The Role of Ghrelin, Neuropeptide Y and Leptin Peptides in Weight Gain after Deep Brain Stimulation for Parkinson's Disease

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Key Words

Parkinson's disease • Deep brain stimulation • Weight • Neuropeptide Y • Ghrelin • Leptin • Neuroprotection • Hypothalamus

Abstract

Background: The exact mechanism of weight gain (WG) after deep brain stimulation (DBS) of the subthalamic nucleus (STN) in patients with idiopathic Parkinson's disease remains unknown. **Objectives:** To investigate a possible involvement of ghrelin, neuropeptide Y (NPY) and leptin in WG after DBS. **Methods:** Twenty-three Parkinson patients were submitted for body composition measurements and blood sampling 3 days before, and 3 and 6 months after STN DBS. Peripheral concentrations of ghrelin, NPY, and leptin were determined, as well as the L-dopa equivalent daily dose. Patients were clinically evaluated using the Unified Parkinson's Disease Rating Scale. **Results:** Three months after surgery, a significant WG was observed (3.09 ± 5.00 kg; $p = 0.007$) with no further increase at 6 months. Three months postoperatively, NPY circulating levels increased significantly ($p = 0.05$), while the increase of ghrelin levels reached statistical significance at 6 months ($p = 0.001$). WG was significantly associated with changes of ghrelin and leptin levels at 3 and 6 months, re-

spectively. **Conclusions:** STN DBS seems to temporarily dysregulate the hypothalamic secretion of NPY and ghrelin. The variation of weight may be attributed to an increased production of ghrelin and leptin. A possible neuroprotective role of DBS, exerted through the increase of ghrelin levels, should be further studied.

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Introduction

Parkinson's disease (PD) is an adult-onset, progressively evolving, neurodegenerative disease. Its cardinal symptoms are bradykinesia, tremor, rigidity, and postural instability, caused by significant dopaminergic striatal denervation. However, there is a spectrum of non-motor symptoms related with PD, such as spontaneous limb pain, urogenital dysfunction, orthostatic hypotension, depression, sleep disorders, dementia, psychosis and weight loss [1–4].

Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an accepted surgical treatment for medically refractory PD. DBS leads to a significant improvement of all motor symptoms of PD, but often causes weight gain (WG), which may hamper the overall clinical

benefit. WG after DBS has been demonstrated in various studies [5–7], but few have examined the etiopathogenetic mechanisms [6, 7]. However, ‘peripheral’ and ‘central’ mechanisms are currently hypothesized.

The ‘peripheral’ hypothesis entails that WG after DBS is either due to decreased energy expenditure, mostly through the reduction of motor fluctuations, tremor and dyskinesias [6–8], or to decreased resting energy expenditure due to the reduction of rigidity and to increased appetite [8, 9]. The latter may be due to the reduction of anorexia and nausea following the lower dosage of the antiparkinsonian medications [10]. Furthermore, a reduction of the total daily dose of L-dopa may have an additional role, via probable lipolytic effects [11], as well as a central effect on the satiety/appetite hypothalamic centers [12]. Improvement in mood and functional independence may also contribute to WG [5].

The ‘central’ hypothesis on the regulation of energy implicates the hypothalamus. The hypothalamus has a central role in the regulation of energy homeostasis, appetite and food intake [13–17]; it receives, elaborates, and interprets orexigenic and anorexigenic signals in order to coordinate food intake. Ghrelin is a powerful orexigenic peptide: it increases food intake and promotes adipogenesis [18–21]. It is primarily synthesized by endocrine cells in the stomach and in lower amounts by the bowel, kidney, placenta, heart, thyroid and hypothalamus. Ghrelin exerts its orexigenic effects by stimulating neurons in the arcuate nucleus which produce neuropeptide Y (NPY) and agouti-related protein and by inhibiting neurons that produce proopiomelanocortin and cocaine- and amphetamine-regulated transcript [21–23]. NPY is also an orexigenic peptide, which has an essential role in body weight homeostasis under physiological conditions [13]. NPY-producing neurons are principally situated in the brain stem, in the arcuate nucleus and dorsomedial nucleus of the hypothalamus. NPY synthesis and release is stimulated by ghrelin and inhibited by leptin. Leptin is an anorexigenic hormone produced predominantly by the white adipose tissue and its circulating concentrations reflect the body’s energy stores. The primary role of leptin is to reduce hyperphagia and fat accumulation. These effects are mediated by the Ob-Rb receptor, which is expressed in the hypothalamus, in the medial preoptic area and in the brain stem [24]. Leptin inhibits the activity of orexigenic neurons (NPY- and agouti-related protein-producing neurons) and stimulates anorexigenic neurons (proopiomelanocortin and cocaine- and amphetamine-regulated transcript-producing neurons) [16, 22, 24]. Recent studies support the hypothesis that WG after STN DBS might be due to a regional effect

