Hormonal regulators of food intake and weight gain in Parkinson's disease after subthalamic nucleus stimulation

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Abstract

OBJECTIVES: Weight gain has been reported in patients with Parkinson's disease (PD) treated with deep brain stimulation of the subthalamic nucleus (STN-DBS). To evaluate the influence of STN-DBS on weight changes, we studied food-related hormones.

DESIGN: Anthropometric parameters and food-related hormones (leptin, adiponectin, resistin, ghrelin, cortisol, insulin, and thyroid stimulating hormone) were measured in 27 patients with STN-DBS during a 12 month period following electrode implantation.

RESULTS: Besides marked motor improvements on STN-DBS, PD patients significantly gained weight. The mean weight gain at 12 months was 5.2±(SD)5.8 kg. A significant decrease in cortisol levels compared to baseline appeared at month 2 and persisted at 12 months (p<0.01, corrected), with no significant changes in other hormones tested.

CONCLUSIONS: Changes in peripheral food-related hormones do not appear to cause weight gain in PD patients. Direct effects of STN-DBS on hypothalamic catabolic/anabolic peptide balance remain hypothetical and necessitate further elucidation.

Abbreviations:

STN-DBS	- Deep brain stimulation of the subthalamic nucleus
PD	- Parkinson's disease
CRF	- Corticotropin-releasing factor
BMI	- Body mass index
UPDRS	- Unified Parkinson disease rating scale
IGF-1	- Insulin-like growth factor 1
TSH	- Thyroid stimulating hormone
LEDD	- Levodopa equivalent daily dose

ORIGINAL ARTICLE

INTRODUCTION

Weight gain has been repeatedly reported following subthalamic nucleus deep brain stimulation (STN-DBS) in patients with advanced Parkinson's disease (PD) (Barichella *et al.* 2003; Gironell *et al.* 2002; Macia *et al.* 2004; Novakova *et al.* 2007; Strowd *et al.* 2010). Improved mobility, the resolution of dyskinesias, as well as increased appetite or restoration of hormonal balance have been suggested as contributing factors (Barichella *et al.* 2009). However, little is known about hormones involved in the regulation of energy homeostasis in PD patients treated by STN-DBS.

The food-related hormones leptin, adiponectin, and resistin are produced by adipocytes. If the amount of body fat increases, leptin elevates and acts on the brain, in particular the hypothalamus, reducing food intake and stimulating energy expenditure (Anubhuti &

Arora 2008; Arora & Anubhuti 2006). Adiponectin and resistin primarily target peripheral organs (Fruebis *et al.* 2001; Qi *et al.* 2004). In obese patients, adiponectin is decreased and resistin increased (Arita *et al.* 1999). Ghrelin is an appetite inducing hormone mainly secreted by gastric cells in the empty stomach (Cummings *et al.* 2001). The hypothalamus plays a crucial role in the regulation of energy and food metabolism. In an obese individual, elevated leptin and decreased ghrelin incite hypothalamic neurons to produce anorexigenic peptides, such as proopiomelanocortin and hypothalamic corticotropin-releasing factor (CRF), in order to reduce food intake (Leibowitz & Wortley 2004). Glucocorticoids act as key modulators of body weight and food intake, promoting leptin secretion and limiting central leptin induced effects (Leal-Cerro *et al.* 2001). Several reports have been published regarding food-related hormones in PD (Aziz *et al.* 2011; Evidente *et al.* 2001; Fiszer *et al.* 2010; Lorefalt *et al.* 2009), however only scarce data are available for PD patients treated by STN-DBS (Corcuff *et al.* 2006).

The aim of this study was to explore whether weight gain in STN-DBS treated patients is associated with changes of hormones involved in the regulation of energy homeostasis and food intake.

MATERIAL AND METHODS

Twenty-seven PD patients that received STN-DBS were enrolled in the study (21 men, 6 women; age at time of intervention: mean 56.8±(SD)7 years, range 42–68; disease duration: mean 12.5±4 years, range 7–23. All subjects suffered from severe motor fluctuations that were not improved by adjustments in antiparkinsonian medication. The study was approved by the local Ethics Committee, and all participants provided signed, informed consent prior to enrollment.

