Deep Brain Stimulation of the Subthalamic Nucleus Regulates Postabsorptive Glucose Metabolism in Patients With Parkinson’s Disease

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Objective: Subthalamic nucleus-deep brain stimulation (STN-DBS) is an alternative treatment for patients with uncontrolled symptoms of Parkinson’s disease (PD), but it has other nonmotor impact. Because STN-DBS alters the energy expenditure in humans, we hypothesized that STN-DBS may affect postabsorptive glucose metabolism in patients with PD.

Research Design and Methods: Endogenous glucose production (EGP) and whole-body glucose disposal rates (GDRs) were assessed in the postabsorptive state during a primed continuous iv infusion of D-[6,6-2H2]glucose for 5 hours in 8 STN-DBS-treated patients with PD, without (Stim-OFF) and during STN-DBS (Stim-ON) treatment. EGP and GDR in PD patients were compared with glucose kinetics of 8 matched healthy control subjects. Plasma concentrations of insulin, glucagon, and free fatty acids were also determined.

Results: EGP and GDR were higher in PD patients in Stim-OFF conditions than in the control group (2.62 ± 0.09 vs. 2.27 ± 0.10 mg/kg·min, P < .05). Despite no significant changes in blood glucose throughout the kinetic study, a significant and consistent 22% decrease in EGP occurred in PD patients during Stim-ON (2.04 ± 0.07 mg/kg·min⁻¹, P < .01), and whole-body glucose kinetics in Stim-ON patients were no more different from those of the control subjects (P = NS). No difference in insulin, glucagon, or free fatty acid concentrations was observed in the patients between Stim-OFF and Stim-ON conditions.

Conclusions: Deep brain stimulation in patients with PD affects EGP glucose disposal, suggesting that a cross talk between the central nervous system and peripheral tissues may regulate glucose homeostasis. (J Clin Endocrinol Metab 98: E1050–E1054, 2013)
changes in daily energy expenditure after surgery (2). The central regulation of energy metabolism might be involved in this phenomenon because regional effects of DBS-STN on hypothalamic centers cannot be excluded because several hypothalamic fibers cross close to the subthalamic nucleus (3). Therefore, the underlying mechanisms for these metabolic changes may involve an effect of STN-DBS on the activity of the autonomic nervous system, which partly influences tissue or organ metabolic activity. Thus, we hypothesized that other metabolic activities like glucose homeostasis could be affected by STN-DBS.

To test the hypothesis that STN-DBS affects peripheral glucose metabolism via a direct or an indirect effect, notably through pancreatic hormones, we investigated whole-body glucose kinetics in STN-DBS-treated patients with PD during the postabsorptive state. Endogenous glucose production (EGP) and glucose disposal were determined in PD patients and matched control healthy subjects, using stable isotope labeled glucose, during sequential short-term STN-DBS interruption and reactivation.

Subjects and Methods

Patients

Eight patients with PD treated by STN-DBS were recruited and matched with healthy control subjects. To be included, patients should have electrodes in place for more than 6 months; have an excellent acute efficacy of STN-DBS (>50%, assessed using part III of the United Parkinson’s Disease Rating Scale); and have no modification of the antiparkinsonian treatment 7 days before the inclusion. We excluded all subjects with the following: 1) treated with treatments that could interfere with the protocol, 2) presenting significant heart, respiratory, psychiatric, metabolic, hepatic, kidney diseases, diabetes, heart failure, chronic kidney disease, untreated thyroid disease, 3) with metabolic and/or biological disturbances, 4) with a high consumption of alcohol and tobacco.

The study protocol was approved by the local Medical School Ethical Committee (number AU723) and was performed according to the principles set out in the Declaration of Helsinki and to French legislation. The study was also registered to the clinical trial specific web site (NCT: 00663312). Written informed consent was obtained from each participant.

Materials

D-[6,6-2H2]glucose [99 M percent excess] was obtained from Cambridge Isotope Laboratories, Inc (Andover, Massachusetts). The isotopic and chemical purity was checked by gas chromatography-mass spectrometry as previously described (4).

Clinical investigation

Patient examinations including anthropometry, blood sampling, and body composition measured by dual-energy x-ray absorptiometry (QDR-4500A; Hologic, Inc, Waltham, Massachusetts) were performed. The acute efficacy of STN-DBS (>50%)

was verified using United Parkinson’s Disease Rating Scale part III (items 18–31).

Protocol scheme

The day before the experiment, each patient received a standardized meal (767 kcal and 624 kcal for men and women, respectively, containing 11% protein, 34% lipid, and 54% carbohydrate).