of the electrical current on the hypothalamus [5, 8, 25, 26] or, alternatively, on its afferent or efferent tracts [26].

We set out to examine prospectively the circulating levels of ghrelin, NPY and leptin in patients with idiopathic PD before and after bilateral STN DBS and to associate these peptides with WG.

Methods

Patients and Measurements

Twenty-three patients with idiopathic PD who were also candidates for STN DBS (according to the CAPSIT criteria) were included in the study. All patients were euthyroid with normal pituitary function. Patients with psychosis, neoplasia, severe depression, diabetes, thyroid disease and cognitive decline (Mini Mental State Examination score <24) were excluded. None of the patients presented nausea or anorexia due to dopaminergic medication, and none of them changed their dietary habits throughout the whole study.

The patients were investigated at 3 different time points: 3 days before surgery, and 3 and 6 months after DBS surgery. At each clinical appointment, all patients underwent body composition measurements and blood sampling. The body composition measurements included: body weight, body mass index (BMI), fat mass (FM) and fat-free mass (FFM). Measurements were obtained with Futrex 5000 (Futrex, Inc., Gaithersburg, Md., USA), which estimates FM and FFM based on infrared analysis [27]. According to their BMI, the patients were classified as normal weight (BMI = 18.5–25), overweight (BMI = 25.1–30) and obese (BMI >30). The waist circumference was also measured. Blood samples were collected after an overnight fast between 8:00 and 8:30 a.m. in order to minimize variability; the plasma was kept at –80°C until further analysis for the determination of total ghrelin, NPY, leptin, cortisol, thyroid-stimulating hormone, follicle-stimulating hormone, free T3, free T4, luteinizing hormone, prolactin, antithyroid peroxidase antibodies, estradiol II, testosterone, albumin and total protein concentrations. Total ghrelin, NPY and leptin were measured by commercially available radioimmunoassays (LINCO Research, St. Charles, Mo., USA and Euro-Diagnostica AB, Medeon, Malmö, Sweden). The remaining hormones were measured by ELISA.

At the first appointment (3 days before surgery), the patients were evaluated in the off-medication state (i.e. after a 12-hour withdrawal of the antiparkinsonian medication) and in the on-medication state, following the administration of an appropriate challenge dose of L-dopa, using part III and IV of the Unified Parkinson’s Disease Rating Scale (UPDRS), Hoehn and Yahr scale, and Schwab and England ADL scale. Six months after surgery, the same clinical evaluations were carried out in both off- and on-medication state with the patients always in the on-DBS state. The use of L-dopa equivalent daily dosage (LEDD) was recorded at baseline and 6 months later. LEDD was determined as follows: 100 mg L-dopa = 140 mg L-dopa CR, 10 mg bromocriptine, 6 mg ropinirole, 1 mg pramipexole, 1 mg pergolide, 10 mg apomorphine, 1 mg lisuride and 2 mg cabergoline [28].

All subjects provided informed consent before taking part in the study, and the research protocol was approved by the hospital’s Ethics Committee.

Table 1. Body composition of all patients (n = 23) before surgery, and 3 and 6 months after surgery

Body composition	Before surgery	3 months after surgery (on DBS)	p*	6 months after surgery (on DBS)	p*
Body weight, kg	79.08 ± 21.01	82.17 ± 22.10	0.009	82.15 ± 20.99	0.013
BMI, kg/m ²	28.68 ± 4.79	29.77 ± 4.78	0.007	29.71 ± 4.39	0.025
FM, kg	24.06 ± 9.62	24.76 ± 9.80	0.050	26.29 ± 10.17	n.s.
FFM, kg	56.95 ± 14.98	56.28 ± 13.87	n.s.	57.81 ± 15.13	n.s.
Waist circumference, cm	102.68 ± 17.06	106.54 ± 14.62	0.010	107.65 ± 13.62	0.004

Results are expressed as means ± standard deviation.

