

7. Hod Y, Pentylala SN, Whyard TC, El-Maghrabi MR. Identification and characterization of a novel protein that regulates RNA-protein interaction. *J Cell Biochem* 1999;72:435–444.
8. Takahashi K, Taira T, Niki T, et al. DJ-1 positively regulates the androgen receptor by impairing the binding of PIAS α to the receptor. *J Biol Chem* 2001;276:37556–37563.
9. Mitsumoto A, Nagakawa Y. DJ-1 is an indicator for endogenous reactive oxygen species elicited by endotoxin. *Free Radic Res* 2001;35:885–893.
10. Mitsumoto A, Nagakawa Y, Takeuchi A, et al. Oxidized forms of peroxiredoxins and DJ-1 on two-dimensional gels increased in response to sublethal levels of paraquat. *Free Radic Res* 2001;35:301–310.
11. Trotter EW, Kao CM, Berenfeld L, et al. Misfolded proteins are competent to mediate a subset of the responses to heat shock in *Saccharomyces cerevisiae*. *J Biol Chem* 2002;277:44817–44825.

Effect of Subthalamic Deep Brain Stimulation on the Function of the Urinary Bladder

Christoph Seif, MD,¹ Jan Herzog, MD,²
 Christof van der Horst, MD,¹ Bettina Schrader, MD,³
 Jens Volkmann, MD, PhD,²
 Guenther Deuschl, MD, PhD,²
 Klaus-Peter Juenemann, MD, PhD,¹
 and Peter M. Braun, MD¹

Detrusor hyperreflexia is a relevant clinical symptom for patients suffering from Parkinson's disease. In a series of 16 patients, we demonstrated that subthalamic deep brain stimulation has a significant and urodynamically recordable effect leading to a normalization of pathologically increased bladder sensibility.

Ann Neurol 2004;55:118–120

A significant proportion of patients with Parkinson's disease suffers from lower urinary dysfunction. The predominant symptoms are urinary urgency, increased urinary frequency, or incontinence.¹ Urodynamic ex-

From the Departments of ¹Urology, ²Neurology, and ³Neurosurgery, Christian-Albrechts-University Kiel, Kiel, Germany.

Received May 16, 2003, and in revised form Aug 29. Accepted for publication Sep 2, 2003.

Address correspondence to Dr Deuschl, Department of Neurology, Christian-Albrechts-University of Kiel, Niemanssweg 147, 24105 Kiel, Germany. E-mail: g.deuschl@neurologie.uni-kiel.de

amination in these patients shows a detrusor hyperreflexia with involuntary contractions of the bladder resulting in a reduced bladder capacity and an early desire to void.¹

The pathophysiological mechanism for the detrusor hyperreflexia in Parkinson's disease is not yet understood. Experimental data show that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys develop a urinary dysfunction similar to human patients.² Because MPTP causes mainly a depletion of dopaminergic neurons of the substantia nigra pars compacta, the resulting detrusor hyperreflexia has been attributed to a loss of inhibition of the micturition reflex by central dopaminergic receptors. This observation provided an indication of the influence of basal ganglia structures on the micturition reflex.

Deep brain stimulation of the subthalamic nucleus (STN-DBS) leads to a significant amelioration of Parkinsonian motor symptoms and is becoming an important therapeutic option for patients with advanced disease.^{3,4} However, its influence on the bladder function is still unclear.

Patients and Methods

We studied 16 patients (9 women, 7 men; age 62 ± 5 years; disease duration 15 ± 5 years) with idiopathic Parkinson's disease 6 to 29 months after bilateral implantation of STN-DBS leads. The patients were selected randomly regardless of whether they had symptoms of urinary dysfunction. STN-DBS resulted in a significant reduction of the motor part of Unified Parkinson's Disease Rating Scale by 50.9% in the medical off-state (stimulation OFF 44.2 ± 13.9 ; stimulation ON 21.7 ± 11.5 , $p < 0.001$).

Twelve hours after withdrawal of antiparkinsonian medication two videourodynamic examinations were performed with STN-DBS turned off (OFF_{stim}) and on (ON_{stim}) in a randomized order. Between the measurements, there was an interval of at least 20 minutes. The urodynamic investigation was conducted according to criteria proposed by the International Continence Society with filling of the bladder by warm isotonic saline at a speed of 25ml/min.⁵ During the filling phase, the initial desire to void, the maximal bladder capacity, the detrusor contractions, the detrusor pressure, and the compliance of the bladder were documented. During the voiding phase, we measured the following parameters: maximum detrusor pressure (P_{det}), maximum urinary flow (Q_{max}), and residual urine volume (RU). External sphincter electromyogram activity was recorded by surface skin electrodes.

