Subthalamic deep brain stimulation can improve gastric emptying in Parkinson’s disease

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It is established that deep brain stimulation of the subthalamic nucleus improves motor function in advanced Parkinson’s disease, but its effects on autonomic function remain to be elucidated. The present study was undertaken to investigate the effects of subthalamic deep brain stimulation on gastric emptying. A total of 16 patients with Parkinson’s disease who underwent bilateral subthalamic deep brain stimulation were enrolled. Gastric emptying was expressed as the peak time of $^{13}$CO$_2$ excretion ($T_{\text{max}}$) in the $^{13}$C-acetate breath test and was assessed in patients with and without administration of 100–150 mg levodopa/decarboxylase inhibitor before surgery, and with and without subthalamic deep brain stimulation at 3 months post-surgery. The pattern of $^{13}$CO$_2$ excretion curve was analysed. To evaluate potential factors related to the effect of subthalamic deep brain stimulation on gastric emptying, we also examined the association between gastric emptying, clinical characteristics, the equivalent dose of levodopa and serum ghrelin levels. The peak time of $^{13}$CO$_2$ excretion ($T_{\text{max}}$) values for gastric emptying in patients without and with levodopa/decarboxylase inhibitor treatment were 45.6 ± 22.7 min and 42.5 ± 13.6 min, respectively ($P$ = not significant), thus demonstrating levodopa resistance. The peak time of $^{13}$CO$_2$ excretion ($T_{\text{max}}$) values without and with subthalamic deep brain stimulation after surgery were 44.0 ± 17.5 min and 30.0 ± 12.5 min ($P < 0.001$), respectively, which showed that subthalamic deep brain stimulation was effective. Simultaneously, the pattern of the $^{13}$CO$_2$ excretion curve was also significantly improved relative to surgery with no stimulation ($P = 0.002$), although the difference with and without levodopa/decarboxylase inhibitor was not significant. The difference in peak time of $^{13}$CO$_2$ excretion ($T_{\text{max}}$) values without levodopa/decarboxylase inhibitor before surgery and without levodopa/decarboxylase inhibitor and subthalamic deep brain stimulation after surgery was not significant, although motor dysfunction improved and the levodopa equivalent dose decreased after surgery. There was little association between changes in ghrelin levels ($\Delta$ghrelin) and changes in $T_{\text{max}}$ values ($\Delta T_{\text{max}}$) in the subthalamic deep brain stimulation trial after surgery ($r = -0.20$), and no association between changes in other characteristics and $\Delta T_{\text{max}}$ post-surgery in the subthalamic deep brain stimulation trial. These results showed that levodopa/decarboxylase inhibitor did not influence gastric emptying and that subthalamic deep brain stimulation can improve the dysfunction in patients with Parkinson’s disease possibly by altering the neural system that controls gastrointestinal function after subthalamic deep brain stimulation. This is the first report to show the effectiveness of subthalamic deep brain stimulation on gastrointestinal dysfunction as a non-motor symptom in Parkinson’s disease.
Keywords: deep brain stimulation; ghrelin; gastric emptying; Parkinson’s disease; body weight
Abbreviations: DCI = decarboxylase inhibitor; STN-DBS = subthalamic deep brain stimulation; $T_{\text{max}}$ = peak time of $^{13}$CO$_2$ excretion

Introduction

Parkinson’s disease is a progressive neurodegenerative disease, mainly characterized by the loss of dopamine neurons in the substantia nigra pars compacta, culminating in motor symptoms. Furthermore, long-term treatment with anti-parkinsonian medications produces motor fluctuation and motor complications at advanced stages of Parkinson’s disease. In addition to motor dysfunction, there are a variety of non-motor symptoms associated with Parkinson’s disease. Gastrointestinal dysfunction such as dysphagia, reflux and constipation, is a common non-motor dysfunction of Parkinson’s disease. Patients with Parkinson’s disease also complain of early satiety, abdominal discomfort, postprandial bloating and weight loss. Impaired gastric emptying (gastroparesis) and abnormal gastric motility occur both in untreated and treated Parkinson’s disease and might be one of the causes of gastrointestinal symptoms. The gastrointestinal dysfunction likely results from degeneration of extranigral lesions related to neural control of gastrointestinal tract function such as in the dorsal vagal nucleus and the intramural plexus of the whole intestine prior to degeneration of the substantia nigra (Del Tredici et al., 2002; Cerosimo and Benarroch, 2008; Jost, 2010) and occur secondarily to unstable absorption of levodopa (Hardoff et al., 2001). The ideal strategy for the management of gastrointestinal dysfunction remains uncertain.

