

High frequency stimulation of the subthalamic nucleus modulates neurotransmission in limbic brain regions of the rat

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Abstract Despite the benefit high frequency stimulation (HFS) of the subthalamic nucleus (STN) has on motor symptoms of Parkinson's Disease (PD), accumulating data also suggest effects of STN-HFS on non-motor behavior. This may be related to the involvement of the STN in the limbic basal ganglia-thalamocortical loops. In the present study we investigated the effect of acute STN-HFS on neurotransmission in associated structures of these pathways, i.e. the nucleus accumbens (NAc) core and shell as well as the ventral tegmental area (VTA) using *in vivo* microdialysis. Experiments were performed in anaesthetized naïve rats

and rats selectively lesioned in the substantia nigra pars compacta (SNc) or VTA. We demonstrate that: 1. STN-HFS leads to an increase in DA in the NAc, 2., these effects are more pronounced in the NAc shell than in the NAc core, 3. STN-HFS leads to a decrease in GABA in the VTA, 4. preceding lesion of the SNc does not seem to affect the effect of STN-HFS on accumbal DA transmission whereas 5. preceding lesion of the VTA seems to prohibit further detection of DA in the NAc. We conclude that STN-HFS significantly affects neurotransmission in the limbic system, which might contribute to explain the non-motor effects of STN-HFS.

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Introduction

High frequency stimulation (HFS) of the subthalamic nucleus (STN) improves motor symptoms in Parkinson's Disease (PD) (Deuschl et al. 2006; Kumar et al. 1998; Limousin et al. 1998). However, HFS of the STN or closely adjacent structures also affects psychiatric functions: altered mood and depressive symptoms (Bejjani et al. 2002; Czernecki et al. 2005; Doshi et al. 2002; Funkiewiez et al. 2004, 2006; Okun et al. 2003; Thobois et al. 2002; Witt et al. 2006) with suicide (Albanese et al. 2005), transient manic episodes partly with psychotic symptoms (Herzog et al. 2003; Mandat et al. 2006), mirthful laughter, hilarity (Krack et al. 2001), acute reinforcing psychotropic effects (Funkiewiez et al. 2003; Romito et al. 2002) as well as reduction of craving behavior (Witjas et al. 2005) and obsessive compulsive symptoms (Fontaine et al. 2004;

Mallet et al. 2002) have been observed in PD patients receiving STN-HFS.

These side effects may be related to the subdivision of the STN in three functionally segregated territories: a motor, an associative and a limbic subregion. Thus, the STN interconnects not only to the motor but also to the limbic basal ganglia-thalamocortical circuitry, involving orbitofrontal and cingulate cortices, nucleus accumbens (NAc), limbic globus pallidus and ventral putamen, substantia nigra (SN), and ventral tegmental area (VTA) (Alexander et al. 1986, 1990; Alexander and Crutcher 1990). Consequently, PET studies in PD-patients demonstrate that STN-HFS increases activity (Ceballos-Baumann et al. 1999; Limousin et al. 1997; Stefurak et al. 2003) (or rather reduces abnormal background noise (Payoux et al. 2004) in the anterior cingulate and prefrontal cortex as well as the temporal and parietal cortex (Hilker et al. 2004). To date, however, little is known about the mechanisms of how STN-HFS modifies non-motor behavior of PD patients. One way of addressing this question is to investigate the neurochemical consequences of STN-HFS in relevant limbic brain structures via in vivo microdialysis in animals.

Previous experimental studies have demonstrated that STN-HFS modulates extracellular levels of GABA and glutamate in the striatum and substantia nigra (Bruet et al. 2003; Windels et al. 2000, 2003) and increases DA-transmission in the dorsolateral striatum of naïve and hemiparkinsonian rats. This effect has been suggested to contribute to the clinical motor improvement and the reduction of DAergic medication in PD patients under chronic STN-HFS (Lee et al. 2006; Meissner et al. 2001, 2003; Paul et al. 2000). With the functional subdivision of the STN and its integration into motor as well as limbic circuitries, it is possible that STN-HFS may also induce neurochemical changes in limbic structures which might attribute to the co-occurrence of psychiatric effects under STN-HFS.

The present study investigates the impact of STN-HFS on the DAergic transmission in the NAc and GABAergic transmission in the VTA using in vivo microdialysis in rats. For further investigation of the pathways involved in mediating the STN-HFS-dependent effects on DA-transmission in the NAc, two separate groups were included, receiving selective 6-hydroxydopamine (6-OHDA)-lesions of either the substantia nigra pars compacta (SNc) or the VTA prior to STN-HFS and microdialysis analysis.

Material and methods

Animals

Principles of laboratory animal care (NIH publication No. 86–23, revised 1985) and of the European Communities

Council Directive (86/609/EEC) for care of laboratory animals were followed as well as guidelines of local ethical authorities where applicable. Naive male Wistar rats (Harlan-Winkelmann, Borcheln, Germany; $n = 78$, 280–320 g during the experiment) were housed in a temperature- and humidity-controlled vivarium with a 12-h light/dark cycle. Food and water were available ad libitum. All experiments were performed during day time and in anaesthetized rats only.

