Deep Brain Stimulation Induces Striatal Dopamine Release in Obsessive-Compulsive Disorder

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Background: Obsessive-compulsive disorder is a chronic psychiatric disorder related to dysfunctional dopaminergic neurotransmission. Deep brain stimulation (DBS) targeted at the nucleus accumbens (NAc) has recently become an effective treatment for therapy-refractory obsessive-compulsive disorder, but its effect on dopaminergic transmission is unknown.

Methods: We measured the effects of NAc DBS in 15 patients on the dopamine $D_{2/3}$ receptor availability in the striatum with [^{123}I]iodobenzamide ([^{123}I]IBZM) single photon emission computed tomography. We correlated changes in [^{123}I]IBZM binding potential (BP) with plasma levels of homovanillic acid (HVA) and clinical symptoms.

Results: Acute (1-hour) and chronic (1-year) DBS decreased striatal [^{123}I]IBZM BP compared with the nonstimulated condition in the putamen. BP decreases were observed after 1 hour of stimulation, and chronic stimulation was related to concurrent HVA plasma elevations, implying DBS-induced dopamine release. BP decreases in the area directly surrounding the electrodes were significantly correlated with changes in clinical symptoms (45% symptom decrease).

Conclusions: NAc DBS induced striatal dopamine release, which was associated with increased HVA plasma levels and improved clinical symptoms, suggesting that DBS may compensate for a defective dopaminergic system.

Key Words: Deep brain stimulation, dopamine, homovanillic acid, neuroimaging, nucleus accumbens, obsessive-compulsive disorder

Deep brain stimulation (DBS) has recently become an effective treatment for therapy-refractory obsessive-compulsive disorder (OCD) (1). The effects of DBS are substantial, with on average almost 50% improvement of obsessive-compulsive symptoms (2). Despite these promising clinical observations, remarkably little is known about the underlying mechanism of action. OCD has been related to abnormalities in dopaminergic neurotransmission, predominantly on the basis of clinical evidence and molecular imaging studies. For example, dopamine receptor antagonists are effective as an adjunct to selective serotonin reuptake inhibitors in reducing symptoms in OCD (3), and dopamine agonists may induce obsessive-compulsive behavior (4). Molecular imaging studies consistently showed decreased dopamine $D_{2/3}$ receptor ($D_{2/3}$R) binding in OCD (5), most prominently in the ventral striatum (6). Most effective DBS targets for OCD are in or around the ventral striatum (1), and animal studies suggest that DBS in this area increases dopamine levels in the stimulated area or prefrontal cortex (7,8). We therefore hypothesized that striatal dopamine release may be one of the key mechanisms of action behind DBS for OCD. We analyzed dopaminergic changes of DBS targeted at the border of the nucleus accumbens (NAc) core and anterior limb of the internal capsule in OCD patients, using [^{123}I]iodobenzamide single photon emission computed tomography ([^{123}I]IBZM SPECT) and plasma measurements of the dopamine metabolite homovanillic acid (HVA), which is thought to partially reflect central dopaminergic and noradrenergic changes.

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Received Mar 4, 2013; revised May 22, 2013; accepted Jun 14, 2013.

Methods and Materials

Study Participants

We included 15 DBS-implanted patients with OCD and 18 age- and gender-matched healthy control subjects (Table 1). Patients were recruited from the outpatient clinic for DBS at the Academic Medical Center, Amsterdam, The Netherlands. Healthy control subjects were only included if they were free of any mental disorder, had no family history of any psychiatric disorder, and reported no history of head trauma, neurological or other medical disorders, or alcohol or other substance abuse. Participants provided written informed consent before participation, and the local ethics committee approved this study.

All included patients had a primary diagnosis of OCD, according to DSM-IV criteria using the Structured Clinical Interview for DSM-IV Axis I disorders (9). Eight patients had predominantly OCD symptoms of the subtype contamination fear, four patients had predominantly high-risk assessment and checking symptoms, two patients mainly suffered from perfectionism, and one patient had somatic obsessions. Mean duration of illness was 25.9 years (range 8–48 years). Four patients were diagnosed with comorbid major depressive disorder, one patient was diagnosed with comorbid panic disorder, and three patients were diagnosed with comorbid obsessive-compulsive personality disorder. Nine patients were medication-free for at least 1 year at the time of this investigation. Six patients had been using medication before the study for 11 to 63 months (mean 23 months). Because of potential interference with [^{123}I]IBZM binding to dopamine $D_{2/3}$R,

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.06.021

Table 1. Demographics of the Study Sample

	Patients ($n = 15$)	Controls ($n = 18$)	Statistic
Age, Mean (SD), Years	43.8 (10.1)	38.3 (17.9)	$t = 1.048$ $p = .303$
Gender, Male:Female, *n*	7:8	9:9	$\chi^2 = .133$ $p = .716$

medication was discontinued according to its pharmacological half-life: 16 days before the first scan for clomipramine (three patients), 12 days for paroxetine (one patient), 24 days for fluoxetine (one patient), and 1 week for fluvoxamine (one patient). At the day of the imaging session and within 24 hours before each scanning session, participants were not allowed to consume coffee, alcohol, or nicotine because these substances have been associated with increased striatal dopamine release. Four patients and two control subjects smoked. Patients were chosen from a larger clinical DBS sample when they had finished the treatment optimization phase and remained clinically stable after at least 1 year of stimulation. At this stage, 12 patients had decreases on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) of more than 25%, corresponding to responder status, and 3 patients experienced less than 25% decrease (12% in 1 patient and 17% in 2 patients).