Stimulation was initiated four weeks after implantation of the electrodes. DBS settings and medication were subsequently adapted to achieve the best possible compensation. Each subject was evaluated on the day of intervention (baseline, pre-surgery) after at least 12 hours of discontinuing all antiparkinsonian drugs (MED-OFF), then at one month, before the setting-up (MED-OFF/DBS-OFF), and after the initiation of stimulation (MED-OFF/DBS-ON). Further assessments were completed at 2, 4, 6 and 12 months after surgery. The sum of total electrical energy delivered by DBS in 12 months was calculated using the formula proposed by Koss *et al.* (Koss *et al.* 2005).

Motor status was evaluated using the Unified Parkinson Disease Rating Scale motor subscale (UPDRS III). Eating related questionnaires (food intake, hunger, appetite) were administered at each visit. Anthropometric examination included body weight and height, body mass index (BMI=weight in kg/height in m^2), and waist circumference. At each visit, 5 ml of blood was withdrawn between 7–8 AM following an overnight fast, and serum biochemical parameters (total protein, albumin, prealbumin, cholesterol, triglycerides, insulin, glycemia, glycated hemoglobin and insulin-like growth factor 1 (IGF-1), thyroid stimulating hormone (TSH), cortisol, leptin, adiponectin, resistin and ghrelin were assessed by standard laboratory methods using commercial kits:

Serum insulin concentrations were measured by RIA kit (Cis Bio International, Gif-sur-Yvette, France). Sensitivity was 2.0 μIU/ml, and the intra- and inter-assay variability was 4.2 and 8.8%, respectively. IGF-1: IRMA kit (Immunotech, Prague, Czech Republic), 2 ng/ml, 6.3 and 6.8%. Leptin: ELISA kit (BioVendor, Brno, Czech Republic), 0.12 ng/ml, 1.7 and 8.0%. Adiponectin: RIA kit (Linco Research, St. Charles, MO), 1.0 ng/ml, 1.8 and 9.3%. Resistin: ELISA kit (BioVendor, Brno, Czech Republic), 0.2 ng/ml, 3.1 and 6.5%. Ghrelin: RIA kit (Linko research, Saint Charles, MO), 93 pg/ml, 10 and 14.7%, respectively. The other biochemical parameters were measured by standard laboratory methods using commercial kits.

Daily doses of dopaminergic medication at baseline, 1 month, and 12 months following surgery were converted to Levodopa Equivalent Daily Dose (LEDD; 100 mg of standard levodopa equals 150 mg of CR levodopa, 1 mg pramipexole, or 6 mg ropinirole). Statistical analyses were performed using Statgraphics software (Warrenton, VA). Non-parametric tests were used as a substantial portion of the data did not fit a normal distribution (Mann-Whitney test, Kruskal-Wallis test, paired signed-rank test, Spearman's rank correlation). Wherever appropriate, results were corrected for multiple comparisons by Bonferroni correction.

RESULTS

Motor and Pharmacological Outcomes

Comparison of the MED-OFF state at baseline to the MED-OFF/DBS-OFF condition at one month after surgery did not reveal any significant change, with

mean UPDRS III scores of 33.0 ±(SD)11 and 34.7 ±10, respectively (p<0.8). In the MED-OFF/DBS-ON condition at one month after surgery, the mean UPDRS III score significantly decreased to 17.2±6 (p<0.001). The MED-OFF/DBS-ON UPDRS III score at 12 months did not significantly change (14.5±7, p<0.14) in comparison to one month after surgery.

The LEDD significantly decreased from 1330±538 mg at baseline to 1196±401 mg (p<0.001) at one month, and to 704±429 mg (p<0.001) at 12 months after surgery.

DBS Parameters

The average sum of stimulation energy delivered over the 12 month study period was 3412±1280 J. No correlation between change in body weight and the energy of stimulation was found (12 month vs baseline, r_s = 0.1844, p<0.3).