Previous reports have shown that gastric emptying time is slower in levodopa-treated patients with Parkinson’s disease compared with untreated control subjects (Djaldetti et al., 1996; Hardoff et al., 2001; Thomaides et al., 2005), and that delayed gastric emptying of solids is associated with greater disease severity (Goetze et al., 2005). In addition, delayed gastric emptying is evident in patients with early stage Parkinson’s disease, which suggests that it may be a marker for the preclinical stage of Parkinson’s disease (Krygowska-Wajs et al., 2009; Tanaka et al., 2011). The effect of anti-parkinsonian medication on gastric emptying is not clear. Levodopa treatment has been shown to slow gastric emptying in normal volunteers (Berkowitz et al., 1980; Carrio et al., 1982; Robertson et al., 1990, 1992; Casellas et al., 1999). Gastric emptying time is slower in levodopa-treated patients with Parkinson’s disease compared with untreated control subjects (Djaldetti et al., 1996; Hardoff et al., 2001; Thomaides et al., 2005). Indeed, drugs that block dopamine receptors also accelerate gastric emptying, presumably via an effect on gastric dopamine receptors (McCallum et al., 1985; Soykan et al., 1997).

However, to our knowledge, there have been no reports about the features of gastric emptying in patients with Parkinson’s disease when fasting and just after levodopa intake.

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a surgical treatment for motor dysfunction in advanced Parkinson’s disease. Since its introduction into clinical practice, many studies have reported on its benefits and limitations (Krack et al., 2003; Ford et al., 2004; Rodriguez-Oroz et al., 2004, 2005; Schupbach et al., 2005; Fraix et al., 2006; Derost et al., 2007; Stefani et al., 2007; Benabid et al., 2009). It has previously been shown that non-motor symptoms (i.e. sensory, mood/psychosis, cognition, sleep, abnormal sweating and cardiovascular symptoms) falls may be improved by STN-DBS and reduction of anti-parkinsonian drugs (Holmberg et al., 2005; Witjas et al., 2007; Zibetti et al., 2007; Hwynn et al., 2011). Non-motor dysfunction such as altered sleep patterns, urinary disturbance, sympathetic skin responses, cutaneous sympathetic vasoconstriction and orthostatic regulation differs between the off and on states of STN-DBS, and subthalamic nucleus stimulation has been shown to have influence on cardiovascular function. However, it remains unclear as to whether STN-DBS would be effective in improving gastrointestinal dysfunction. Thus, we evaluated the effect of STN-DBS on gastric emptying.

Subjects and methods

Subjects and bilateral subthalamic nucleus deep brain stimulation

From December 2009 to October 2011, 16 patients underwent bilateral STN-DBS implantation at Chiba Cardiovascular Centre and were followed at Chiba University Hospital. They were diagnosed with Parkinson’s disease on the basis of the UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria (Hughes et al., 1992), as well as the results of cardiac I-metaiodobenzylguanidine (MIBG) testing, and had complained about medication resistant motor fluctuation and motor complications. All 16 patients with Parkinson’s disease that underwent STN-DBS implantation were enrolled in the study. The clinical background of the patients is listed in Table 1. Levodopa/decarboxylase inhibitor (DCI) was administered to patients after they had fasted for 1 h before the start of the ‘ON medication’ study to ensure drug efficacy. The interval and the dose of levodopa/DCI were set based on the dose that we usually used, which is a safety limited dose in Japan. Prior to enrolment in the study, patients had been treated long term with anti-parkinsonian medications and were taking levodopa/DCI and dopamine agonists, but none were taking anti-cholinergics just before and during this study. They had no history of previous gastrointestinal surgery and no change of medication affecting gastric motility for at least 4 weeks. None of the patients had general diseases such as severe liver dysfunction, renal failure, cardiopulmonary disease, uncontrolled diabetes mellitus or gastrointestinal disease. The levodopa equivalent dose of anti-parkinsonian medications in all patients with Parkinson’s disease was converted as described previously (Herzog et al., 2003; Ford et al., 2004). The study was approved by Chiba University Hospital Institutional Review Board and all patients gave informed consent.