* Paired t test, p values refer to the comparison with the preoperative values. n.s. = Not significant (p > 0.05).

Surgery

All patients underwent bilateral implantation of quadripolar DBS electrodes (Medtronic 3389, Minneapolis, Minn., USA) by the same neurosurgeon and STN was the selected target. A Cosman-Roberts-Wells head ring was applied under local anesthesia. A high resolution T₂-weighted MRI was consequently performed (slice thickness: 2 mm without gap), with a 1-Tesla MRI scanner (Philips, Gyroscan, Intera). With the use of the Frame-Link software v. 4.0, the Stealthstation workstation (Medtronic) and the Schaltenbrand and Wahren atlas [29], the mid-sagittal plane, the anterior commissure (AC) and the posterior commissure (PC) were identified. The STN were selected 3–4 mm below AC-PC, 11–12 mm laterally and 2 mm posteriorly to the mid-commissural point.

A single-neuron activity analysis was performed intraoperatively using microelectrode recordings (Lead Point 4.0; Medtronic) to define the electrophysiological limits of the STN, and the patients' responses to stimulation were recorded. The position of the 3389 quadripolar DBS electrode was chosen so that contact 0 was usually placed at the base of the STN. The implantation of the neurostimulator (Kinetra; Medtronic) was performed on the same day under general anesthesia. Postoperatively, the correct position of the electrodes was verified using a computerized tomography, fused with the preoperative MRI.

The pulse generators were activated on the 5th postoperative day and continuous monopolar stimulation of contact 0 or 1 was used (1.5–2.3 V, 60–90 ms and 130 Hz).

Statistical Analysis

Variables were checked for normality using the one-sample Kolmogorov-Smirnov test. The paired t test and Wilcoxon's test were performed for parametric and non-parametric analyses of pairs, respectively. One-way ANOVA was used to compare the means of three samples. Correlations were carried out using Pearson's or Spearman's r correlation tests when appropriate. Multivariate linear regression analysis was carried out for examining the association between WG and those variables which have been found to correlate significantly with WG in the univariate analysis. Data were expressed as means ± standard deviation (SD). Statistical significance (p value) was set at the level of 0.05. SPSS 17.0 for Windows was used for the statistical analysis.

Results

Body Composition

Preoperatively, our 23 PD patients (15 men and 8 women), aged 65.2 ± 8.9 years with a mean disease duration of 12.7 ± 6 years, had a mean body weight of 79.08 ± 21.01 kg (men: 86.28 ± 21.43 kg, women: 65.60 ± 12.25 kg), and a mean BMI of 28.68 ± 4.79 (men: 29.52 ± 4.42, women: 27.11 ± 5.38).

Three months after surgery, a statistically significant WG was observed (mean = 3.09 ± 5.00 kg) without a gender prevalence (males: 3.56 ± 5.36 kg; females: 2.21 ± 4.44 kg; p = 0.20; table 1). Seventeen patients (73.9%) had gained weight (mean = 4.89 ± 4.50 kg), 5 patients had lost weight (mean = -2.42 ± 1.43 kg), and 1 patient had conserved his initial body weight. BMI, FM and waist circumference were also significantly increased at 3 months after surgery (table 1). Men tended to gain FM by 3 months after surgery (mean FM change: 2.22 ± 4.18 kg; p = 0.056) with no significant FFM change (mean FFM change: 0.26 ± 3.65 kg; p = 0.78); whilst in women changes in either FM or FFM were not significant (mean FM change: 0.34 ± 1.15 kg, p = 0.49; mean FFM change: -0.23 ± 2.7 kg, p = 0.79).

The mean WG observed at 3 months was maintained at 6 months after surgery (table 1). At 6 months postoperatively, 16 patients (69.5%) had gained weight (mean = 5.90 ± 3.61 kg), 6 patients (26.1%) had lost weight (mean = -3.96 ± 2.11 kg), and 1 patient did not present any weight change. BMI and waist circumference were also significantly increased compared with the preoperative values. At 6 months after surgery, the FFM in men had increased more than their FM (mean FM change: 0.96 ± 5.21 kg, p = 0.43; mean FFM change: 2.17 ± 4.04 kg, p = 0.04). On the contrary, women tended to have more FM with no

substantial change in their FFM (mean FM change: 2.54 ± 3.6 kg, $p = 0.12$; mean FFM change: -0.86 ± 2.81 kg, $p = 0.43$).