Anthropometric Parameters

On average, we found increases in body weight, BMI, waist circumference and body fat percentage during the entire study period (Table 1). Notably, a significant change in body weight was observed already at one month following surgery, i.e., before stimulation was started, in comparison to baseline: +1.1±2 kg, range –2.6 to 5.0, (p<0.05). Change in mean weight from baseline to 12 months following STN-DBS implantation was +5.18±5.8 kg, range –6.30 to +19.80, (p<0.001) (Figure 1). At month one, taken individually, 17 patients gained weight compared to baseline while weight loss was noted in 10 patients. At month twelve, 24 patients gained weight and 3 patients had lower weight compared to baseline. In examining gender differences, body weight increased at 12 months after STN-DBS implantation by 9.0±5 kg in women (range 5.0 to 18.3) and 4.1±6 kg in men (range –6.3 to 19.8). Body weight and BMI differed significantly between the genders, with a greater increase in women (p<0.05, p<0.01, respectively). A borderline correlation between weight gain following STN-DBS and PD duration was observed (r_s = 0.418, p<0.05), but not with age at PD onset. No significant correlation was found between the change in LEDD and change in weight. Most of the subjects did not report any changes in food intake, hunger or appetite.

Laboratory Parameters

A significant decrease in cortisol levels compared to baseline appeared at month 2 and persisted at 12 months (p<0.01, corrected), with no significant changes in other tested hormones or biochemical parameters (Table 1, Figure 1). A positive correlation between leptin levels and body weight (r_s = 0.299, p<0.001) and body fat percentage (r_s =0.343, p<0.05) was found. Body weight negatively correlated with adiponectin (r_s = –0.604, p<0.001), positively with ghrelin (r_s = 0.253, p<0.01) and did not significantly correlate with cortisol (r_s = –0.114, p<0.2).

DISCUSSION

In this prospective study, we tested the hypothesis that weight changes in PD patients treated with STN-DBS are connected with abnormalities in the hormonal regulation of food intake. In concordance with previous

Tab. 1. Patient anthropometric parameters and select hormonal levels pre-surgery (baseline), 1 month, and 12 months after STN-DBS.

Hormonal and Anthropometric parameters	Pre-surgery DBS	1 month after DBS		12 months after DBS	
	mean±SD	mean±SD	*p*-value	mean±SD	*p*-value
Body weight [kg]	78.7±16	79.8±16	0.0185*	83.9±15	0.0001***
BMI [kg/m2]	25.8±4.0	26.11±3.8	0.0251*	27.51±3.7	0.0001***
Waist circum. [cm]	94.0±13.0	94.95±12.6	0.08	98.76±11.7	0.001**
Body fat [%]	21.6±7.4	21.9±7.4	0.20	25.8±5.9	0.003*
Leptin [ng/ml]	7.6±8.7	6.8±6.7	1.0	9.5±9.0	0.09
Adiponectin [ng/ml]	21.3±12.3	23.13±12.5	0.30	19.8±9.6	0.36
Resistin [ng/ml]	7.2±3.0	6.4±2.8	0.08	6.9±2.7	0.74
Ghrelin [ng/l]	1.3±0.7	1.2±0.4	0.78	1.1±0.4	0.34
Insulin [IU/ml]	7.8±4.6	11.5±12.3	0.34	8.0±3.8	0.56
Cortisol [nmol/l]	689±149	619±160	0.09	531±180	0.0008**
IGF-1 [ng/ml]	181±76	185±67	0.84	170±53	0.21
TSH [mIU/l]	2.3±2.3	1.8±1.2	0.43	1.9±1.5	0.97

DBS, deep brain stimulation; BMI, body mass index; TSH, thyroid stimulating hormone; IGF-1, insulin-like growth factor 1.
Statistical significance of differences in parameters measured at baseline and at months one and twelve, tested by paired signed-rank test; after Bonferroni correction at levels p<0.05 (*), p<0.01 (**), p<0.001(***)

