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Mechanisms of High Frequency Stimulation of the Subthalamic Nucleus in Parkinson's Disease: From Local to Distal Effects on the Basal Ganglia Network

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1. Introduction

1.1 Parkinson's disease, basal ganglia and the value of the subthalamic nucleus as a treatment target

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting about 1% of adults over the age of 60 years (Samii et al., 2004). It is caused by a progressive loss of the dopaminergic neurons of the substantia nigra pars compacta (SNc) and of their axons, which project to the striatum (Ehringer & Hornykiewicz, 1960). Degeneration of the nigrostriatal pathway results in the development of the motor symptoms characteristic of the disease, including tremor, rigidity, postural abnormalities and bradykinesia. These cardinal signs of PD reflect striatal dopamine (DA) depletion, leading to the global disorganization of the activity of the basal ganglia (BG), a complex network of subcortical nuclei involved in the control and execution of motor behavior.

According to the classical model of BG organization (Albin et al., 1989; Alexander et al., 1990; DeLong, 1990), the interruption of dopaminergic transmission induces an imbalance between the activity of the two striatal circuits, the so-called 'direct' and 'indirect' pathways (Fig. 1). The activity of the inhibitory striatal neurons projecting directly to the substantia nigra pars reticulata (SNr) and the globus pallidus internalis (GPi), the direct pathway, is decreased. Conversely, the activity of the inhibitory striatal neurons projecting to the globus pallidus externalis (GPe) is increased, disinhibiting the activity of the subthalamic nucleus (STN), which projects excitatory glutamatergic neurons to the SNr and the GPi (indirect pathway). As efferent neurons of the SNr and GPi are GABAergic and are tonically active, this increase in indirect pathway activity results in an increase in the inhibitory output from the BG output structures to the thalamus and the thalamocortical neurons. The resulting reduction of cortical activation accounts for some of the signs of PD, such as akinesia (Albin et al., 1989; Bolam et al., 2000; DeLong, 1990; Obeso et al., 2008; Parent & Hazrati, 1995a, b). Based on this model and the results of others studies demonstrating the key role of the STN in controlling movement (Kita & Kitai, 1987; Kitai & Deniau, 1981; Smith et al., 1998), it has been suggested that the abnormal glutamatergic hyperactivity observed in the STN in the parkinsonian state plays a critical role in the expression of motor symptoms (Bergman et al.,

1994; Blandini et al., 1996, 2000; Carlsson & Carlsson, 1990; Hassani et al., 1996). Thus, it may be possible to restore equilibrium by decreasing STN neuronal output, through procedures such as lesioning or other manipulations (DeLong, 1990).

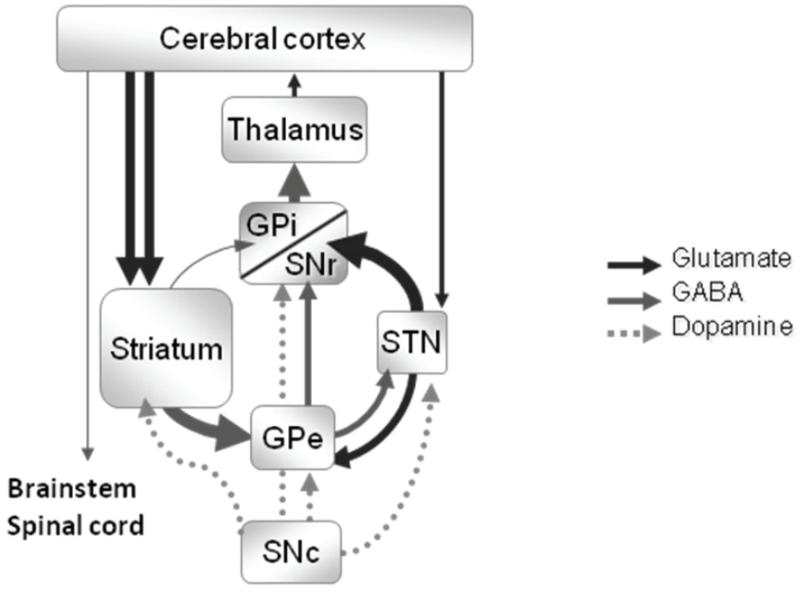

Fig. 1. Functional organization of the basal ganglia and classical pathophysiological model of Parkinson's disease. SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; GPe, globus pallidus externalis; GPi, globus pallidus internalis.