An overall consideration of the weight changes in time (from baseline to 3 and 6 months postoperatively) indicated that 12 patients had gained weight at 3 months and had kept increasing their weight at 6 months ('gained weight subgroup'); 5 patients had gained weight at 3 months, but had lost some weight up to the 6-month appointment, although maintaining a WG from baseline values ('variable weight subgroup'); 6 patients had lost weight at 3 months and had kept losing weight at 6 months ('lost weight subgroup').

Clinical Outcome

STN DBS led to a statistically and clinically important improvement in the mean total scores of all rating scales used, in both on- and off-medication states at 6 months after surgery (table 2). The mean improvement in the UPDRS part III was 48% off medication and 34% on medication. Tremor, rigidity and bradykinesia subscores were also significantly improved (88, 67, and 7% improvement on medication, and 87, 78, and 53% improvement off medication, respectively). Patients' activities of daily living according to the Schwab and England scale were ameliorated (25% improvement on medication and 31% off medication), as well as the Hoehn and Yahr scale scores (25% on medication and 30% off medication).

The LEDD at baseline was 998 ± 252 mg. The clinical improvement of our patients after DBS led to a 39% reduction of the LEDD at 6 months after surgery.

There were no complications related to surgery in this group of patients.

Hormones, Peptides and Other Laboratory Findings

At 3 months after surgery, NPY, albumin and total protein circulating levels had increased significantly, while cortisol levels presented a significant reduction compared with baseline values. Ghrelin levels tended to increase, but this did not reach statistical significance (table 3).

At 6 months after surgery, circulating levels of ghrelin had only increased significantly compared with the values before surgery. NPY remained increased compared with baseline values, but this did not reach statistical significance. Albumin levels also remained significantly increased compared with baseline values.

The circulating levels of the remaining hormones and peptides, measured at the 3 set time points, did not differ significantly (table 3).

Table 2. Clinical evaluation and LEDD of all patients ($n = 23$) before surgery and 6 months after

	Before surgery	6 months after surgery (on DBS)	p*
UPDRS part III			
On medication	20.34 ± 9.70	14.40 ± 13.15	0.017
Off medication	46.47 ± 16.45	24.13 ± 20.30	0.000
UPDRS part IV			
On medication	6.55 ± 3.20	1.85 ± 1.91	0.000
Hoehn and Yahr scale			
On medication	2.30 ± 0.46	1.73 ± 1.03	0.011 [§]
Off medication	3.04 ± 0.87	2.11 ± 0.82	0.001 [§]
Schwab and England scale			
On medication	74.5 ± 13.16	81.66 ± 11.5	0.002
Off medication	60 ± 18.60	75 ± 17.01	0.001
LEDD, mg	998 ± 252	612 ± 305	0.000

Results are expressed as means $\pm$ standard deviation.

* Paired t test, p values refer to the comparison with the preoperative values. [§] Wilcoxon test.

WG Correlations and Preoperative Predictors of WG

As expected, WG was highly correlated with an increase of BMI, waist circumference and FM throughout the study (table 4).

At the 3-month follow-up visit, WG was significantly correlated with increased ghrelin circulating levels (table 4). Multivariate linear regression analysis confirmed that only the changes of ghrelin levels (baseline to 3 months) were significantly associated with WG [Beta coefficient 0.011 (95% CI 0.002–0.020), $p = 0.022$] after accounting for age, sex, changes in NPY and leptin.

At the 6-month follow-up, WG was correlated with an improvement of tremor and bradykinesia in the off-medication state (table 4). However, multivariate linear regression analysis showed that only the changes of leptin levels (baseline to 6 months) were significantly associated with WG [Beta coefficient 0.522 (95% CI 0.068–0.977), $p = 0.029$] after accounting for age, sex, changes in NPY and ghrelin, improvement of tremor and bradykinesia in the off-medication state, and LEDD reduction.