Surgery

All surgeries were performed under general anesthesia (for microdialysis sampling: chloral hydrate, 400 mg/kg i.p.; Merck, Darmstadt, Germany, for stereotaxic lesions: pentobarbital, 60 mg/kg, i.p.; Sigma Aldrich, Taufkirchen, Germany (Meissner et al. 2001; Paul et al. 2000). For in vivo microdialysis, microdialysis probes were stereotaxically inserted into the left NAc core (A: 1.6; L: 1.4; V: –7.4), the left NAc shell (A: 1.6; L: 0.7; V: –7.7; CMA 11), or the probe was inserted suchlike that it collected simultaneously from the left NAc core and shell (A: 1.7; L: 1.3; V: –8.2), or the VTA (A: –6.0; L: 0.6; V: –8.3; coordinates with respect to bregma (Paxinos and Watson 1997). Microdialysis probes for separate measures in the NAc core and shell were 0.24 mm in diameter and 1 mm in length (CMA 11, CMA, Solna, Sweden), and for simultaneous collection from the NAc core and shell 0.5 mm in diameter and 2 mm in length (CMA 12). During the same surgical session, a concentric bipolar stimulation electrode (SNEX 100; Rhode Medical Instruments, Woodland Hills, CA, USA) was placed into the left STN in all animals (A: –3.8; L: 2.5; V: 7.6).

Selective 6-OHDA lesions were performed 2 weeks prior to STN-HFS and microdialysis sampling. 7 µg 6-OHDA (Sigma Chemical Co., St. Louis, MO, USA), dissolved in 2 µl saline containing 0.1% ascorbic acid, were applied stereotaxically into the left SNc (A: –5.3; L: 2.3; V: –7.2) or the left VTA (A: –5.3; L: 0.6; V: –7.8) through a 25 gauge stainless steel canula attached to a 20 µl Hamilton microsyringe.

Microdialysis and HFS

Microdialysis procedures were performed as previously described (Meissner et al. 2001; Paul et al. 2000). Briefly, microdialysis probes were perfused with artificial cerebrospinal fluid (125 mM NaCl, 1 mM CaCl₂, 1 mM MgCl₂ × 6 H₂O, 2.5 mM KCl, 5 mM Na₂SO₄, 2.7 mM NaHCO₃, 0.5 mM NaH₂PO₄ × 2 H₂O, 2.4 mM NaH₂PO₄ (pH 7.4) adjusted with H₃PO₄) with a constant flow rate of 1.1 µl per min. Samples were collected at 20-min intervals in 5 µl of 1 M perchloric acid for immediate analysis of extracellular concentrations of DA, its metabolites

3,4-dihydroxyphenyl-acetic acid (DOPAC) and homovanillic acid (HVA) by HPLC (Synergi 4 μ Hydro-RP 80A, 150 \times 2 mm, Phenomenex, Aschaffenburg, Germany) and electrochemical detection (LC-4C, BAS, West Lafayette, USA). GABA was analyzed by HPLC after precolumn derivatization with phthalaldehyde (Merck) and fluorescence detection. Prior to stimulation, samples were collected until at least four consecutive stable values were measured. Thereafter, one sample was collected during STN stimulation and five thereafter. For STN-HFS the following parameters were applied: alternating pulses (130 Hz for HFS, pulse width 60 μ s) with an amplitude of 300 μ A in a constant current mode for 20 min using an isolated stimulator (Coulbourn Instruments, Allentown, PA, USA). Frequencies of 130 Hz and a narrow pulse duration of 60 μ s were chosen according to the parameters generally applied in rats for inducing net inhibitory effects of the STN (Benazzouz et al. 1995; Meissner et al. 2003; Salin et al. 2002; Windels et al. 2000) and were comparable to the clinical application (Moro et al. 2002). Current intensities of 300 μ A were chosen to allow comparability with values that have previously been shown to induce behavioral and biochemical changes (Boulet et al. 2006; Meissner et al. 2001, 2003).

Control animals received no stimulation (insertion of the electrodes and connection to the stimulation device only). Microdialysis experiments were performed in anaesthetized rats only.

Histological verification and immunocytochemistry

After the experiment all animals were transcardially perfused with 0.1 M phosphate buffer saline and 4% paraformaldehyde in deep anesthesia. Free floating 40 μ m thick coronal sections of the NAc (+2.9 to +0.5), the STN (−3.4 to −4.3), the SNc (−4.8 to −6.3), and the VTA (−4.52 to −6.3) were prepared. To verify location of electrode, microdialysis probe, and injection canula, every second section of the respective region was mounted and processed for cresyl violet (CV) staining. Only rats with accurate placement of all devices were included into data analysis.

For assessing the extent of the toxic lesions, tyrosine hydroxylase (TH) immunostaining was performed in rats that previously received 6-OHDA application into the SNc or the VTA (plus respective controls). One-in-six series of 40- μ m sections (microtome setting) from the rostrocaudal extent of the SNc and the VTA (240 μ m apart) were incubated with monoclonal antisera against TH (Sigma Chemical Co., diluted at 1:500). Immunostaining was visualized by avidin-biotin complex and 3,3'-diaminobenzidine as described previously (Winter et al. 2000, 2006). With this, a total of eight nigral and VTA-sections per animal, respectively, were stereologically

analyzed for TH-positive cells as described previously (Kempermann et al. 1997; Steiner et al. 2004, 2006). Shortly, the boundaries of the SNc and the VTA were determined with reference to internal anatomic landmarks (Paxinos and Watson 1997; Steiner et al. 2006). The total numbers of positive cells were determined with the optical fractionator method using the semi-automated stereology system StereoInvestigator and as implemented in the software (MicroBrightfield, Magdeburg, Germany). The setup uses a Hitachi HV-C20A video camera attached to a Leica DM-RXE microscope. The coefficient of error (CE, ranging between 0.05 and 0.1) due to estimation was calculated according to Gundersen and Jensen (Gundersen and Jensen 1987). For quantification of TH-labeled cells, numbers were expressed as percentages of contralateral unlesioned side.