This hypothesis has been supported by several experimental studies in animal models of PD in which neurotoxic lesions (Aziz et al., 1991; Bergman et al., 1990) and pharmacological blockade of the STN (Levy et al., 2001) or the administration of glutamatergic (NMDA) antagonists (Greenamyre & O'Brien, 1991) are used to reduce motor impairments. These results obtained, together with the observation that the gold standard pharmacological treatment of PD - the daily administration of the DA precursor levodopa (L-DOPA) - induces severe side effects, such as motor fluctuations and dyskinesia after several years of use (Poewe et al., 1986; Rascol, 2000; Starr, 1995), have excited renewed interest in surgical approaches to PD treatment, with the STN as a target of choice. Surgical or accidental lesions of the STN in PD patients improve parkinsonian symptoms, including the tremor in particular, and are associated with a large decrease in the dose of L-DOPA required (Barlas et al., 2001; Gill & Heywood, 1997; Patel et al., 2003). However, such lesions may also result in permanent hemiballismus (for a review, see Guridi & Obeso, 2001). The behavioral effects of high-frequency stimulation (HFS) are usually similar to those of lesions of the structure stimulated. Futhermore, it has been demonstrated in a primate model of PD that STN-HFS improves parkinsonian motor symptoms (Benazzouz et al., 1993). This led to the initiation of clinical trials using STN-HFS for the treatment of PD (Limousin et al., 1995a, b).

Many studies on the efficacy of STN-HFS for the treatment of parkinsonian motor syndrome have since been carried out. STN-HFS has been reported to induce clinical improvement in both PD patients and experimental animal models, resulting in large decrease in L-DOPA requirement, and consequently decreasing L-DOPA-induced dyskinesia (Bejjani et al., 2000;

Benabid et al., 1998, 2000; Krack et al., 1998, 2003; Krause et al., 2001; Moro et al., 1999). STN-HFS is now widely agreed to be a powerful surgical option for the treatment of advanced PD. Nevertheless, despite its remarkable clinical efficacy, the precise mechanisms by which STN-HFS exerts its effects remain a matter of debate.

2. Mechanisms of action of subthalamic nucleus high frequency stimulation: inhibition or excitation?

2.1 The first hypothesis

As the functional effects of STN-HFS resemble those of STN lesion (Benazzouz et al., 1995), it was initially assumed that HFS inhibited STN neurons (Benabid et al., 2002; Dostrovsky & Lozano, 2002) via a depolarization-induced blockade of their activity, resulting in depression of the STN-driven BG output nuclei. This HFS-induced inhibition hypothesis was supported by several lines of experimental evidence, including slice recordings (Beurrier et al., 2001; Magarinos-Ascone et al., 2002), in vivo recordings in rodents (Benazzouz et al., 2000; Tai et al., 2003) and primates (Boraud et al., 1996) and recordings in human patients (Benabid et al., 1998; Filali et al., 2004). However, due to technical problems precluding recording during the stimulation period, most of these electrophysiological data were obtained immediately after STN-HFS was stopped. Furthermore, they concerned very short periods of stimulation (5 seconds to 1 minute).

These technical limitations, together with the work of Benazzouz et al. reporting the activation of 100% of GP cells immediately after STN-HFS cast doubt on the depolarization block hypothesis (Benazzouz et al., 1995). However, the first real challenge to the silencing hypothesis came in the form of neurochemical data obtained in normal anesthetized rats subjected to one hour of subthalamic stimulation applied with therapeutic parameters. These data showed that STN-HFS induced the release of glutamate in the SNr and entopeduncular nucleus (EP, the rat equivalent of GPi), two direct target structures of STN neurons (Windels et al., 2000, 2003). This effect, measured during stimulation, conflicted with the depolarization block hypothesis as it showed that STN neurons and their axons could be activated during HFS. Following technical improvements, these pioneering results were soon supported by electrophysiological recordings. In particular, data acquired in MPTP-treated monkeys showed that STN-HFS, when applied at parameters that decrease akinesia, changes the spontaneous irregular firing of STN target cells (GPe and GPi) to a high-frequency regular pattern of discharge time-locked to the stimulation and resulting in a significant increase in the mean discharge rate of both structures (Hashimoto et al., 2003). Another study in rats suggested that the activity of SNr cells was increased by the application of STN-HFS at a 'high' stimulation intensity (Maurice et al., 2003). However, although the authors described this intensity (300 μA) as 'high' based on a comparison with the other intensities used in their study (20-80 μA), it corresponds to intensities commonly used in rats. Finally, Garcia et al. showed that the application of HFS at clinical parameters drove the STN activity in rat slices in vitro, suppressing all types of spontaneous STN activity and imposing a new pattern of activity on STN neurons (Garcia et al., 2003). All these studies argue against the notion that HFS totally silences STN neurons, thereby reducing the excitatory input of basal ganglia output nuclei. However, these results are consistent with previous work showing that STN neurons are able to fire at much higher frequencies than 130 Hz, following current injections, suggesting that they are unlikely to