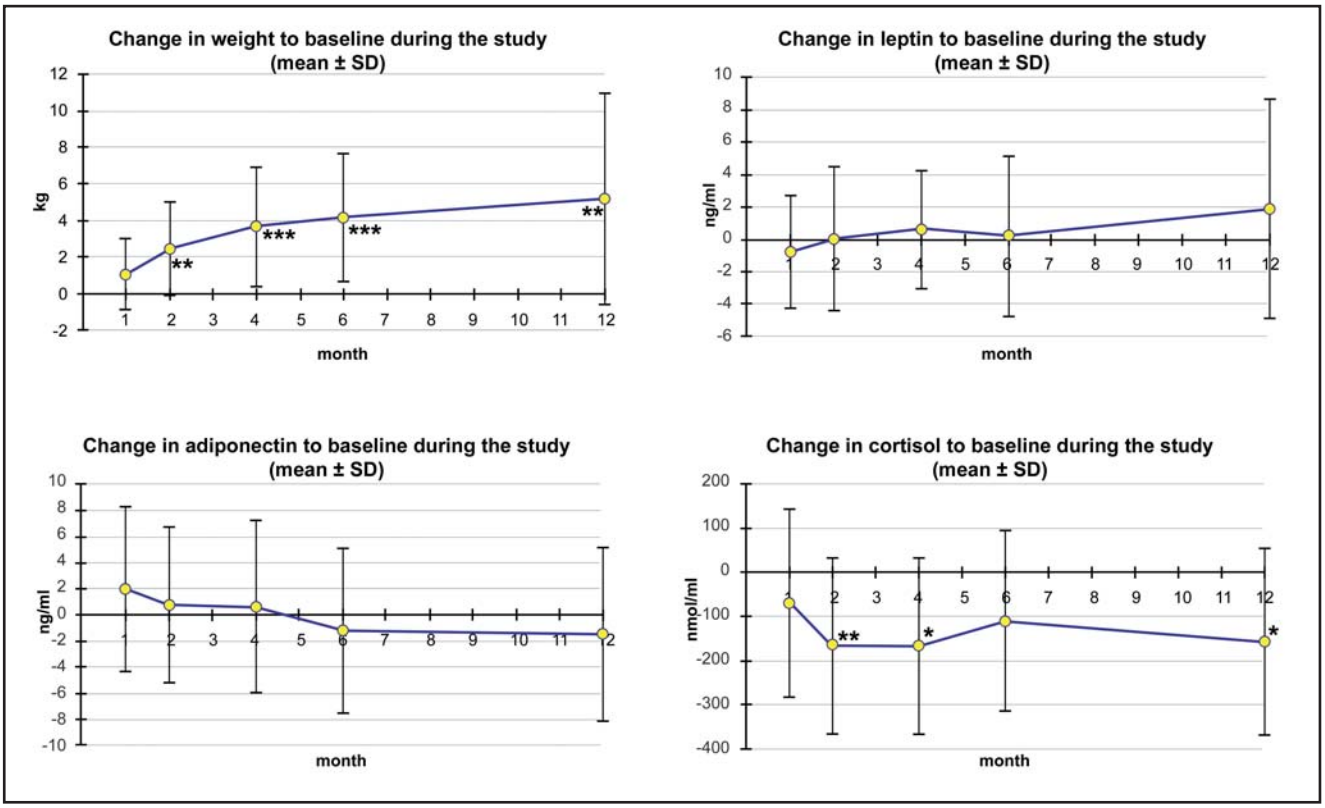

Fig. 1. Mean changes in weight, leptin, adiponectin, and cortisol during the study. X axis: individual measurements at 1, 2, 4, 6, and 12 months after surgery. Y axis: difference from baseline, measured parameter.

studies (Barichella *et al.* 2003; Macia *et al.* 2004; Montaurier *et al.* 2007; Perlemoine *et al.* 2005; Tuite *et al.* 2005), body weight increased in most of our patients, together with increasing BMI, waist circumference and body fat percentage within one year on STN-DBS. Body weight correlated positively with serum levels of leptin and inversely with adiponectin, which correspond to the physiological regulatory mechanisms of food related processes (Meier & Gressner 2004). In addition, ghrelin positively correlated with weight in our patients. This corroborates previous findings that were considered paradoxical in PD patients where weight loss usually occurs with the disease progression – the lower BMI was, the lower ghrelin levels were found (Fiszer *et al.* 2010). However, in accordance with Corcuff *et al.*, we did not observe any increase in ghrelin following STN-DBS (Corcuff *et al.* 2006).. In fact, since the peripheral ghrelin was measured, the results may not reflect possible changes in centrally released ghrelin that mainly participates in the regulation of food intake and body weight.