Data analysis

Baseline for microdialysis samples was defined as the mean of the last four dialysate samples collected before HFS/sham-HFS. Stability of baseline values was assessed with respect to raw data. All data then were converted to percent of baseline (defined as 100%) in relation to the peak area of the chromatograms (Meissner et al. 2001). Statistical analysis was performed using two-way repeated measures (RM) ANOVA, with stimulation (HFS/control) or lesion (VTA/SNc/control) as the between subjects factor and time bin as the repeated within-subjects factor. If appropriate, this was followed by a Holm Sidak post hoc *t*-tests corrected for multiple comparisons. A probability level of $P < 0.05$ was considered significant. Data are shown as mean \pm SEM. Baseline values are given as fmol/20 μ l dialysate for DA and pmol/20 μ l dialysate for DOPAC and HVA.

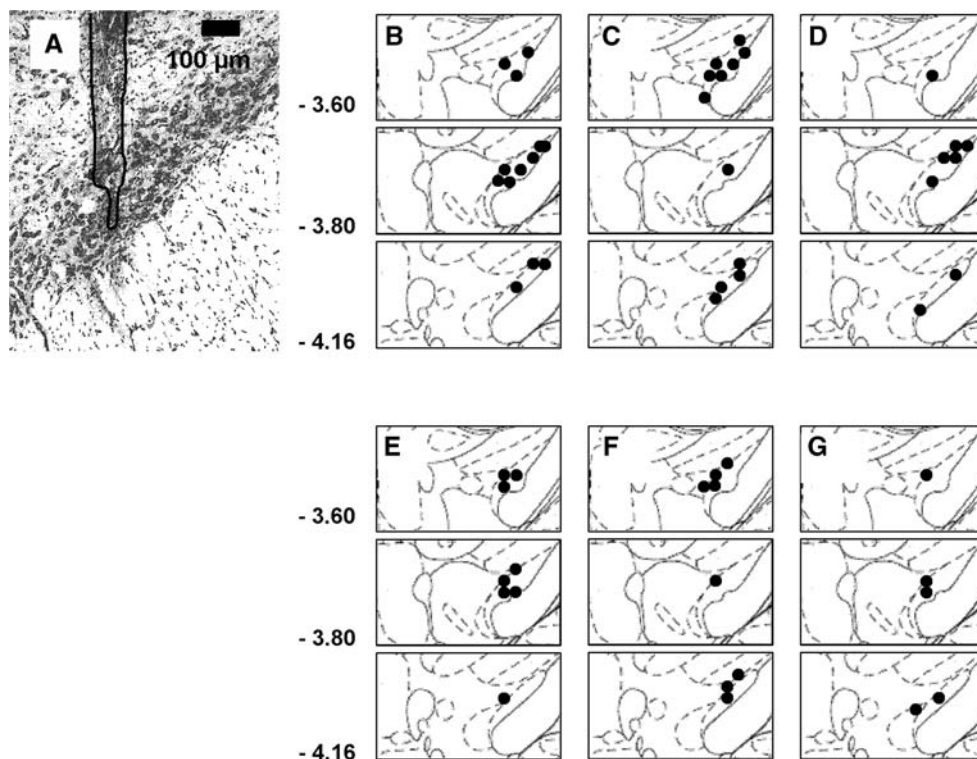
Results

Figure 1a presents a representative photomicrograph of a coronal section taken from a rat implanted with an electrode in the STN. Figure 1b show schematic reconstructions of the stimulating electrodes, placed correctly in the STN of all experimental animals included into the study.

Experiment 1

For investigating the effects of STN-HFS on extracellular DA in the NAc, 41 rats were divided into two subgroups. For the first group (1A; HFS, $n = 13$; controls, $n = 9$), microdialysis sampling was performed in the NAc core, for the second group (1B; HFS, $n = 12$, controls, $n = 7$) in the NAc shell.

Fig. 1 PostMortem Histology. **a** Photomicrograph of a coronal section stained with *cresyl violet* and taken from a representative rat showing the tip of the electrode with respect to bregma as assessed by small insertion trauma. **b–g** Schematic reconstructions of electrodes in the STN of experimental animals of the following experimental paradigm: **b** Exp. 1: HFS, microdialysis in NAc core, **c** Exp. 1: HFS, microdialysis in NAc shell, **d** Exp. 2: HFS, microdialysis in VTA, **e** Exp. 3: HFS, microdialysis in NAc core/shell, preceding lesion of VTA, **f** Exp. 3: HFS, microdialysis in NAc core/shell, preceding lesion of SNc, **g** Exp. 3: HFS, microdialysis in VTA, no preceding lesion



STN-HFS and DAergic transmission in the NAc core

Two-way RM ANOVA revealed a significant difference across stimulation as well as time and a significant interaction between the factors stimulation/sham stimulation and time for DOPAC and HVA, but not for DA (Table in Fig. 2). STN-HFS led to a reversible and non-significant trend towards increasing extracellular levels of DA when compared to baseline and non-stimulated controls ($P > 0.05$; Fig. 2a). Furthermore, STN-HFS significantly and reversibly increased extracellular levels of DOPAC, and HVA when compared to baseline (DOPAC: $t = 0-40$ min; HVA: $t = 20-60$ min $P < 0.05$) and non-stimulated controls (DOPAC: $t = 0-60$ min; HVA: $t = 20-60$ min, $P < 0.05$; Fig. 2b, c).