Gastric emptying study

The gastric emptying study was carried out using the $^{13}$C-acetate breath test with a slight modification (Sanaka et al., 2008; Sanaka and Nakada, 2010; Tanaka et al., 2011). Gastric emptying can also
be evaluated using the aceterminophen absorption test and by technetium-99m scintigraphy. However, the acetaminophen absorption test requires repeated blood sample collection, and scintigraphy requires specialized instrumentation. In contrast, the 13C-acetate breath test can be performed at the patient’s bedside and the results have been shown to correlate well with those obtained using scintigraphy (Chapman et al., 2011). Therefore, we chose the 13C-acetate breath test to determine the prevalence of delayed gastric emptying in patients with Parkinson’s disease. 13C-sodium acetate administered orally with a test meal moves from the stomach and is absorbed from the digestive tract, where it is then metabolized to 13CO2, and finally expired by the lungs. Thus, measurement of 13CO2 in expired breath is an indirect measure of gastric emptying. Patients with Parkinson’s disease were tested after an overnight 12-h fast. First, a breath sample was obtained following the ingestion of a liquid test meal (Racol, 200 kcal/200 ml; Otsuka Pharmaceutical Co., Ltd) containing 100 mg of 13C-sodium acetate (Sigma-Aldrich). The test meal was consumed in <5 min and breath samples were then collected at 5, 10, 15, 20, 30, 40, 50, 60, 75, and 90 min after consuming the test meal. Patients remained in a seated position throughout the examination. All breath samples were analyzed by infrared isotope spectrometry (UBit-IR200; Otsuka Electronics Co., Ltd). Gastric emptying time was expressed as the peak time of 13CO2 by infrared isotope spectrometry (UBit-IR200; Otsuka Electronics Co., Ltd). Gastric emptying time was expressed as the peak time of 13CO2 by infrared isotope spectrometry (UBit-IR200; Otsuka Electronics Co., Ltd).

Measurement of serum ghrelin levels

Blood samples were collected from fasted subjects, not treated with typical anti-parkinsonian medications, with and without stimulation 3 months after STN-DBS implantation. The samples were immediately centrifuged at 1500g for 15 min at 4°C, and HCl was added at a ratio of 1:10 (v/v). The samples were then stored at −80°C until analysis. The levels of ghrelin in serum were measured according to the manufacturer’s instructions (Matsumura et al., 2010; Arai et al., 2012).

### Statistical analysis

All data values are expressed as the mean ± standard error (SE). Commercially available SPSS software was used for the statistical analysis. Parameters before and after administration of levodopa, STN-DBS and surgery were compared within subjects by paired t-test and chi-square test. The level for significance was P < 0.05. The association between gastric emptying, clinical backgrounds, levodopa equivalent dose and serum ghrelin levels was established statistically using Pearson’s correlation coefficient test or Spearman’s correlation coefficient by rank test.

### Results

#### The effect of subthalamalic deep brain stimulation

All the procedures were performed without complications in all cases. Results of the clinical evaluation of the effects of STN-DBS are listed in Table 1. There were significant improvements in the Unified Parkinson’s Disease Rating Scale III and Hoehn and Yahr scores in the ON compared with OFF medication condition before STN-DBS implantation (P < 0.001), and on stimulation compared with the off stimulation condition 3 months after surgery (P < 0.001). Furthermore, there were also significant improvements in these scores in the OFF medication-off stimulation condition after surgery compared with OFF medication condition before surgery (P < 0.05). The levodopa equivalent dose of anti-parkinsonian drugs was reduced by 43.3% from baseline after surgery (P < 0.001). There was a significant 3.8 ± 1.0kg increase