As the most prominent hormonal change, serum levels of cortisol were found to significantly decrease on STN-DBS, although cortisol should typically increase in the course of truncal fat accumulation and increasing body weight (Reynolds 2010). Hence, direct effects of STN stimulation on adjacent nerve fibers and nuclei must be considered. STN-DBS may hypothetically act on the hypothalamus by suppressing the secretion of CRF with a subsequent decrease in the production of cortisol, leading to a predominance of anabolic reactions. Indeed, in rats exposed to high-frequency electrical stimulation of the lateral hypothalamus, body weight changes occurred even if no difference was observed in food intake between stimulated and unstimulated animals (Sani *et al.* 2007). Accordingly, no consistent changes in food-related behavior were recorded in our patients. This is in agreement with previous studies indicating no changes in food related behavior connected to STN-DBS weight gain (Bannier *et al.* 2009; Macia *et al.* 2004; Montaurier *et al.* 2007; Perlemoine *et al.* 2005). Alternatively, body weight gain could be attributed to indirect factors such as decreased energy expenditure after DBS (Barichella *et al.* 2003; Gironell *et al.* 2002; Montaurier *et al.* 2007). However, in a study comparing weight gain and energy intake after STN-DBS versus pallidal DBS, changes in BMI were correlated with reduction of dyskinesias in the pallidal but not in the STN-DBS group (Sauleau *et al.* 2009). This supports a direct or indirect effect of subthalamic stimulation on the hypothalamic homeostatic centers regulating energy balance, resulting in hormonal dysregulation and weight gain. Finally, for the sake of completeness, we must consider that decreased serum

cortisol following DBS may simply be a non-specific observation, representing the reversal of a temporary perioperative increase in cortisol levels due to surgical stress (Desborough 2000).

In conclusion, our findings did not reveal the cause of weight gain in patients with PD treated by STN-DBS. We found only physiological changes in peripheral food-related hormones corresponding to prevalent weight gain. Even if decreased cortisol production might be connected with STN-DBS and lead to subsequent weight gain, direct effects of STN-DBS on hypothalamic catabolic/anabolic peptide balance remain hypothetical and necessitate further elucidation.