DBS Settings

All patients had electrode implantation in the same target area [for details, see Denys *et al.* (2)]: two quadripolar electrodes (Model 3389, Medtronics Inc., Minneapolis, Minnesota) with contact points 1.5-mm long and separated from adjacent contacts by .5 mm were implanted bilaterally following the anterior limb of the internal capsule into the target nucleus, with an anterior angle of approximately 75° to the intercommissural line. Target coordinates for the electrode tip were 7 mm lateral to the midline, 3 mm anterior to the anterior border of the anterior commissure, and 4 mm inferior to the intercommissural line. We included only patients who had completed the optimization phase of 1 to 2 years during which they were evaluated every 2 weeks for severity of symptoms and optimal stimulation parameters. For all 15 patients, receiving monopolar stimulation on the two dorsal contact points, the most effective stimulation area was located at the border of the NAc core and anterior limb of the internal capsule. At time of entrance of the study, patients were stimulated with an average of 4.8 V (range 3.5–6.2), a frequency of 130 hertz (11 patients) or 185 hertz (4 patients), and a pulse-width of 90 microseconds (12 patients), 130 microseconds (2 patients), or 150 microseconds (1 patient).

Symptom Measures

We assessed symptom severity in patients during chronic stimulation (Session 1: clinically stable after at least 1 year of stimulation), during DBS OFF (Session 2: after 8 days of DBS discontinuation), and during acute stimulation (Session 3: 1 hour after turning the stimulator back on). Symptom severity was assessed using the Y-BOCS (10,11), the Hamilton Depression Rating Scale (12), and the Hamilton Anxiety Rating Scale (13).

SPECT Data Acquisition

All patients were scanned on three separate occasions: during chronic stimulation, DBS OFF and acute stimulation (Sessions 1-3). All healthy control subjects were scanned once. Subjects received a potassium iodide solution to block thyroid uptake of free radioactive iodide. For administration of the radiotracer, we used a sustained equilibrium/constant infusion technique to achieve stable regional brain activity levels during scanning (14,15). In Session 1, $D_{2/3}R$ were measured with the well-validated radiotracer [^{123}I]IBZM, whereas the patients were on chronic DBS stimulation. In this session, approximately 80 MBq [^{123}I]IBZM (specific activity >200 MBq/nmol and radiochemical purity >95%) was administered intravenously as bolus, followed by 3 hours of continuous infusion of 20 MBq/hour [^{123}I]IBZM. Acquisition of the images started 2 hours after the bolus injection when a state of sustained binding equilibrium can be expected (15). Also the healthy control subjects were scanned using this paradigm. In Session 2, patients were scanned after 8 days DBS discontinuation (DBS OFF). In Session 3, 1 hour after Session 2, patients were scanned after 1 hour of acute stimulation. For Sessions 2 and 3, approximately 80 MBq [^{123}I]IBZM was administered intravenously as bolus, followed by 5 hours of continuous infusion of 20 MBq/h [^{123}I]IBZM. In the interval 2 to 3 hours after [^{123}I]IBZM bolus injection, patients were scanned to measure $D_{2/3}R$ in the DBS OFF situation. The stimulation was then reactivated, and 1 hour later (i.e., the interval between 4 and 5 hours after [^{123}I]IBZM bolus injection), the patients were scanned again to assess the effects of acute stimulation because previous [^{123}I]IBZM SPECT studies have shown that 1 hour after the induction of dopamine release, a new steady state is established (15). The SPECT scans were acquired on a 12-detector single-slice brain-dedicated scanner (Neurofocus 810, which is an upgrade of the Strichmann Medical Equipment, Medfield, Massachusetts), with a full-width at half maximum resolution of approximately 6.5 mm, throughout the 20 cm field-of-view (http://www.neurophysics.com). After positioning of the subjects with the head parallel to the orbitomeatal line, axial slices parallel and upward from the orbitomeatal line to the vertex were acquired in 5-mm steps. Each acquisition consisted of approximately 10 to 12 slices with 5-minute scanning time per slice, acquired in a 64 × 64 matrix. The energy window was set at 135 to 190 keV.

Magnetic Resonance Imaging Data Acquisition

Coregistered T1-weighted structural images of all implanted patients were acquired on a 1.5-Tesla Siemens MAGNETOM Avanto Scanner (Siemens AG, Healthcare Sector, Erlangen, Germany). To minimize exposure of the DBS device to the pulsed radiofrequency field, we scanned all subjects using a transmit/receive head coil. Two minutes before patients entered the scanner, the DBS system was turned off and programmed at 0 V in bipolar mode. Specific absorption rate levels were limited to .1 W/kg. For T1-weighted structural images, the following parameters were used: field of view 256 mm, voxel size 1 × 1 × 1 mm^3, slice thickness = 1 mm.

SPECT Data Analysis

SPECT data were reconstructed and analyzed while blind to clinical data. Our primary outcome parameter was nondisplaceable binding potential (BP_{ND}) of [^{123}I]IBZM, as a measure of $D_{2/3}R$ availability. BP_{ND} was calculated as [^{123}I]IBZM binding in the target tissue minus activity in the reference tissue divided by activity in the reference tissue. We used binding in the occipital cortex, which is devoid of $D_{2/3}R$, as reference tissue. We first performed attenuation correction of all SPECT images and then reconstructed them in three-dimensional (3D) mode (http://www.neurophysics.com) (14,15). With these 3D images, we performed two different region of interest (ROI) analyses. First, for quantification of BP_{ND} in the striatum and its subdivisions in