The preoperative off-medication UPDRS part III scores and tremor subscores were significantly correlated with WG at 3 and 6 months after surgery. The preoperative off-medication UPDRS part IV scores were significantly correlated with WG at 3 months, whilst the preoperative NPY levels were significantly correlated with WG

Table 3. Laboratory findings of all patients (n = 23) before and after surgery

Hormones	Before surgery	3 months after surgery (on DBS)	p*	6 months after surgery (on DBS)	p*
Ghrelin, pg/ml	601.04 ± 257.34	652.76 ± 201.86	n.s.	809.12 ± 287.7	0.001
Leptin, pg/ml	12.70 ± 11.18	12.63 ± 8.05	n.s.	13.15 ± 7.20	n.s.
NPY, pmol/l	99.26 ± 23.60	107.10 ± 26.50	0.05	105.82 ± 22.0	n.s.
Cortisol, µg/dl	17.99 ± 5.57	13.71 ± 5.68	0.027	15.81 ± 4.54	n.s.
TSH, µIU/ml	1.87 ± 1.23	2.06 ± 1.32	n.s.	2.40 ± 2.28	n.s. [§]
FT3, pmol/l	4.06 ± 1.89	4.67 ± 0.25	n.s.	4.64 ± 0.53	n.s.
FT4, ng/dl	1.27 ± 0.40	1.16 ± 0.15	n.s.	1.18 ± 0.16	n.s.
FSH, mIU/ml	23.50 ± 23.26	27.42 ± 26.22	n.s.	29.65 ± 28.88	n.s. [§]
LH, mIU/ml	13.12 ± 11.17	13.2 ± 11.68	n.s.	14.43 ± 13.39	n.s.
PRL, ng/ml	8.75 ± 13.1	9.61 ± 24.29	n.s. [§]	5.34 ± 8.41	n.s.
E2, pg/ml	18.27 ± 12.87	10.06 ± 4.95	n.s.	8.15 ± 1.98	n.s.
Anti-TPO, IU/ml	10.58 ± 13.4	12.05 ± 9.7	n.s.	11.27 ± 9.88	n.s.
Testosterone, ng/dl	376.32 ± 141.98	382.97 ± 130.72	n.s.	400.01 ± 99.47	n.s.
ALB, g/dl	4.06 ± 0.49	4.26 ± 0.27	0.007	4.34 ± 0.28	0.013
TP, g/dl	6.75 ± 1.08	7.21 ± 0.46	0.009 [§]	7.18 ± 0.44	n.s. [§]

Results are expressed as means ± standard deviation.

* Paired t test, p values refer to the comparison with the preoperative values. [§] Wilcoxon test. n.s. = Not significant (p > 0.05).

TSH = Thyroid-stimulating hormone; FT3 = free T3; FT4 = free T4; FSH = follicle-stimulating hormone; LH = luteinizing hormone; PRL = prolactin; E2 = estradiol II; Anti-TPO = anti-thyroid peroxidase antibodies; ALB = albumin; TP = total proteins.

Table 4. Study parameters significantly correlated with WG

	3 months after surgery		6 months after surgery	
	r	p	r	p
<i>Body composition</i>				
Changes in BMI	0.988	0.000	0.989	0.000
Changes in FM	0.660	0.002	0.744	0.000
Changes in waist circumference	0.740	0.000	0.571	0.009
<i>Hormones</i>				
Changes in ghrelin	0.542	0.009	–	–
NPY preoperatively	–	–	0.475	0.022
<i>Clinical outcome</i>				
UPDRS III				
Preoperatively/Off medication	0.514	0.012	0.418	0.047
UPDRS IV				
Preoperatively/Off medication	0.479	0.044	–	–
Tremor				
Preoperatively/Off medication	0.563	0.005	0.503	0.014
Changes in tremor				
Off medication	*	*	–0.646	0.003
Changes in bradykinesia				
Off medication	*	*	–0.509	0.026

* These items were not assessed at 3 months after surgery.

r = Correlation coefficient.