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REFERENCES

1 Anubhuti, Arora S (2008) Leptin and its metabolic interactions: an update. Diabetes Obes Metab. **10**: 973–993.
2 Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al (1999) Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun. **257**: 79–83.
3 Arora S, Anubhuti (2006) Role of neuropeptides in appetite regulation and obesity–a review. Neuropeptides. **40**: 375–401.
4 Aziz NA, Pijl H, Frolich M, Roelfsema F, Roos RA (2011) Leptin, adiponectin, and resistin secretion and diurnal rhythmicity are unaltered in Parkinson's disease. Mov Disord. **26**: 760–761.
5 Bannier S, Montaurier C, Derost PP, Ulla M, Lemaire JJ, Boirie Y, et al (2009) Overweight after deep brain stimulation of the subthalamic nucleus in Parkinson disease: long term follow-up. J Neurol Neurosurg Psychiatry. **80**: 484–488.
6 Barichella M, Cereda E, Pezzoli G (2009) Major nutritional issues in the management of Parkinson's disease. Mov Disord. **24**: 1881–1892.
7 Barichella M, Marczewska AM, Mariani C, Landi A, Vairo A, Pezzoli G (2003) Body weight gain rate in patients with Parkinson's disease and deep brain stimulation. Mov Disord. **18**: 1337–1340.
8 Corcuff JB, Krim E, Tison F, Foubert-Sanier A, Guehl D, Burbaud P, et al (2006) Subthalamic nucleus stimulation in patients with Parkinson's disease does not increase serum ghrelin levels. Br J Nutr. **95**: 1028–1029.
9 Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS (2001) A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes. **50**: 1714–1719.
10 Desborough JP (2000) The stress response to trauma and surgery. Br J Anaesth. **85**: 109–117.
11 Evidente VG, Caviness JN, Adler CH, Gwinn-Hardy KA, Pratley RE (2001) Serum leptin concentrations and satiety in Parkinson's disease patients with and without weight loss. Mov Disord. **16**: 924–927.
12 Fiszer U, Michalowska M, Baranowska B, Wolinska-Witort E, Jeske W, Jethon M, et al (2010) Leptin and ghrelin concentrations and weight loss in Parkinson's disease. Acta Neurol Scand. **121**: 230–236.
13 Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, et al (2001) Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad Sci U S A. **98**: 2005–2010.
14 Gironell A, Pascual-Sedano B, Otermin P, Kulisevsky J (2002) Weight gain after functional surgery for Parkinsons disease. Neurologia. **17**: 310–316.
15 Koss AM, Alterman RL, Tagliati M, Shils JL (2005) Calculating total electrical energy delivered by deep brain stimulation systems. Ann Neurol. **58**: 168–169.
16 Leal-Cerro A, Soto A, Martinez MA, Dieguez C, Casanueva FF (2001) Influence of cortisol status on leptin secretion. Pituitary. **4**: 111–116.
17 Leibowitz SF, Wortley KE (2004) Hypothalamic control of energy balance: different peptides, different functions. Peptides. **25**: 473–504.
18 Lorefalt B, Toss G, Granerus AK (2009) Weight loss, body fat mass, and leptin in Parkinson's disease. Mov Disord. **24**: 885–890.
19 Macia F, Perlemoine C, Coman I, Guehl D, Burbaud P, Cuny E, et al (2004) Parkinson's disease patients with bilateral subthalamic deep brain stimulation gain weight. Mov Disord. **19**: 206–212.
20 Meier U, Gressner AM (2004) Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. Clin Chem. **50**: 1511–1525.
21 Montaurier C, Morio B, Bannier S, Derost P, Arnaud P, Brandolini-Bunlon M, et al (2007) Mechanisms of body weight gain in patients with Parkinson's disease after subthalamic stimulation. Brain. **130**: 1808–1818.
22 Novakova L, Ruzicka E, Jech R, Serranova T, Dusek P, Urgosik D (2007) Increase in body weight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Neuro Endocrinol Lett. **28**: 21–25.
23 Perlemoine C, Macia F, Tison F, Coman I, Guehl D, Burbaud P, et al (2005) Effects of subthalamic nucleus deep brain stimulation and levodopa on energy production rate and substrate oxidation in Parkinson's disease. Br J Nutr. **93**: 191–198.
24 Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, et al (2004) Adiponectin acts in the brain to decrease body weight. Nat Med. **10**: 524–529.
25 Reynolds RM (2010) Corticosteroid-mediated programming and the pathogenesis of obesity and diabetes. J Steroid Biochem Mol Biol. **122**: 3–9.
26 Sani S, Jobe K, Smith A, Kordower JH, Bakay RA (2007) Deep brain stimulation for treatment of obesity in rats. J Neurosurg. **107**: 809–813.
27 Sauleau P, Leray E, Rouaud T, Drapier S, Drapier D, Blanchard S, et al (2009) Comparison of weight gain and energy intake after subthalamic versus pallidal stimulation in Parkinson's disease. Mov Disord. **24**: 2149–2155.
28 Strowd RE, Cartwright MS, Passmore LV, Ellis TL, Tatter SB, Siddiqui MS (2010) Weight change following deep brain stimulation for movement disorders. J Neurol. **257:** 1293–1297.
29 Tuite PJ, Maxwell RE, Ikramuddin S, Kotz CM, Billington CJ, Laseski MA, et al (2005).Weight and body mass index in Parkinson's disease patients after deep brain stimulation surgery. Parkinsonism Relat Disord. **11**: 247–252.