleus (STN) is an effective treatment option in long lasting PD. The aims of this study were to examine whether STN stimulation has an influence on functions of the ANS and to compare these effects to those induced by levodopa.

Blood pressure (BP) and heart rate (HR) during rest and orthostatic conditions, HR variability (HRV) and breathing-induced cutaneous sympathetic vasoconstriction (CVC) were tested in 14 PD patients treated with STN stimulation during "ON" and "OFF" condition of the stimulator. The effects of a single dose of levodopa on ANS were tested in 15 PD patients without DBS.

STN stimulation had no influence on cardiovascular ANS functions, whereas CVC was significantly increased. In contrast, levodopa significantly lowered BP and HR at rest and enhanced orthostatic hypotension. Further, HRV, skin perfusion and temperature increased after administration of levodopa.

Our results suggest that in contrast to levodopa, STN stimulation has only minor effects on autonomic functions. Since less pharmacotherapy is needed after STN stimulation, reduced levodopa intake results in relative improvement of autonomic function in deep brain stimulated PD patients.

Autonomic dysfunction is common in Parkinson's disease (PD).[1] In common with other drugs, levodopa alters cardiovascular reflexes.[2–6] Deep brain stimulation of the subthalamic nucleus (STN-DBS) is an effective treatment for motor disability in patients with PD of long duration.[7] As the basal ganglia are connected to areas involved in regulation of the autonomic nervous system (ANS),[8] STN-DBS may affect ANS functions.

The aim of this study was to investigate the influence of STN-DBS on ANS compared with the effects of levodopa administration.

METHODS

Patients

Fourteen patients with PD (mean age 57.7 (2.8) years; 10 males, 4 females), treated with bilateral STN-DBS (Medtronic 3389, Minneapolis, Minnesota, USA), and 15 non-stimulated patients with PD (LD group; mean age 63.4 (2.1) years; 6 males, 8 females), were examined clinically and with autonomic tests. The DBS group remained on their everyday antiparkinson medication and a 30 minute interval was given between turning on/off the stimulator and examination (ON_{stim}, OFF_{stim}).

Except for measurement of skin temperature (see methods), the LD group was investigated after at least 12 h off all antiparkinson medication (OFF_{Med}) and again approximately 30 min after administration of oral soluble levodopa and benserazide (ON_{Med}). The dose of levodopa depended on the patient's regular morning dose of levodopa and was 150–300 mg.

Examinations were in agreement with the local ethics committee. All subjects gave written informed consent.

Autonomic tests

Tests were performed in a quiet environment with a constant room temperature of 24°C.

Heart rate variability

Heart rate variability (HRV) was examined using computer assisted equipment (ProSciCard III; MediSyst GmbH, Germany) at rest and during controlled deep breathing (6 respiratory cycles per minute). The coefficient of variation, root mean square of successive differences, mean circular resultant, expiration–inspiration difference and expiration–inspiration ratio (E/I ratio), as well as a spectral analysis of HRV, were quantified and compared with the normal range of 120 age related healthy subjects.[9]

Tilt test

Blood pressure (BP) and heart rate (HR) were monitored after 10 min of supine rest on a tilt table. Patients were then moved to the erect position (65°) and BP and HR changes recorded at 1, 3 and 5 min of head-up tilt. A decrease in systolic BP >20 mm Hg and diastolic BP >10 mm Hg within 3 min of tilting was regarded as orthostatic hypotension.[10]

Cutaneous sympathetic vasoconstriction and skin temperature

Cutaneous sympathetic vasoconstriction was investigated with patients lying in the supine position using non-invasive laser

Table 1 Heart rate variability parameters in the LD group

Parameter	ON_{Med}	OFF_{Med}	p Value
At rest (n = 14)			
VC (%)	3.5 (0.3)	3.6 (0.4)	NS
RMSSD (ms)	22.4 (2.3)	18.8 (2.3)	<0.05
During deep breathing (n = 11)			
VC (%)	8.3 (1.9)	4.4 (0.8)	<0.01
RMSSD (ms)	39.1 (6.2)	22.3 (4.5)	<0.01
MCR	0.03 (0.01)	0.02 (0)	<0.01
E–I	446.7 (67.1)	184.7 (52.8)	<0.01
E/I ratio	1.9 (0.2)	1.3 (0.1)	<0.01

E–I, expiration–inspiration difference; E/I ratio, expiration–inspiration ratio; MCR, mean circular resultant; RMSSD, root mean square of successive differences; VC, coefficient of variation.
All data are presented as mean (SEM).