On the experiment day, all subjects were studied in the postabsorptive state after a 10-hour overnight fast. They did not receive their antiparkinsonian treatment the morning of the experiment (Supplemental Material, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org). Two venous tracts were laid on the arms. One catheter was used for blood sampling. A second catheter was inserted into the contralateral arm and was used for the tracer infusion as previously described (4). A continuous iv infusion of D-[6,6-2H2]glucose (0.05 mg/kg -1 min -1) was performed during 5 hours (7:00 AM to 12:00 PM), after a primed dose of 3 mg/kg -1 of the glucose tracer. During the first 2.5 hours, the patients were studied without STN-DBS stimulation (Stim-OFF); during the last 2.5 hours, the stimulator was activated (Stim-ON).

Blood samples were taken before the tracer infusion and then 60 minutes after the beginning and at 20-minute intervals during the last hour of each period at plateau (Figure 1A).

Analytical procedure

Plasma glucose concentrations were measured using the glucose oxidase method (Thermo, Vantaa, Finland), and insulin concentrations were determined using an ELISA kit (Trouse Biosource, Carlsbad, California). Plasma glucagon was analyzed by RIA (Trouse YK090, Shizuoka, Japan). Plasma [6,6-2H2]glucose enrichments were determined as previously described (4).

Calculation of endogenous glucose production and disposal

Postabsorptive rates of glucose turnover were calculated as detailed elsewhere. The systemically infused [6,6-2H2]glucose was used to trace the rate of the appearance of endogenously produced glucose. The ratio of plasma concentration of [6,6-2H2]glucose to the plasma concentration of endogenously produced glucose was used to calculate EGP (5).

Statistical analysis

Statistical analyses were performed to compare the PD and control groups and to test the difference between Stim-OFF and Stim-ON conditions in the PD patient group, with values expressed as means ± SEM. Data were compared between both groups by 2-way ANOVA for the differences between controls and patients. The effect of STN-DBS in patients between Stim-OFF and Stim-ON periods was assessed by a paired t test. The level of significant difference was set at P < .05 for all statistical tests.

Results

Clinical characteristics

Clinical data of patients are shown in Table 1. The study enrolled 8 patients with PD (4 men, 4 women) aged
60.6 ± 2.7 years with a mean duration of disease of 12.9 ± 1.5 years. Eight healthy control subjects (4 men, 4 women) aged 64.6 ± 3.3 years were also recruited. There was no difference in age, weight, body mass index, and body composition between PD patients and control subjects (P = NS, Table 1).

### Plasma glucose levels

In PD patients, plasma glucose concentrations did not change throughout the 5-hour study period (Figure 1B). The basal glucose level was significantly higher in the Parkinsonian patient group (1.00 ± 0.04 g/L) vs controls (0.92 ± 0.01 g/L) (P < .05).

### Endogenous glucose production

EGP has been calculated in steady state and nonsteady state. Because blood glucose concentrations were very stable, results were similar and are given in steady-state conditions in the table. EGP in PD patients in the Stim-OFF condition (Figure 1C) was significantly higher than in the control group (2.62 ± 0.09 vs 2.27 ± 0.10 mg/kg⁻¹·min⁻¹, P < .05). A significant and consistent 22% decrease of EGP was observed from Stim-OFF to Stim-ON condition (2.04 ± 0.07 mg/kg⁻¹·min⁻¹; P < .01) (Figure 1D), but the EGP between the PD patients during Stim-ON and the control group was no more different (P = NS) (Figure 1C). The rate of glucose disappearance was significantly higher in the Stim-OFF vs Stim-ON condition (P < .05).

### Pancreatic hormones and free fatty acid concentrations

There was no difference in insulin (9.47 ± 2.09 vs 8.12 ± 1.53 μIU/mL) and glucagon (271.15 ± 64.93 vs 282.04 ± 62.19 pg/mL) concentrations in PD patients in Stim-OFF vs Stim-ON conditions, respectively. Concentrations of plasma free fatty acids were significantly higher in Stim-ON vs Stim-OFF condition (694.00 ± 54.20 vs 556.25 ± 52.41 μmol/L, P < .005).

### Discussion

The present study demonstrates that in patients with PD, STN-DBS modulates EGP independently of changes in plasma glucose or pancreatic hormones. EGP was found to be higher in PD patients than in control subjects when STN-DBS was interrupted, whereas it systematically diminished to the normal values of a control group matched for body weight, age, and body composition when STN-DBS was activated. Results of this study do not indicate that STN-DBS modulates plasma glucose concentrations directly, but rather that it modulates the metabolic response to glucose infusion. This finding is consistent with previous studies showing that STN-DBS modulates glucose metabolism through alterations in the activity of brain regions involved in the regulation of energy metabolism, such as the hypothalamus and the amygdala. The present study provides further evidence for the involvement of the hypothalamic-pituitary axis in the modulation of glucose metabolism by STN-DBS, and supports the hypothesis that STN-DBS modulates glucose metabolism through changes in the activity of hypothalamic neurons involved in the regulation of energy homeostasis.
DBS was activated in the postabsorptive state. So this study demonstrated in humans a cross talk between the central nervous system and peripheral glucose metabolism, leading to the concept that activated circuits in the brain regulate peripheral glucose metabolism to maintain glucose homeostasis. It also suggests that severe neurodegenerative disorders like PD may be associated with impaired glucose homeostasis that may be induced by specific alterations of the circuits between the brain and peripheral tissues.