STN-HFS and DAergic transmission in the NAc shell

Two-way RM ANOVA revealed a significant difference across stimulation as well as time and a significant interaction between the factors stimulation/sham stimulation and time for all parameters investigated, i.e., DA, DOPAC, and HVA (Table in Fig. 2). STN-HFS significantly and reversibly increased extracellular levels of DA, DOPAC, and HVA when compared to baseline (DA: $t = 0-60$ min; DOPAC: $t = 0-80$ min; HVA: $t = 0-100$ min; $P < 0.05$) and non-stimulated controls (DA: $t = 20-60$; DOPAC: $t = 0-120$; HVA: $t = 0-120$; $P < 0.05$; Fig. 2d–f). Maximal increases of extracellular concentrations of all parameters were

significantly more pronounced in the NAc shell than the NAc core (t -test, $P < 0.05$).

Experiment 2

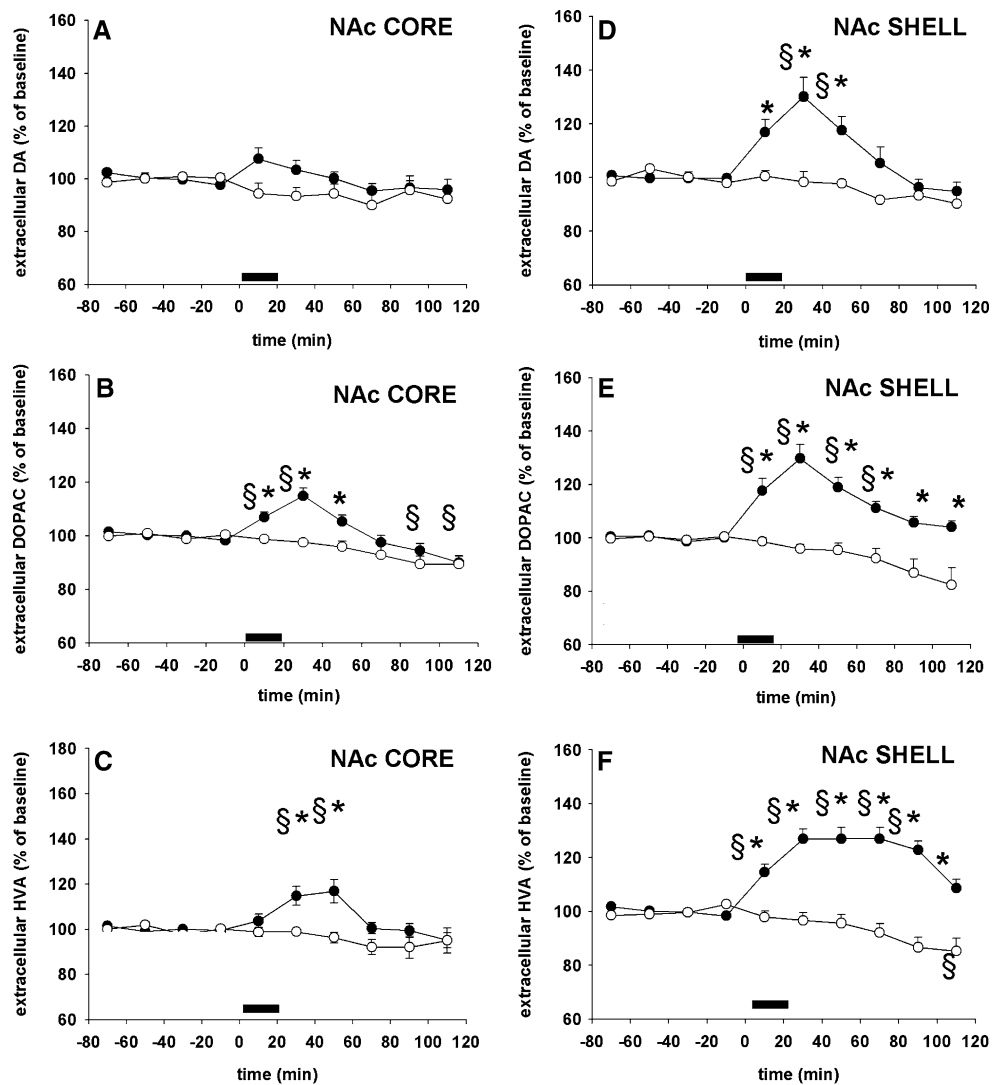
In 16 rats (HFS, $n = 8$; controls, $n = 8$) the effects of STN-HFS on extracellular contents of GABA in the VTA was investigated.