Abbreviations: ANS, autonomic nervous system; BP, blood pressure; E/I ratio, expiration–inspiration ratio; HR, heart rate; HRV, heart rate variability; PD, Parkinson's disease; STN-DBS, deep brain stimulation of the subthalamic nucleus

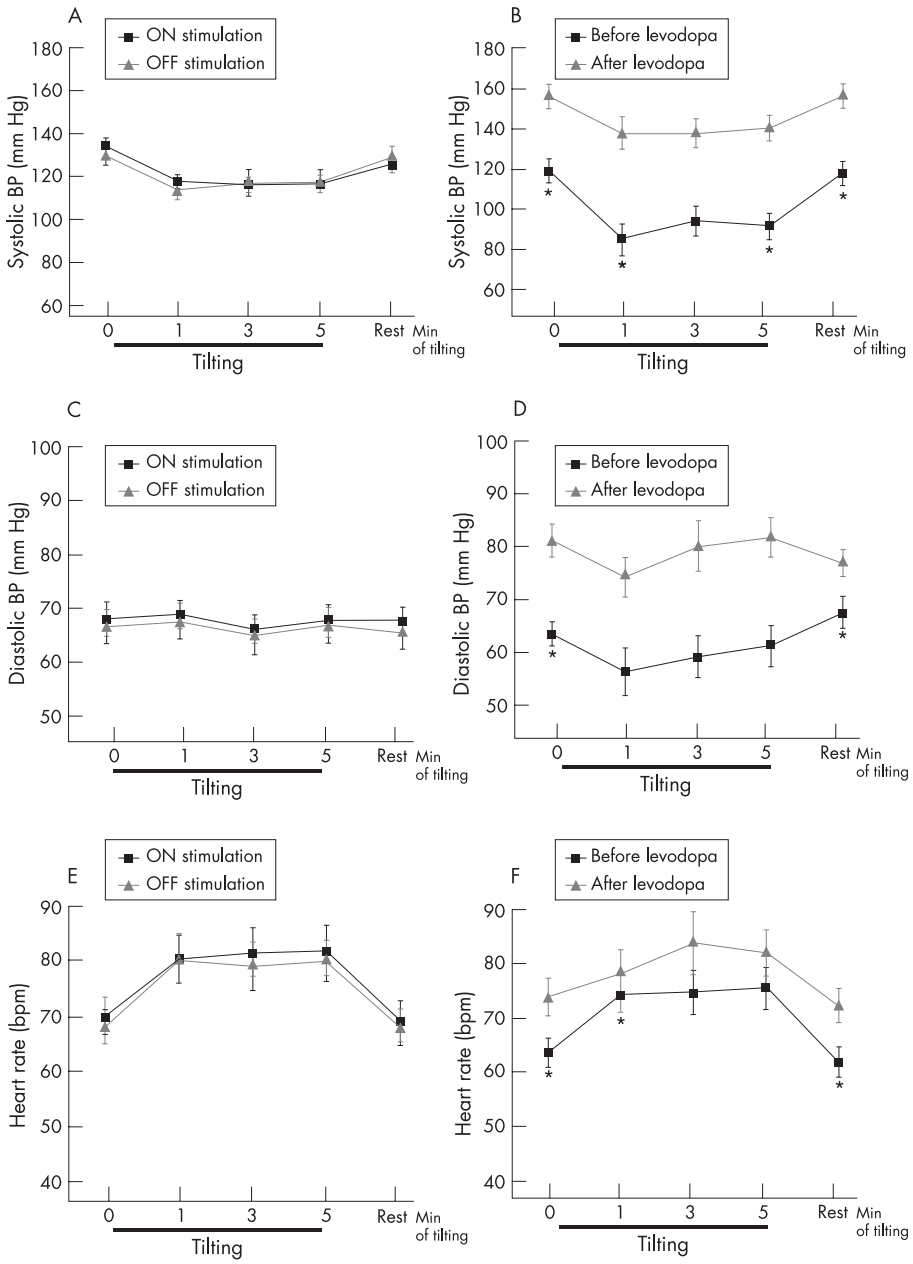

Figure 1 Blood pressure (BP) and heart rate (HR) at rest and during tilting. (A, C, E) Systolic (A) and diastolic (C) BP and HR (E) during ON_{stim} and OFF_{stim} (mean (SEM)). (B, D, F) Systolic (B) and diastolic (D) BP and HR (F) before and after administration of levodopa (mean (SEM)). *$p<0.05$ for comparison between ON and OFF.

Doppler flowmetry (PeriFlux 5000; Perimed AB, Stockholm, Sweden) on the index finger of the non-tremor dominant hand. Cutaneous blood flow (in perfusion units, Pu) during rest and after five deep inspirations was recorded and the reduction in blood flow calculated as follows: (baseline flow−minimal flow after inspiration)/baseline ×100. The mean decrease was determined averaging the three measurements with the highest decrease in blood flow.

Skin temperature in the DBS group was assessed at the tip of the little finger with an infrared thermometer. In the LD group, skin temperature was assessed continuously for the whole period of the examination, with small loggers affixed to one finger that measured temperature every 6 min (Kooltrak, Geisenheim, Germany).

Statistics

The Wilcoxon signed rank test, U test and Spearman's rank test were used, and $p<0.05$ was considered statistically significant. Data are presented as mean (SEM).

RESULTS

For the DBS group, mean time after surgery was 17.2 (4.3) months (mean stimulation parameters 3.1 (0.2) volts, 147.5 (6) Hz on both sides). Motor disability, as measured using the Unified Parkinson's Disease Rating Scale III, was significantly reduced by STN-DBS (26.9 (5.1) vs 11.9 (1.9); $p<0.05$) and by administration of levodopa (43.1 (3.6) vs 18.8 (2.4); $p<0.05$).