### Table 1 Clinical evaluation of the effects of STN-DBS implantation

<table>
<thead>
<tr>
<th></th>
<th>Before DBS</th>
<th>3 months after DBS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 ± 6.9 (49–76)</td>
<td>21.9 ± 3.4 (18.0–26.8)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>7/9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>20.6 ± 3.6 (18.7–25.3)</td>
<td>21.9 ± 3.4 (18.0–26.8)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Duration of Parkinson’s disease (years)</td>
<td>13.7 ± 4.6 (7–21)</td>
<td>4.6 (7–21)</td>
<td></td>
</tr>
<tr>
<td>Levodopa (mg)</td>
<td>329 ± 469 (252–1200)</td>
<td>100–150 mg levodopa</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Unified Parkinson’s Disease Rating Scale-III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ON medication</td>
<td>26.1 ± 5.2</td>
<td></td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>OFF medication</td>
<td>55.1 ± 11.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On stimulation</td>
<td>–</td>
<td>30.1 ± 6.1</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Off stimulation</td>
<td>–</td>
<td>46.4 ± 10.7</td>
<td></td>
</tr>
<tr>
<td>Hoehn and Yahr staging</td>
<td>2.6 ± 0.4</td>
<td>2.7 ± 0.4</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>ON medication</td>
<td>4.4 ± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OFF medication</td>
<td>–</td>
<td>3.9 ± 0.5</td>
<td></td>
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</tbody>
</table>

| a The levodopa equivalent dose expressed in mg/day represented the sum of the doses of levodopa and dopamine agonist. Dopamine agonist equivalent doses were calculated with the following equivalences: 100 mg levodopa = 10 mg apomorphine = 1 mg pergolide = 2 mg cabergoline = 1 mg pramipexole = 10 mg bromocriptine = 5 mg ropinirole (Herzog et al., 2003). *Paired t-test; **Wilcoxon signed-rank test.

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in body weight at 3 months after surgery, equivalent to a mean increase of 6.5 ± 7.3% (P = 0.0054). An increase or decrease of >0.5 kg was designated as ‘weight gain’ or ‘weight loss’, respectively. Twelve cases showed significant weight gain at 3 months after surgery and four cases showed no change.

Gastric emptying study
Before surgery, the $T_{\text{max}}$ values in the OFF and ON medication conditions were 45.6 ± 22.7 min and 42.5 ± 13.6 min, respectively, indicating that administration of levodopa/DCI did not correct the delayed gastric emptying (Fig. 1A). Individually, six patients showed deterioration and three patients showed no change in gastric emptying. At 3 months after surgery and without the use of anti-parkinsonian medication, the $T_{\text{max}}$ values in the off and on stimulation conditions were 44.0 ± 15.7 min and 30.0 ± 12.5 min, respectively; the improvement in the on stimulation condition was significant (P < 0.001; Fig. 1B). Individually, 12 patients showed significant improvement of gastric emptying, while three patients showed no change. However, the difference between the $T_{\text{max}}$ values in the OFF medication condition before surgery and in the OFF medication–off stimulation conditions after surgery, was not significant. There were no significant associations between body weight and clinical background features such as age, gender, disease duration, gastric emptying ($T_{\text{max}}$), ghrelin levels, levodopa equivalent dose (mg) or motor scores. There was also no association between the rate of change in $T_{\text{max}}$ ($\Delta T_{\text{max}}$) and changes in other characteristics.

The $^{13}$CO$_2$ excretion curve showed two patterns: a steep curve with an obvious peak, or a flattened curve without an obvious peak, designated as peak and non-peak patterns, respectively. Before surgery, there were 10 patients with peak pattern and six patients with non-peak pattern in the OFF medication condition, and seven with peak and three with non-peak pattern in the ON medication condition. There were no significant differences in the curve patterns between the OFF and ON medication conditions. After surgery, there were nine patients with peak pattern and six patients with non-peak pattern in the off stimulation condition, and 15 with peak and one with non-peak pattern in the on stimulation condition. The improvement in the number of patients with peak pattern in the on stimulation condition was statistically significant compared with the off stimulation condition (P = 0.002). The difference between the pattern of the $^{13}$CO$_2$ excretion curve in the OFF medication condition before and in the OFF medication–off stimulation condition after surgery was not significant (Table 2).