Table 5. Ghrelin, leptin and NPY circulating levels and clinical outcome stratified by the 3 subgroups of patients based on weight changes

	Lost weight (n = 6)	Gained weight (n = 12)	Variable weight (n = 5)
<i>Ghrelin, pg/ml</i>			
Baseline	663.8 ± 318.3	567.8 ± 202.7	605.6 ± 339.5
3 months after surgery	651.7 ± 285.4	665.1 ± 173.1	607.2 ± 235.3
6 months after surgery	834.3 ± 369.9	821.0 ± 233.3	750.5 ± 359.1
p value	0.59	0.016	0.71
<i>Leptin, pg/ml</i>			
Baseline	22.5 ± 13.5	9.3 ± 8.2	9.2 ± 8.8
3 months after surgery	15.3 ± 10.7	10.0 ± 5.1	14.5 ± 10.9
6 months after surgery	15.1 ± 8.3	13.0 ± 7.6	11.2 ± 5.8
p value	0.45	0.40	0.64
<i>NPY, pmol/l</i>			
Baseline	92.9 ± 10.9	106.3 ± 25.0	90.0 ± 29.8
3 months after surgery	99.6 ± 16.6	117.6 ± 28.6	89.5 ± 19.6
6 months after surgery	98.3 ± 22.8	113.4 ± 24.0	97.5 ± 10.9
p value	0.79	0.57	0.81
<i>UPDRS – off medication</i>			
Baseline	35.2 ± 11.2	49.3 ± 16.4	53.2 ± 17.7
6 months after surgery	14.8 ± 8.8	22.6 ± 18.0	37.2 ± 29.4
p value	0.55	0.001	0.33
<i>UPDRS – on medication</i>			
Baseline	15.5 ± 8.6	21.7 ± 10.9	23.0 ± 7.0
6 months after surgery	8.8 ± 7.6	15.8 ± 13.0	16.8 ± 18.3
p value	0.21	0.24	0.50

at 6 months (table 4). Age, gender, duration of the disease, and LEDD were not associated with WG at these 2 study points. The analysis was then repeated for BMI and found similar correlations (data not shown).

Table 5 shows the ghrelin, leptin, and NPY circulating levels at baseline, and 3 and 6 months after surgery, and the UPDRS scores (off and on medications) at baseline and 6 months postoperatively stratified by the 3 subgroups: those who ‘lost weight’ (n = 6), those who ‘gained weight’ (n = 12) and those with ‘variable weight’ (n = 5). In all 3 subgroups, ghrelin tended to increase postoperatively, but it only reached statistical significance in the ‘gained weight’ subgroup. Leptin and NPY did not differ between the groups. The UPDRS off-medication values were also significantly decreased in the ‘gained weight’ subgroup.

There were no differences between the groups regarding the final position of the electrodes, parameters of the stimulation and active electrode contacts.

Discussion

This study investigated the effects of STN DBS on the hypothalamic regulation of orexigenic and anorexigenic peptides. An increase of body weight at 3 and 6 months postoperatively was observed. In addition, our data showed that DBS was followed by an increased secretion of the orexigenic peptides ghrelin and NPY, and that WG was significantly associated with changes of ghrelin and leptin levels at 3 and 6 months after surgery, respectively.

The patients in our study gained on average 3 kg during the first 3 months after surgery, with no further gain at 6 months. The early increase of body weight after subthalamic DBS surgery is consistent with previous studies [8, 25]; studies with longer follow-up indicated that patients had kept gaining weight, though at a slower rate, even at 12 months after surgery [10]. Men in our study initially appeared to put on FM, which, later in time, was replaced by FFM, whilst women mostly gained

FM during the 6 months' follow-up. Interindividual variability and gender-related differences regarding the quality of WG found in our study are also in agreement with other reports [8]. Age or disease duration was not correlated with WG, and this is also in agreement with previous studies [8, 25]. Overweight or obesity in patients with PD may aggravate motor function and limit the beneficial effects of DBS, although individualized nutritional intervention can effectively control WG after DBS [30].

Patients with PD start losing weight several years before the clinical diagnosis; this process continues during the course of the disease and is correlated with the stage of PD [8, 31]. Increased energy expenditure, due to increased muscle tone, motor fluctuations and L-dopa-induced dyskinesias, has been proposed as a plausible mechanism to explain weight loss [8]. L-dopa has also been implicated in weight loss via a lypolytic effect [32]. Several other hypothesis have been proposed including a decrease of food intake, loss of appetite, decreased nutrient absorption, hypothalamic dysregulation, depression, use of neuroleptics, nausea and anorexia (the latter two as side effects of antiparkinsonian medication) [33–36]. Therefore, it could be suggested that WG following DBS could only be a homeostatic response of the body in those who had lost weight during the course of PD. Our data indicate that this is not the case; none of our patients was underweight preoperatively (fig. 1). High preoperative BMIs have also been reported in other studies [26, 37].