No differences were found for disease duration or number of drugs with potential side effects on the ANS between the two groups. The dose of levodopa and the effective dose equivalents of antiparkinson drugs were lower in the DBS group compared with the LD group (558.9 (86.4) vs 926.7 (88.8) mg/24 h; $p<0.05$).

Heart rate variability

Because of increased tremor or rigidity during the *OFF* condition, HRV could not be examined in all patients. HRV parameters did not differ between OFF_{stim} and ON_{stim} during both resting conditions and deep breathing in the entire group

(n = 11). The results of HRV parameters in the LD group are shown in table 1.

No correlation between the amount of levodopa administered, daily levodopa dose or duration of disease and HRV parameters was observed.

Tilt test

In the STN-DBS group, three patients showed orthostatic hypotension during ON_{stim}, two in OFF_{stim} and three during both conditions. No significant differences in BP or HR between ON_{stim} and OFF_{stim} were observed. There was no correlation between the decrease in BP in OFF_{stim} and ON_{stim} or between the BP response and motor response to stimulation, age or daily levodopa dose (fig 1).

In the LD group, four patients showed orthostatic hypotension in ON_{Med} and 7 in both conditions. Mean systolic, diastolic, mean arterial BP and HR at rest were significantly lower, and mean systolic BP was significantly more decreased 1 min after tilting in ON_{Med} compared with OFF_{Med} (fig 1). No correlations between duration of disease or amount of soluble levodopa applied and values of BP or HR at rest or during tilting were found.

Cutaneous sympathetic vasoconstriction and skin temperature

Cutaneous vasoconstriction was increased during ON_{stim} compared with OFF_{stim} (−57.2 (3.7) vs −44.8 (5.8)%; $p<0.05$) whereas blood flow at rest and skin temperature did not differ.