Changes in ghrelin levels
The ghrelin levels, before surgery, in the OFF and ON medication conditions were 18.0 ± 14.1 fmol/ml and 13.9 ± 11.3 fmol/ml, respectively, and these values did not differ significantly. The ghrelin levels were increased in three cases, decreased in five cases and unchanged in one case in the ON medication condition. The ghrelin levels, 3 months after surgery, in the off and on stimulation conditions without anti-parkinsonian medication were 15.8 ± 10.6 fmol/ml and 14.3 ± 12.1 fmol/ml, respectively, which also did not differ significantly. Ghrelin levels were increased in seven cases, decreased in five cases and unchanged in one case in the on stimulation condition. There was little association between changes in ghrelin levels (Δghrelin) and changes in $T_{\text{max}}$ values ($\Delta T_{\text{max}}$) in the OFF versus ON medication conditions before surgery ($r = 0.475$) and in the off versus on stimulation conditions 3 months after surgery ($r = -0.198$) (Fig. 2A and B).

Discussion
STN-DBS is the preferred surgical treatment for advanced Parkinson’s disease. Despite limited evidence-based data, STN-DBS has been shown to produce improvements in dopaminergic function.
drug-sensitive symptoms as well as reductions in subsequent drug dose and motor complication such as dyskinesias and dystonias (Vingerhoets et al., 2002; Arai et al., 2008; Benabid et al., 2009), although STN-DBS implantation can lead to severe surgical complications. In our cases, STN-DBS improved motor dysfunction in patients with Parkinson’s disease measured using Unified Parkinson’s Disease Rating Scale-III and Hoehn and Yahr staging criteria, as reported in previous studies (Herzog et al., 2003; Krack et al., 2003; Rodriguez-Oroz et al., 2004, 2005; Schupbach et al., 2005; Fraix et al., 2006; Derost et al., 2007). Therefore, physicians should assess the risk and benefit of STN-DBS for each patient. The levodopa equivalent dose of anti-parkinsonian drug was also reduced by 43.3% with respect to baseline, in agreement with previous reports (Schupbach et al., 2005; Fraix et al., 2006). In addition, some studies have reported rapid weight gain and increased body mass index in subjects following STN-DBS (Ford et al., 2004), which were also observed in the present study.

There have been few previous reports about the association between STN-DBS and gastrointestinal dysfunction, a common non-motor symptom of Parkinson’s disease. Recently, the $^{13}$C-acetate breath test has been widely recognized as a useful method for evaluating gastric emptying because $^{13}$C is less invasive than other isotopes or acetaminophen-based methods (Tanaka et al., 2011). In this study, by using the $^{13}$C-acetate breath test, we showed that STN-DBS improved gastric emptying in patients with Parkinson’s disease. To the best of our knowledge, this is the first published investigation of the effect of STN-DBS on gastric emptying in patients with Parkinson’s disease. Although it is controversial as to whether or not levodopa treatment can improve gastric emptying in patients with Parkinson’s disease (Hardoff et al., 2001; Thomaides et al., 2005; Tanaka et al., 2011), we found that early morning treatment with levodopa/DCI at typical doses did not alter the $T_{\text{max}}$ value, indicating that gastric emptying was resistant to levodopa therapy. In contrast, STN-DBS produced a significant improvement in gastric emptying.

Table 2 The pattern of $^{13}$CO$_2$ excretion curves

<table>
<thead>
<tr>
<th>DBS implantation</th>
<th>Medication$^a$</th>
<th>DBS stimulation</th>
<th>Pattern of $^{13}$CO$_2$ excretion (Peak / non-peak)</th>
<th>*P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before ON</td>
<td>–</td>
<td>–</td>
<td>7/3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Before OFF</td>
<td>–</td>
<td>–</td>
<td>10/6</td>
<td>0.03</td>
</tr>
<tr>
<td>After OFF</td>
<td>On</td>
<td>–</td>
<td>15/1</td>
<td>0.002</td>
</tr>
<tr>
<td>After OFF</td>
<td>Off</td>
<td>Off</td>
<td>9/6</td>
<td></td>
</tr>
</tbody>
</table>

The $^{13}$CO$_2$ excretion value showed an obvious peak (peak pattern), or gentle climb and descent without an obvious peak (non-peak pattern). $^a$ The gastric emptying study was performed twice with (ON) or without (OFF) administration of 100–150 mg levodopa/decarboxylase-inhibitor early in the morning. * $^2$ test; n.s. = not significant.