Two-way RM ANOVA revealed a significant difference across stimulation [$F(1, 84) = 52.68$; $P < 0.001$] as well as time [$F(6, 84) = 11.4$; $P < 0.001$] and a significant interaction between the factors stimulation/sham stimulation and time [$F(6, 84) = 3.4$; $P = 0.005$]. As shown in Fig. 4, STN-HFS significantly decreased extracellular levels of GABA in the VTA when compared to baseline and non-stimulated controls ($t: 0-120$, $P < 0.05$; Fig. 3). Notably, baseline values of HFS-stimulated and controls were not stable {ANOVA, HFS: [$F(3, 39) = 15.04$; $P < 0.05$]; controls: [$F(3, 39) = 11.825$; $P < 0.05$]}. The first stimulation value, however, was significantly different to the mean baseline and the last baseline value indicating that the drop in GABA following HFS did not represent the extension of a trend originating during baseline sampling, but was an independent finding.

Experiment 3

To investigate the involvement of the SNc and the VTA in mediating the potential effects of STN-HFS on DAergic

Fig. 2 Neurotransmission in the NAc under STN-HFS. **a–f** Extracellular DA (A + D), DOPAC (B + E), and HVA (C + F) in the NAc core (A–C) and NAc shell (D–F) before, during and after STN-HFS. Baseline concentrations of the NAc core were 21.15 ± 1.05 fmol DA/20 μ l, 14.36 ± 0.35 pmol DOPAC/20 μ l, and 8.57 ± 0.37 pmol HVA/20 μ l. Baseline concentrations of the NAc shell were 37.47 ± 3.17 fmol DA/20 μ l, 12.75 ± 1.08 pmol DOPAC/20 μ l, and 6.63 ± 0.40 pmol HVA/20 μ l. Baseline concentrations of DA, DOPAC, and HVA were significantly higher in the NAc shell than in the NAc core ($P < 0.05$). Data are expressed as mean \pm SEM. § $P < 0.05$ versus baseline, * $P < 0.05$ versus non-stimulated controls. The dead space in the microdialysis tubing is responsible for a lag time of 10 min before analysis. Filled rectangular: duration of HFS, filled circle: HFS of the STN, open circle: controls. The table below the figure describes the two-way ANOVA assessing the effect of STN-HFS and time on transmission of DA and its metabolites in the NAc. For further details see text



SUBSTANCE	SOURCE	NAc CORE			NAc SHELL		
		DF	F	p	DF	F	p
DA	stim	1,120	3.63	0.078	1,102	5.47	0.023
	time	6,120	2.17	0.054	6,102	4.7	< 0.001
	stim*time	6,120	1.88	0.094	6,102	2.34	0.039
DOPAC	stim	1,120	6.05	0.024	1,102	63.55	< 0.001
	time	6,120	18.52	< 0.001	6,102	4.67	< 0.001
	stim*time	6,120	4.33	< 0.001	6,102	3.06	0.008
HVA	stim	1,120	5.26	0.033	1,102	29.77	< 0.001
	time	6,120	8.16	< 0.001	6,102	11.86	< 0.001
	stim*time	6,120	4.8	< 0.001	6,102	10.2	< 0.001

neurotransmission in the NAc, 21 rats were subdivided into three groups depending on pre-treatment 2 weeks prior to microdialysis sampling and HFS: 6-OHDA lesion of the SNc ($n = 8$) versus 6-OHDA lesion of the VTA ($n = 8$) versus no lesion ($n = 5$). Microdialysis sampling was performed simultaneously in the NAc core and shell.

Immunocytochemistry

SNc-lesioning resulted in a $88.66 \pm 9.97\%$ reduction of TH positive nigral cells when compared to contralateral (control)

side (Fig. 4a–c). VTA-lesioning resulted in a $81.98 \pm 8.10\%$ reduction of TH positive VTA cells when compared to contralateral (control) side (Fig. 4b–d). Only animals were included, in which the SNc- or VTA-lesioning resulted in a loss of not more than 15 or 30% of TH expressing neurons in the adjacent VTA or SNc, respectively (Fig. 4b–c).

Microdialysis

Following VTA-lesion, DAergic metabolites remained below detection limit of the HPLC system applied, in all

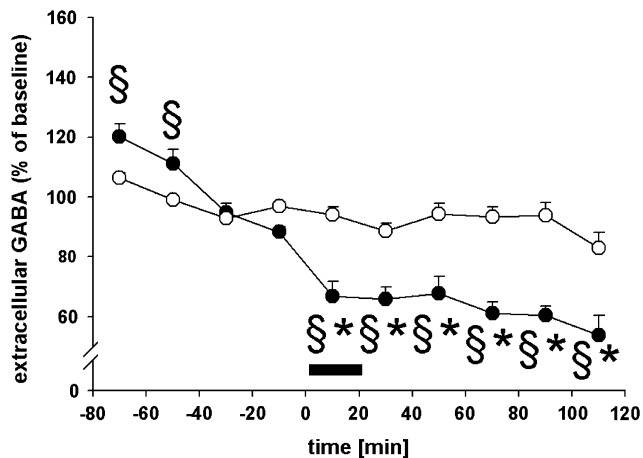


Fig. 3 Neurotransmission in the ventral tegmental area. Extracellular GABA in the VTA before, during, and after STN-HFS. Baseline concentrations of the VTA were 4.53 ± 0.38 pmol GABA/20 μ l. Data are expressed as mean \pm SEM. § $P < 0.05$ versus baseline. * $P < 0.05$ versus non-stimulated controls. The dead space in the microdialysis tubing is responsible for a lag time of 10 min before analysis. Filled rectangular: duration of HFS, filled circle: HFS of the STN, open circle: controls