In the LD group, cutaneous vasoconstriction did not differ significantly between ON_{Med} and OFF_{Med} (−34.9 (3.6) vs −40.4 (3.9)%; NS) but was out of the 95% confidence interval during ON_{Med}, according to Schüller *et al*.[11] Skin temperature started to increase approximately 30 min after administration of levodopa and was significantly higher 60 min (32.6 (0.6)℃), 66 min (33 (0.7)℃), 72 min (33.5 (0.4)℃) and 78 min (34 (0.4)℃) after administration of levodopa compared with the baseline value (29.5 (1.3)℃; $p<0.05$). At this time, skin perfusion at rest was higher in ON_{Med} compared with OFF_{Med} (298 (20.6) vs 179.2 (38.5) Pu; $p<0.05$). No correlation between dose of levodopa administered and blood flow at rest, skin temperature or cutaneous vasoconstriction was observed.

In both groups, no correlation was observed between disease duration or daily levodopa dose and blood flow at rest, skin temperature or cutaneous sympathetic vasoconstriction.

DISCUSSION

STN-DBS significantly decreased motor disability but had no direct effect on autonomic cardiac innervation or muscle vasoconstrictor neurons.

Our results are in agreement with other studies that did not find changes in BP or its responses to tilting when examining stimulated patients with PD on 2 consecutive days during ON_{stim} and OFF_{stim}[12] or before and 1 year after initiation of STN-DBS.[13]

Interestingly, STN-DBS in patients with PD during surgery increased HR and BP.[14] Different findings between intraoperative and post-surgery investigations could be explained by slightly different intraoperative locations of the STN electrodes,[15 16] short lasting alterations in autonomic functions[17] or psychological factors (eg, patients are more excited during surgery).

Cutaneous sympathetic vasoconstriction was enhanced in ON_{stim} compared with OFF_{stim}. Is it possible that STN-DBS improves selective autonomic functions? For the sympathetic nervous system it has been shown that innervation to the different target organs is controlled separately.[18] STN-DBS acts on fibres and cell bodies close to the implanted electrode.[19] Thus an effect of STN-DBS on specific autonomic pathways may be possible. Accordingly, STN-DBS has been shown to improve sympathetic skin responses[12] and neural regulation of the bladder.[20]

In contrast with STN-DBS, levodopa significantly lowered BP and HR at rest. Furthermore, we found a positive correlation between the decrease in BP in OFF_{Med} and ON_{Med}, suggesting that in patients with orthostatic hypotension, levodopa even worsened autonomic dysregulation.

Skin temperature, skin perfusion and HRV were increased, and cutaneous sympathetic vasoconstriction decreased in ON_{Med}. These effects could be explained by a decreased central sympathetic outflow caused by the central D_2 agonist action of levodopa.[21] Peripherally mediated vasodilation in the vascular bed of skeletal muscle and skin[4 5] is unlikely as it would have induced a baroreceptor reflex mediated increase in HR, which was not observed, despite an intact baroreceptor reflex, as indicated by a rise in HR during tilt table testing.

In conclusion, our results suggest that STN-DBS has some selective positive effects on autonomic functions without any effect on the cardiovascular ANS. In contrast, levodopa induced several negative effects on autonomic functions by lowering BP and HR as well as cutaneous vasodilation, all contributing to worsening orthostatic hypotension. As treatment with STN-DBS allows reduction of the daily dose of levodopa,[19] reduced levodopa intake may result in relative improvement of autonomic function in deep brain stimulated patients with PD.

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This work was supported by the Bundesministerium für Bildung und Forschung (BMBF, 01EM05/04), der Deutschen Forschungsgemeinschaft (DFG Ba1921/1-1/3) and der Alexander-von-Humboldt-Stiftung and Pfizer Deutschland (unrestricted educational grant). None of the sponsors was involved in the design or conduct of the study, or in the collection, management, analysis, interpretation or preparation of the data, or review or approval of the manuscript.

Competing interests: None.

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Received 4 August 2006
Revised 22 February 2007
Accepted 23 February 2007
Published Online First 19 March 2007

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NEUROLOGICAL PICTURE

doi: 10.1136/jnnp.2006.111773

Acute strokes in the setting of a persistent primitive trigeminal artery

A persistent primitive trigeminal artery (PPTA) is the most common of the embryonic carotid–basilar anastomoses that remain into adulthood; an incidence of 0.1–1.0% has been reported.[1] Although typically an incidental finding on angiogram or non-invasive vascular imaging, the condition has been found in association with trigeminal neuralgia[2] and various vascular anomalies. We present imaging from a patient with acute ischaemia in the setting of a PPTA that is presumed to be embolic along the distribution of this anastomosis.