Figure 2 Correlation between changes in $T_{\text{max}}$ ($\Delta T_{\text{max}}$) and serum ghrelin levels ($\Delta$ghrelin) in patients with Parkinson’s disease (A) with or without levodopa/DCI before surgery ($n = 10$, $r = 0.475$) and (B) with or without STN-DBS after surgery ($n = 14$, $r = -0.198$). The values for $\Delta T_{\text{max}}$ and $\Delta$ghrelin are expressed as the difference subtraction of that after DBS surgery from that before it. There was no correlation between $\Delta T_{\text{max}}$ and $\Delta$ghrelin before or after DBS implantation, or with and without stimulation (based on Pearson’s correlation coefficients).
which could not be improved by the administration of levodopa/DCI before surgery. The ability of levodopa/DCI to influence gastric emptying in patients with Parkinson’s disease is unclear since few studies have investigated the effect of levodopa on gastric emptying in patients with Parkinson’s disease. It has been established experimentally that orally administered levodopa induces gastric relaxation (Valenzuela et al., 1976), decreases gastric motility (Nagahata et al., 1995) and inhibits gastric emptying in normal humans (Berkowitz, 1980; Carrio et al., 1982; Robertson et al., 1990, 1992; Casellas et al., 1999). In our study, by using the $^{13}$C-acetate breath test, we found that early morning treatment with levodopa/DCI at typical doses improved motor dysfunction, but did not improve the $T_{\text{max}}$ value and individually some slight deterioration was shown in 66.7% of patients. Our results are similar to those of previous studies, which showed that levodopa could cause deterioration of gastric emptying. These findings indicate that gastric emptying may be resistant to levodopa therapy, although we did not assess the effects of higher doses of levodopa/DCI on gastric emptying. Therefore, to achieve consensus regarding the effect of levodopa/DCI on gastric emptying, further studies are required.

The pattern of the $^{13}$CO$_2$ excretion curve changed to show an obvious peak in almost all cases in the on stimulation condition after surgery. We surmised that the peak in the early phase was associated with the coordinated movement and efficiency of gastric emptying, because almost all of our cases with obvious peaks had low gastric emptying ($T_{\text{max}}$) compared with cases without an obvious peak. Thus, not only can STN-DBS improve the rate of gastric emptying, it also causes it to become more dynamic and to empty more smoothly (Sanaka and Nakada, 2010).

In this study, body weight slightly increased 3 months after surgery. Other studies have reported that weight gain after STN-DBS cannot be inadequately explained by motor improvement or reduced dopaminergic drug dosage (Sauleau et al., 2009). The mechanism of body weight increase after STN-DBS is complex and influenced by various factors that are thought to be associated with increased appetite and food intake, reduction of energy output related to amelioration of parkinsonism and dyskinesias, improved alimentation and the direct influence on function of homeostatic control centres such as the lateral hypothalamus (Barichella et al., 2003; Montaurier et al., 2007; Novakova et al., 2007); however, some studies investigating these processes have general conflicting results. After STN-DBS, unpredictable motor fluctuations such as ‘delayed-on’ and ‘no-on’ phenomena dramatically improve. It has been suggested that this is mainly due to improvement in OFF medication motor symptoms. Delayed gastric emptying can delay the absorption of levodopa by interfering with its accessibility to the duodenum, and this might lead to non-motor fluctuations. Therefore, improvement of abnormal gastric emptying mediated by SNT-DBS could contribute partly to the improvement of unpredictable motor fluctuations, although it is mainly mediated by improvement in OFF medication.

The mechanism by which STN-DBS might alter gastric emptying time and the $^{13}$CO$_2$ excretion curve pattern is unknown. Although Mann et al. (2009) reported that STN-DBS is associated with a lead implantation effect on motor dysfunction after surgery, $T_{\text{max}}$ values in the OFF medication condition before and in the OFF medication-off stimulation condition after surgery did not show any difference. In contrast, motor dysfunction improved, the levodopa equivalent dose decreased, and body weight increased after surgery. Thus, our results suggest that lead implantation and other changes after STN-DBS, such as improvement of motor dysfunction, decrease in anti-parkinsonian drug dose, and increase in body weight may not affect post-surgical gastric emptying.