It is recognized that deep brain stimulation works through the focal modulation of functionally specific brain circuits including inhibition of glutamatergic cells belonging to the subthalamic nucleus (6). From the results of our study, we can hypothesize that the direct effect of STN-DBS on the thalamus may modulate peripheral glucose homeostasis. Indeed, several studies suggest a link between the thalamus and glucose metabolism (7, 8). In particular, hypoglycemia is able to induce synaptic activation in the dorsal midline thalamus. Also, a stimulation of afferents or efferents within the stimulated nucleus itself may prominently involve passing fibers within the range of stimulation (6).

Animal studies have explored the possibility of a metabolic brain-liver circuit through the modulation of the hypothalamic sensing of substrate in regulating glucose homeostasis. Indeed, central administration of glucose in the central nervous system of rats was able to inhibit peripheral glucose production, especially by inactivating neuronal KATP channels in glucose-responsive neurons of the ventromedian hypothalamus related to the sympathetic nervous center (9, 10). The regulation of EGP by a central pathway in humans remains unclear. Recently human study showed that diazoxide, an oral ATP-sensitive potassium channel activator, decreased EGP in humans independently of pancreatic hormone secretion (11). From the results of the present study, it is anticipated that modifications in the regional activity of the hypothalamic neurons induced by STN-DBS in humans might affect peripheral glucose metabolism via vagal efferent fibers because no change in hormones like insulin or glucagon was detected.

Localized neurodegeneration in the hypothalamus region have been described in PD (12) so that an impaired central glucose sensing could produce a signal to the liver for a feedback increase in glucose supply to the brain. Positron emission tomography (PET) study with 18F-fluorodeoxyglucose in patients with PD has revealed a reduced metabolism of glucose at the level of specific cortical and subcortical structures (13). Noticeably, hypothalamic D2 receptor availability has been investigated in PD patients using PET with 11C-raclopride. The results provide evidence of dopaminergic dysfunction in the hypothalamus of PD patients (12). Conversely, STN-DBS restores glucose uptake in these regions (14). More recently, Volonte et al (15) showed an increase in deep brain stimulation site in the on vs off condition in parkinsonian patients. Thus, the improvement of glucose metabolism in specific brain areas might contribute to the normalization of endogenous glucose production in Stim-ON situation.

It was shown that the autonomic nervous system regulates glycogen metabolism in liver through a nerve drive (16). PD is associated with neurodegeneration in the hypothalamus but also at the level of sympathetic and parasympathetic ganglia (17). Interestingly, STN-DBS improves autonomic nervous system activity (18). This improvement in STN-DBS patients may include a normalization of whole-body glucose turnover with reference to matched control subjects in the postabsorptive state. It remains to be investigated whether the effect of STN-DBS still persists in the fed state or other metabolic situations. Actually very few studies have been dedicated to glucose disturbances in PD patients. A positive association between diabetes and PD has been found in some epidemiological studies (19) but not in others.

In summary, the present study demonstrates that STN-DBS used for the treatment of patients with severe PD regulates peripheral glucose metabolism as reflected by changes in endogenous glucose production and glucose use, according to the stimulation conditions. This central action is independent of changes in pancreatic hormone secretions demonstrating a probable brain-liver circuit in humans. These new results raise many questions about the brain’s contribution to glucose homeostasis in humans and highlight possible new mechanisms of glucose intolerance or diabetes occurring in clinical situations (20).

Acknowledgments

We thank all the staff of the Human Nutrition Research Center (Centre de Recherche en Nutrition Humaine Auvergne) and the Department of Neurology of the University Hospital of Clermont-Ferrand. We are grateful to the nurses, especially Noëlle Mathieu and Suzanne Faure, who were in charge of the patients during the isotope dilution protocol, and to the hospital pharmacists and Carole Migné for the labeled glucose preparation and analysis. We also thank all the patients and the volunteers enrolled in the clinical trial. M.B.L. performed the experiment and data analyses and contributed to the discussion and the writing of the manuscript. I.R. and C.G. performed the experiment, participated in the coordination of the study, and contributed to the discussion. E.P. performed the analysis, and B.M. participated in the discussion. J.J.L. contributed to the patient surgery and reviewed the manuscript. F.D. and Y.B. conceived the study and its design and contributed to the coordination and the dis-
Y.B. drafted the manuscript. All authors read and approved the final manuscript. The trial was registered with the Clinical Trial with the number NCT: 00663312.

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This work was supported by the “Programme Hospitalier de Recherche Clinique” and from the Centre Hospitalier Universitaire de Clermont-Ferrand.

Disclosure Summary: The authors have nothing to disclose.

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