A 54-year-old man with undiagnosed diabetes and hyperlipidaemia presented to our hospital with 20 min of rapidly improving aphasia, dysarthria and right hemiparesis. His initial head CT was unremarkable. Although clinically he had what would be considered a transient ischaemic attack, his MRI demonstrated several areas of restricted diffusion in what appeared to be the left middle cerebral artery and posterior cerebral artery territories (fig 1A, B). The pattern of infarction was suggestive of embolic phenomena. A left persistent primitive trigeminal artery was seen on magnetic resonance angiography (fig 1C–E). He had a diminutive vertebrobasilar system caudal to the basilar influx. Incidental note was made of an absent right A_1 segment. His carotid arteries were without haemodynamically significant stenosis but mild atherosclerotic changes were appreciated in the intracranial vessels. Transoesophageal echocardiography was unrevealing, with the exception of an atrial septal aneurysm. Holter monitoring failed to show occult atrial fibrillation on 24 h sampling. Although no clear artery-to-artery embolic or cardioembolic source could be demonstrated, the pattern of infarction suggested a source at or proximal to the origin of his PPTA; in situ thrombosis of two different vascular distributions would seem unlikely.

A PPTA has rarely been reported in the setting of stroke. There are reports in the literature of brainstem infarcts in patients with a PPTA.[3 4] Poor anterograde flow from atretic vertebral arteries may play a role in posterior fossa ischaemia. A patient with a PPTA and bilateral occipital infarcts secondary to carotid artery disease has been published.[5] Here we present a unique case of supratentorial strokes in atypical vascular distributions occurring in the setting of this rare vascular anomaly. As with a posterior cerebral artery of fetal origin, the normal boundaries between what is generally considered anterior circulation and posterior circulation are blurred. In this case, an anterior circulation thrombus can cause a "posterior" circulation event.

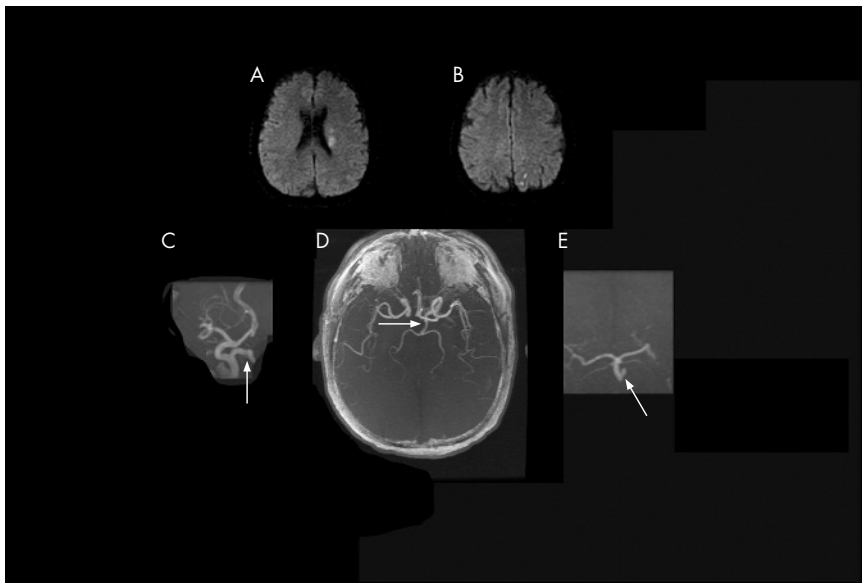

Figure 1 Brain MRI/magnetic resonance angiography (MRA). Diffusion weighted imaging demonstrated acute infarcts in the left corona radiata (A) and occipital lobe (B). Time of flight MRA showed a persistent trigeminal artery (arrows) connecting the left internal carotid (C) and basilar arteries (E). An overview of the circle of Willis shows this anomaly as well as an absent right A_1 segment (D).

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Competing interests: None declared

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