animals investigated and under both, baseline and stimulation conditions. VTA-lesioned animals were consequently not included in further statistical analysis. For the control and SNc-lesioned animals, two-way RM ANOVA solely revealed a significant difference across time for both, DOPAC, and HVA (Table in Fig. 5). In unlesioned animals, STN-HFS significantly and reversibly increased extracellular accumbal levels of DOPAC and HVA when compared to baseline (DOPAC: $t = 0$ –80 min; HVA: $t = 20$ –100 min, Fig. 5a, b), reflecting what we have observed in experiment 1. Also, in SNc-lesioned animals, STN-HFS significantly and reversibly increased extracellular levels of DOPAC and HVA when compared to baseline, though the effects on HVA were less pronounced than in control animals (DOPAC: $t = 0$ –80 min; HVA: $t = 20$ –40, Fig. 5a, b). Notably, however, baseline concentrations of all parameters investigated were significantly lower in SNc-lesioned animals when compared to control animals ($P < 0.05$, Fig. 5).

Discussion

Main findings of the present study comprise: 1. HFS of the STN increases DA neurotransmission and metabolism in the NAc shell and partly also NAc core. 2. Lesions of the VTA but not of the SNc prevent the modulatory impact of STN-HFS on the DA-system of the NAc. 3. HFS of the STN decreases GABA in the VTA. These data suggest that activation of DAergic neurons in the VTA, possibly via

decreased inhibition of GABA, is largely responsible for the STN-HFS-induced increase in DA in the NAc.

The present animal findings indicate that STN-HFS modulates DAergic neurotransmission in limbic areas functionally interconnected with the STN. These data are selective for STN-stimulation at high frequencies as in an additional experiment we could not find any effect on accumbal DAergic neurotransmission following low-frequency stimulation (5 Hz) of the STN (Supplementary Fig. 1). The interconnections of the STN within the limbic basal ganglia-thalamo-cortical circuitry and the similarity between lesion and STN-HFS induced psychiatric effects in both, humans and rats (Absher et al. 2000; Hilker et al. 2004; Mandat et al. 2006; Stefurak et al. 2003; Temel et al. 2006; Trillet et al. 1995; Trost et al. 2006) suggest that the observed effects could be due to a specific action on the STN function. Yet, the present experimental design does not allow to differentiate, whether this effect is mediated by direct modulation of the STN or by current spread to adjacent structures (Ranck Jr. 1975). For instance, the STN is directly adjacent to the lateral hypothalamus (LH), which is highly interconnected with the NAc (DiLeone et al. 2003) and involved in the motivational aspects of behavior. Conceivably, current spread to passing fibers such as the medial forebrain bundle and/or adjacent brain areas such as the LH may potentially contribute to the effects of STN-HFS. In order to distinguish between direct HFS-dependent modulation of the STN activity from unspecific effects to neighboring brain areas and fiber tracts, the comparative investigation of different stimulation parameters (pulse duration, current intensity, and frequency), affecting the extent by which current spreads would be essential. Also an electrochemical method with higher temporal resolution, i.e., in vivo cyclic voltammetry (Lee et al. 2006), would allow more detailed temporal information about the coupling of STN-HFS and DA release. The aim of the present study was, however, much more modest, and restricted to test the possibility that HFS of the STN as used in the clinical situation may have effects on neurotransmission in relevant limbic areas, which may contribute to explain the limbic side effects observed in PD patients undergoing STN-HFS. Importantly, current may spread and affect neighboring brain areas and nerve fibers, both, in the animal experimental as well as in the clinical situation (McIntyre et al. 2004a; Stefurak et al. 2003). Conclusive studies on how exactly STN-HFS affects limbic brain function would ultimately require clinical postmortem anatomical reconstruction and computational modeling, which to date are largely missing.

Data from human (Filali et al. 2004; Welter et al. 2004) and animal studies (Benazzouz et al. 2004; Meissner et al. 2005; Salin et al. 2002; Tai et al. 2003) show that selective stimulation of the STN at high frequencies reduces the