All patients gave their informed consent. The study was approved by the ethical committee of the Department of Medicine. Statistical analysis between different classifications was by Wilcoxon signed rank test for paired connections with a significance level of p value less than 0.05.

Results

In the OFF_{stim} condition, the initial desire to void occurred at a mean value of 135 ± 43 ml. The mean

maximal capacity of the bladder was 174 ± 52 ml. Compliance of the bladder was reduced. No abnormalities were found in the myography of the external sphincter. Unstable detrusor contractions (>20 cm H₂O) occurred in five patients. Nine patients were able to void in the testing room. In these patients, mean P_{det} was 23 ± 10 cm H₂O and mean Q_{max} 11 ± 5 ml/s with a RU of 114 ± 37 ml.

In the ON_{Stim} condition, the initial desire to void occurred at a mean value of 199 ± 57 ml. The maximum capacity of the bladder was 302 ± 101 ml. Compliance of the bladder was normal. No detrusor contractions or abnormalities were found with compound electromyography. In the voiding phase ($n = 9$), P_{det} averaged 32 ± 12 cm H₂O, Q_{max} 13 ± 5 ml/sec, and RU 71 ± 33 ml.

There was a significant difference between the OFF_{Stim} and ON_{Stim} condition for the initial desire to void and the maximum bladder capacity ($p < 0.005$), whereas P_{det} , Q_{max} and RU were not found to differ significantly (Fig).

Discussion

This is the first study to our knowledge to show that STN-DBS has a significant influence on the bladder function in patients with Parkinson's disease. In the OFF_{Stim} condition, the parameters of the urodynamic measurement showed the typical signs of detrusor hyperreflexia presenting as an "overactive bladder" with a markedly reduced initial desire to void and reduced bladder capacity. These findings are representative for the classic bladder disturbance found in patients with Parkinson's disease not treated by STN-DBS.¹ Similar symptoms also are found in monkeys with Parkinso-

nian symptoms induced by MPTP.^{1,2} The ON_{Stim} condition in our patients, however, leads to a normalization of the storage phase and the induction of the micturition reflex with a significant increment of both the initial desire to void and the maximal bladder capacity. Because turning off STN-DBS was accompanied by an unpleasant deterioration of the motor state for the patients, we decided to keep an interval between the two measurements not longer than 20 minutes. A recent study,⁶ however, has shown a sequential return of parkinsonian signs after turning off STN-DBS with a maximum of worsening in axial symptoms after 3 to 4 hours. In contrast, urinary parameters respond rapidly to changes in STN-DBS. On the other hand, it cannot be excluded that a longer interval between two measurements may lead to an even more pronounced effect.

The underlying physiological mechanism for this observation is not completely understood. Earlier studies have demonstrated profound influences of basal ganglia nuclei on the micturition reflex. Electrical stimulation of the substantia nigra pars compacta resulted in an inhibition of the micturition reflex in the cat.⁷ On the other hand, lesions of the basal ganglia caused a disinhibition of the reflex.⁸ Pharmacological studies in MPTP-lesioned parkinsonian monkeys have shown that application of D1 dopaminergic receptor agonists leads to an inhibition of the micturition reflex whereas D2 agonists have excitatory effects.² In our proposed model of the micturition reflex, the sensory signal of the urinary bladder is conveyed to the periaqueductal gray and from there to the micturition center of the pons.⁹ Its output reaches the urinary bladder through sacral parasympathetic preganglionic neurons causing contractions of the urinary bladder.

The central control of this reflex pathway by the basal ganglia is not yet extensively studied. On the one hand, the STN could influence the pontine micturition center directly considering its widespread excitatory projections to brainstem structures.¹⁰ In the current model of the basal ganglia, the loss of nigrostriatal dopaminergic activity leads to an increased excitation of both globus pallidus internus/substantia nigra pars reticulata (GPI/SNr) and STN neurons.¹¹ This could result in a facilitation of the micturition reflex by activation of excitatory projections of the STN on brainstem structures. STN-DBS most likely functions by diminishing pathologically increased neuronal activity inside the nucleus.¹² Consecutively, this could have an inhibitory effect on the micturition reflex pathway on the brainstem level, leading clinically to an improvement of detrusor hyperreflexia.