To determine the underlying mechanism, we assessed the serum levels of ghrelin, which are strongly correlated with appetite and gastric emptying (Kojima et al., 1999; Murray et al., 2005; Corcuff et al., 2006; Fiszer et al., 2010; Matsumura et al., 2010). We found little association between changes in ghrelin levels ($\Delta$ghrelin) and changes in $T_{\text{max}}$ values ($\Delta T_{\text{max}}$) induced by administration of levodopa/DCI and STN-DBS. Ghrelin is a peptide hormone produced and secreted in the stomach. The effect of ghrelin is driven largely by the high expression of the ghrelin receptors in the CNS, e.g. in the hypothalamus and pituitary gland. There have been no reports on the relationship between serum ghrelin levels and gastric emptying in patients with Parkinson’s disease during treatment with levodopa, or after STN-DBS. Some previous reports showed that serum levels of ghrelin were unchanged before and after STN-DBS and that changes in ghrelin levels did not appear to cause appetite and weight gain in Parkinson’s disease (Corcuff et al., 2006; Novakova et al., 2011). The mechanisms of action of STN-DBS are not well understood. STN-DBS has been shown to activate various brain areas including some of the centres of autonomic control (Limousin et al., 1997; Schulte et al., 2006; Klein et al., 2011). The subthalamic nucleus, basal ganglia and various centres of autonomic control are interconnected (Canteras et al., 1990) and there are neurons in the subthalamic nucleus that are related to urinary storage/voiding cycles (Sakakibara et al., 2003). Autonomic centres such as the frontal cortex, cingulate cortex, insula, thalamus, basal ganglia and periaqueductal grey matter are also associated with gastric motility (Ladabaum et al., 2001; Stephan et al., 2003; Vandenbergh et al., 2005). Stimulation of the ventral and dorsal-most region can produce autonomic responses (Benedetti et al., 2004). In fact, STN-DBS has been shown to affect sympathetic skin responses (Priori et al., 2001), bladder function (Seif et al., 2004; Herzog et al., 2006, 2008), and cutaneous sympathetic vasoconstriction (Ludwig et al., 2007). Although other autonomic symptoms were not evaluated in the present study, some patients experienced autonomic symptoms such as insomnia, frequent urination, constipation and excessive sweating (data not shown). Non-motor dysfunctions such as sleep disruption, urinary disturbance, sympathetic skin responses, cutaneous sympathetic vasoconstriction and orthostatic regulation differed between the off and on states of STN-DBS. These findings indicate that STN-DBS may influence and improve some non-motor functions. Although direct spread to the hypothalamus nevertheless seems unlikely, activation of nerve fibres projecting from or to the hypothalamus and crossing the subthalamic nucleus might be a possibility of the autonomic and homeostatic effects on gastrointestinal movement induced by STN-DBS. Thus, an effect of STN-DBS on neural regulation of gastric emptying is possible.

Our study has some limitations, namely, the absence of a control group, a small number of patients and a short period of
follow-up. Although the study included only a small number of patients, the cohort comprised all of the patients treated with STN-DBS in our hospital, which precludes selection bias. Although, our study used only a 3 month follow-up period, several prior studies have shown that improvements in clinical and motor scores following STN-DBS persist considerably longer (Herzog et al., 2003; Rodriguez-Oroz et al., 2004, 2005; Schupbach et al., 2005). Additional studies with longer follow-up intervals are needed to confirm our findings.

This study demonstrated improvement of gastric emptying and the results suggest that improvement of gastric emptying can improve upper gastrointestinal symptoms such as heavy feeling in the stomach, bloating, nausea or feeling sick and belching. A previous report showed that these symptoms could be influenced by placebo effect (Moayyedi et al., 2004). As mentioned above, it was not feasible to use a control group in this study; therefore, we did not evaluate clinical symptoms before and after STN-DBS implantation. Further studies involving a larger patient cohort are needed to rule out the possibility of the placebo effect.

In conclusion, we demonstrated that STN-DBS improved anti-parkinsonian drug resistant gastric emptying dysfunction in patients with Parkinson’s disease, possibly by altering neural control systems regulating gastrointestinal function. To our knowledge, this is the first report to demonstrate the effectiveness of STN-DBS treatment for gastric emptying dysfunction, a common non-motor dysfunction associated with Parkinson’s disease.

References


STN-DBS can improve gastric emptying

Brain 2012; 135; 1478–1485


Changes in cerebral activity pattern due to subthalamic nucleus or subcortical regions. Gastroenterology 2001; 120: 369–76.