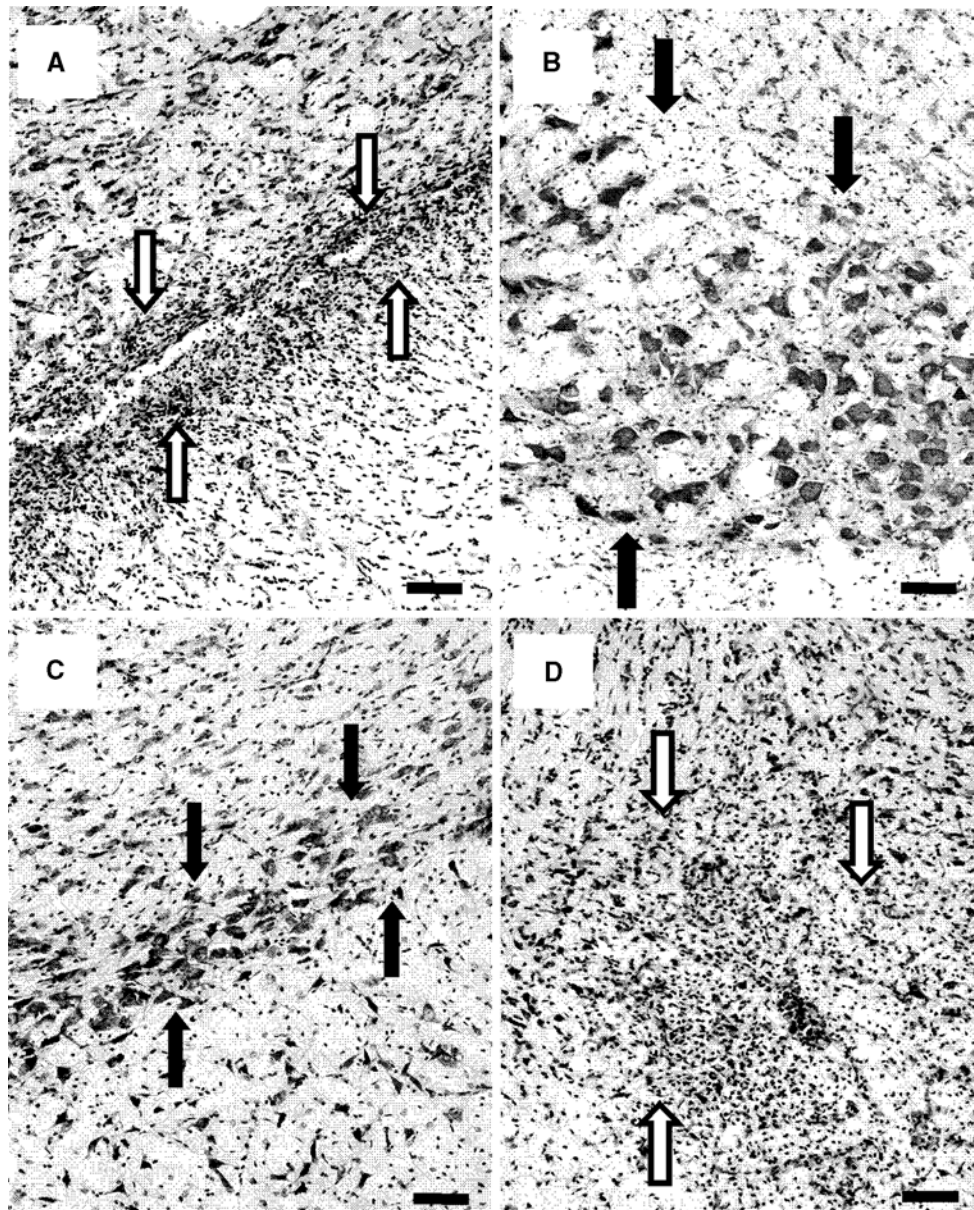


Fig. 4 Histological Verification of the lesion site. Microphotographs of cresylviolet stainings of the SNc (**a + c**) and the VTA (**b + d**). **a + b**: Exemplary microphotographs of a rat selectively lesioned in the SNc (**a**) with the VTA left intact (**b**). **c + d** exemplary microphotograph of

a rat selectively lesioned in the VTA (**d**) with the SNc left intact (**c**). Arrows mark boundaries of intact (*solid arrow*) and lesioned (*open arrow*) neuronal regions. Scale bar 100 μ m

activity of subthalamic neurons. In line with this hypothesis, similar behavioral effects of STN-HFS, STN lesion and pharmacological inactivation of the STN have been observed in both, PD patients and animal models of parkinsonism (Benazzouz et al. 1996; Darbaky et al. 2003; Deuschl et al. 2006; Levy et al. 2001; Limousin et al. 1995; Wichmann et al. 1994). Electrical stimulation is generally believed to excite nerve fibers rather than to directly act on cell bodies (Holsheimer et al. 2000; Nowak and Bullier 1998a, b). Consequently, the presumed inhibitory effect of STN-HFS might be due to a stimulation of presynaptic

GABAergic axon terminals. Provided that inhibition of STN neurons represents the main mechanism, STN-HFS could relieve the projection sites of the STN from their excitatory glutamatergic input and normalize the thalamocortical information flow. Furthermore, modulatory effects of STN-HFS on glutamatergic STN efferens have been suggested to contribute to STN-HFS efficacy (Hashimoto et al. 2003; Maurice et al. 2003; McIntyre et al. 2004b; Stefani et al. 2005; Windels et al. 2000).

The results of the present study concerning involvement of VTA and GABA on STN-HFS-induced modulation of