A reduction of energy expenditure after DBS has been considered as a possible cause of WG. In our study, the reduction of tremor and bradykinesia subscores according to UPDRS III was not significantly correlated with WG at 6 months, after accounting for confounders in a multilinear regression analysis. Furthermore, the improvement of the parkinsonian motor symptoms, according to the total UPDRS III score, was also not correlated with WG. This is in agreement with some investigators' findings [9, 25] but not with others [6, 10]. The lack of association between WG and reduction of LEDD was confirmed by the findings of Escamilla-Sevilla et al. [25] and contrary to the findings of Macia et al. [9]. A possible effect of the reduction of L-dopa dosage on weight may be hidden in the overall reduction of other antiparkinsonian drugs, which may not be implicated in this process. Our relatively limited number of cases did not allow meaningful subgroup analysis.

Bilateral neurostimulation of the STN was associated with a statistically significant increase of the circulating

Fig. 1. Changes of the proportion of normal weight, overweight and obese PD patients before, and 3 and 6 months after DBS surgery.

levels of NPY and ghrelin at 3 and 6 months after surgery, respectively. WG was independently associated with increased leptin levels at 6 months postoperatively. Escamilla-Sevilla et al. [25] reported increased leptin levels without the expected decrease of NPY levels and, thus, introduced the hypothesis of a DBS-induced resistance to the action of leptin. WG was also independently associated with increased ghrelin and leptin levels at 3 and 6 months after surgery, respectively, after accounting for possible confounders. Corcuff et al. [38] have measured ghrelin circulating levels in patients with or without ongoing STN neurostimulation and found no increase. This could be either due to an undetected hypothalamic release, own to ghrelin's minor contribution to the circulating levels, or to the timing of measurement. It has also been suggested that ghrelin levels may be inversely associated with the decrease of LEDD [38]; we found no significant correlation between ghrelin and LEDD (data not shown). It is, therefore, plausible that the hypothalamus is temporarily dysregulated by STN neurostimulation. Furthermore, recent studies have attributed an important neuroprotective action to ghrelin [39, 40]. If this is the case, one can speculate that DBS has a protective role and could slow PD progression through increased ghrelin levels.

The hypothesis that STN DBS causes a hypothalamic dysregulation cannot be dismissed just because NPY was

not significantly correlated with WG; the peripheral concentration of centrally released peptides may not reflect their exact concentration in the central nervous system [41]. High preoperative NPY levels and the severity of PD, as reflected by the high preoperative off-medication UPDRS part III, IV and tremor scores, were found to be predictors of WG after neurostimulation. Surprisingly, Montaurier et al. [8] have reported the opposite, i.e. patients with high preoperative UPDRS part III scores had the lowest risk of gaining weight.

A limitation of our study is that no blood specimen was taken before the WG and, thus, it cannot be ascertained that hormonal and peptide dysregulation is its cause rather than secondary to other factors. Furthermore, dose adjustments of the antiparkinsonian drugs may have obscured an association with WG. Another limitation is that the near infrared interactance method used to quantify FM and FFM may introduce a relative error [42].

Conclusions

STN DBS is an effective treatment for medically refractory PD, but it often leads to WG and obesity. DBS seems to temporarily dysregulate the hypothalamic secretion of NPY and ghrelin. Interindividual variability and gender-related differences regarding the quality of WG were identified. WG is likely to be multifactorial. However, increased levels of the orexigenic peptide ghrelin were associated with WG, whilst the NPY levels were not. Disease severity and increased preoperative NPY levels were the only identified risk factors for WG after DBS.

WG in patients with severe PD may compromise the beneficial effects of DBS and may cause significant functional disability as well as increase the risk of co-morbidities. A low-fat diet and a physical activity program may prove beneficial. Further studies with larger numbers of patients are required to confirm the role of peptide dysregulation in WG after neurostimulation and to investigate a potential neuroprotective role that DBS may exert through the increase of ghrelin.

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