On the other hand, the STN essentially is integrated in the corticobasal gangliathalamocortical loops. In the case of Parkinson's disease, there is an excessive inhibi-

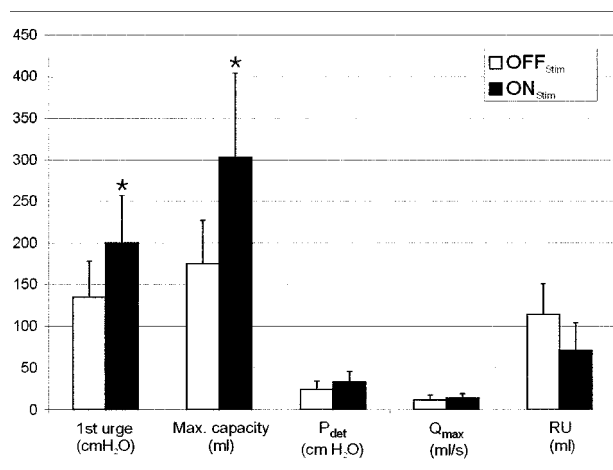


Fig. Comparison of the urodynamic filling and micturition parameters with deep brain stimulation of the subthalamic nucleus (STN-DBS) switched on and switched off (* $p < 0.005$). RU = residual urine.

tion of thalamocortical neurons, whereas STN-DBS leads to a disinhibition of thalamocortical projections.¹¹ There is evidence, however, that STN not only is involved in motor control circuits, but also plays a role in the regulation of associative and limbic functions.^{13,14} Both investigations in positron emission tomography and in the functional magnetic resonance tomography⁹ have demonstrated that micturition is accompanied by an activation of prefrontal and cingular cortex areas. Moreover, both cortical areas are found to be modulated during bladder storage.¹⁵ This corresponds to cortical areas that are disinhibited by STN stimulation.¹⁶ A release of cingular and prefrontal cortex from abnormal inhibition therefore might contribute to a more effective bladder control. Whether STN-DBS acts on bladder function through descending pontine pathways or thalamocortical projections needs to be determined in subsequent animal models.

Our results show a profound effect of STN stimulation on the neural regulation of bladder function leading to a normalization of these abnormal urodynamical values. This may indicate a profound therapeutic effect of STN-DBS on voiding functions. These patients did not have clinical symptoms of urinary incontinence. Future studies should address specifically the clinical effects of STN-DBS in patients with accompanying continence problems.

References

1. Araki I, Kitahara M, Oida T, Kuno S. Voiding dysfunction and Parkinson's disease: urodynamic abnormalities and urinary symptoms. *J Urol* 2000;164:1640–1643.
2. Yoshimura N, Mizuta E, Yoshida O, Kuno S. Therapeutic effects of dopamine D1/D2 receptor agonists on detrusor hyperreflexia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned parkinsonian cynomolgus monkeys. *J Pharmacol Exp Ther* 1998;286:228–233.
3. Deuschl G, Fogel W, Hahne M, et al. Deep-brain stimulation for Parkinson's disease. *J Neurol* 2002;249(suppl 3):36–39.
4. Herzog J, Volkmann J, Krack P, et al. Two year follow-up of subthalamic deep brain stimulation in Parkinson's disease. *Mov Disord* (in press).
5. Mattiasson A, Djurhuus JC, Fonda D, et al. Standardization of outcome studies in patients with lower urinary tract dysfunction: a report on general principles from the Standardisation Committee of the International Continence Society. *Neurourol Urodyn* 1998;17:249–253.
6. Temperli P, Ghika J, Villemure JG, et al. How do parkinsonian signs return after discontinuation of subthalamic DBS? *Neurology* 2003;60:78–81.
7. Yoshimura N, Sasa M, Yoshida O, Takaori S. Dopamine D1-receptor-mediated inhibition of micturition reflex by central dopamine from the substantia nigra. *Neurourol Urodyn* 1992;11:535–545.
8. Bors E, Comarr A. *Neurological urology*. Basel, Muenchen, Paris, New York: Karger, 1971.
9. Blok BF. Central pathways controlling micturition and urinary continence. *Urology* 2002;59(suppl 1):13–17.
10. Carpenter MB, Carleton SC, Keller JT, Conte P. Connections of the subthalamic nucleus in the monkey. *Brain Res* 1981;224:1–29.
11. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trend Neurosci* 1990;13:281–285.
12. Lozano AM, Carella F. Physiologic studies in the human brain in movement disorders. *Parkinsonism Relat Disord* 2002;8:455–458.
13. Funkiewiez A, Ardouin C, Krack P, et al. Acute psychotropic effects of bilateral subthalamic nucleus stimulation and levodopa in Parkinson's disease. *Mov Disord* 2003;18:524–530.
14. Schneider F, Habel U, Volkmann J, et al. Deep brain stimulation of the subthalamic nucleus enhances emotional processing in Parkinson disease. *Arch Gen Psychiatry* 2003;60:296–302.
15. Athwal BS, Berkley KJ, Hussain I, et al. Brain responses to changes in bladder volume and urge to void in healthy men. *Brain* 2001;124:369–377.
16. Limousin P, Greene J, Pollak P, et al. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. *Ann Neurol* 1997;42:283–291.