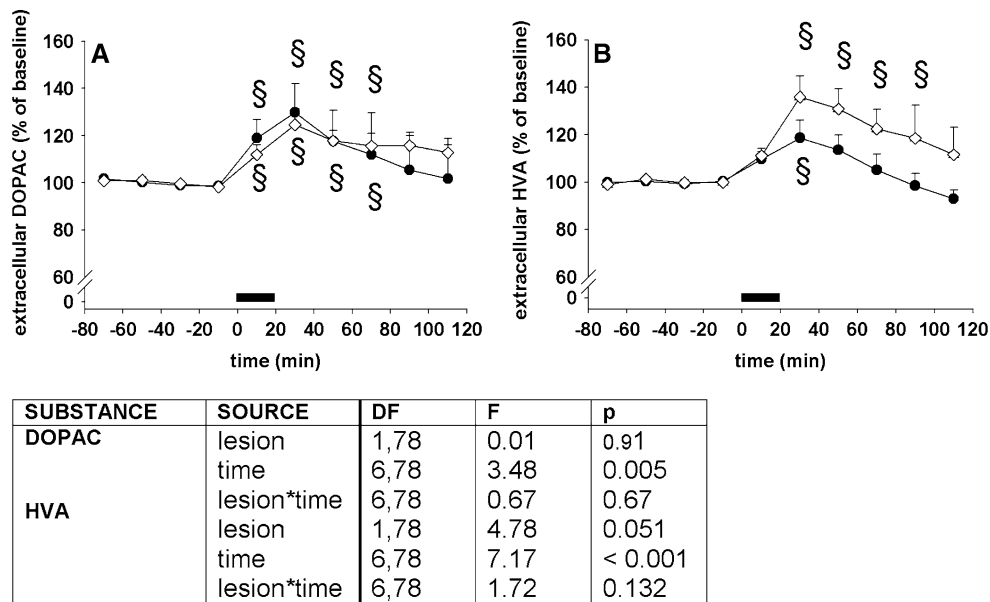


Fig. 5 Neurotransmission in the NAc of rats prelesioned in either the SNc. Extracellular DOPAC (a) and HVA (b) in the NAc before, during and after STN-HFS of control rats and rats lesioned in the SNc. Baseline concentrations of unlesioned control animals were 21.58 ± 1.82 pmol DOPAC/20 μ l and 11.17 ± 0.48 pmol HVA/20 μ l. Baseline concentrations of SNc-prelesioned animals were 7.39 ± 1.21 pmol DOPAC/20 μ l, pmol and 4.89 ± 0.53 HVA/20 μ l. Data are expressed as mean \pm SEM. §Significant difference in comparison to baseline ($P < 0.05$).

*Significant difference between lesioned and control HF-stimulated rats ($P < 0.05$). The dead space in the microdialysis tubing is responsible for a lag time of 10 min before analysis. Filled rectangular duration of STN-HFS, filled circle SNc-lesion, open diamond controls. The table below the figure describes the two-way analysis of variance assessing the effect of substantia nigra pars compacta lesion and time on subthalamic nucleus high frequency dependent transmission of dopamine metabolites in the NAc. For further details see text

DAergic neurotransmission in the NAc [i.e., (a) toxic prelesion of the VTA antagonizes the effects of STN-HFS on DAergic neurotransmission in the NAc; (b) STN-HFS decreases GABA in the VTA] comply with previously reported clinical and experimental data: Thus, converging data from neuroanatomical studies of animals suggest that the STN is directly and/or indirectly connected to the VTA and NAc (Bonci and Malenka 1999; Hamani et al. 2004; Woods et al. 2002). Furthermore, VTA DA-neurons project to the NAc (Groenewegen et al. 1999) and are under the control of inhibitory GABAergic VTA-interneurons (Ikemoto et al. 1997; Westerink et al. 1996). These GABAergic VTA-interneurons may receive some modulating glutamatergic input from the STN, as has previously been suggested by an in vitro study of glutamate effects on VTA neurons in slices (Bonci and Malenka 1999). Thus, STN-HFS might relieve VTA DAergic neurons from their inhibitory GABAergic tone by modulating the excitatory drive on VTA interneurons, finally resulting in increased levels of DA in the NAc. Further studies allowing a definite coupling of STN-HFS and GABAergic control of DAergic VTA-NAc projection are needed to prove this hypothesis.

The assessment of the presented baseline values of accumbal DA reveals a structure-dependent differentiation of the DAergic load in the NAc core and shell, with basal

DA levels being significantly higher in the NAc shell than in the NAc core. Interestingly, the HFS-dependent increases of DA and DA-metabolites were predominantly observed in the NAc shell; in fact, the increase of DA in the NAc core following STN-HFS failed to reach statistical significance. Ascending projections from the mesencephalon (A9 and A10) provide the DAergic innervation of the NAc, with the SNc (A9) projecting mainly to the NAc core and the VTA (A10) to the NAc shell (Groenewegen et al. 1999; Lindvall and Bjorklund 1974). Prelesions of VTA (A10) DAergic neurons lead to larger decreases in DAergic neurotransmission than prelesions of the SNc (A9). Anatomical differences might account for the quantitatively higher basal load and stronger effect of STN-HFS on DAergic transmission in the NAc shell when compared to the NAc core. Alternatively or additionally, different proportions of DA and its receptors in these subregions could be associated with the differential effects of STN-HFS-induced modulation of dopaminergic neurotransmission in the NAc shell versus core (Bassareo et al. 2002; Cadoni and Di 2000; Groenewegen et al. 1999; Ito et al. 2000).

Obviously, and as pointed out by two recent publications, STN-HFS dependent alteration in the DAergic neurotransmission of the NAc may not be the only way by which STN-HFS induces limbic effects: Accordingly, Mallet et al.

(2007) found in a recent clinical study PET activation of cortical and thalamic regions under STN-HFS which were paralleled by a hypomanic state in two parkinsonian patients. Furthermore, Baunez et al. (2007) found that STN-HFS had partly similar effects in a visual attention task in both naïve and bilaterally DA-depleted rats, suggesting that some STN-HFS mediated limbic and/or cognitive functions may be independent of an intact DA system.

In conclusion, the present study supplies *in vivo* evidence in rats for a functional interaction of the STN with the DAergic VTA-NAc projection. Previously, a STN-HFS dependent increase in striatal DA has been suggested to contribute to the acute reversibility of PD symptoms while DAergic medication can be reduced up to 50% under STN-HFS (Lee et al. 2004, 2006; Meissner et al. 2003) Likewise, the present STN-HFS dependent increase in accumbal DA in naïve and SNc-pretreated rats might present one possible explanation of some of the psychiatric effects of STN-HFS in PD.

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