show a substantial depolarization block in the frequency range generally known to have therapeutic effects (Bevan & Wilson, 1999).

2.2 Sites of action within the brain

Many others neurochemical (Galati et al., 2006; Lee et al., 2007; Stefani et al., 2005; Windels et al., 2005), electrophysiological (Degos et al., 2005; Kita et al., 2005; Li et al., 2010; Shi et al., 2006) and functional imaging (Hilker et al., 2008) studies in both animal models and PD patients have generated apparently conflicting results on the effects of HFS on neuronal activities. Based on these observations, the impact of therapeutic STN-HFS cannot be limited to the simple blockade of STN neurons activity. Instead, it probably involves complex and distinct effects on the cell soma and axons, combining local inhibitory and excitatory effects and resultant distal effects.

2.2.1 Effects at the local level

A number of studies have revealed the complexity of the effects of HFS on STN neuron activity. Three main types of effects have been reported: 1) extinction or strong inhibition of neuronal activity 2) an increased in activity and 3) dual effects combining inhibition and the induction of high frequency bursts (Fig. 2).

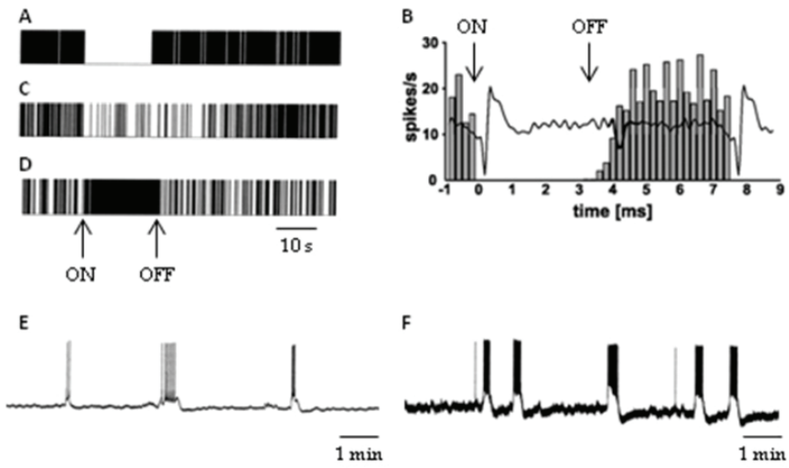

Fig. 2. Electrophysiological effects of STN-HFS at local level. Raster displays (A, C and D) and filter analogue recordings (B) representing a typical example of complete (*A and B*) and partial inhibition (*C*) or of excitation (D) in STN neurons during HFS of the STN. A, C and D modified from Tai et al. (2003), B modified from Meissner et al. (2005). E and F, control spontaneous bursting activity of STN neurons (E) and bursting activity of STN neurons (F) evoked by 10 minutes duration 185Hz HFS, modified from Garcia et al. (2003).

The inhibition and suppression of STN activity are the effects most frequently induced by stimulation in both animal models of the disease and humans (Fig. 2A, B and C). Indeed, while recording STN discharge during surgery in PD patients, both Welter et al. (2004) and Filali et al. (2004) reported the inhibition of activity in a significant number of STN neurons (50 to 75%), associated with a decrease in the mean firing rate of the cells. However, this decrease did not prevent residual neuronal activity, which persisted in 70% of the recorded

neurons and was associated in some cases with a change in the firing pattern (Welter et al., 2004).This change in firing pattern, although not systematically observed, may make an important contribution to the clinical effects of STN-HFS. Indeed, studies recording the activity of STN neurons activity in PD patients during clinically effective deep brain stimulation (DBS) have reported a change in discharge pattern, with about one half of the neurons originally classified as bursting or tonic firing neurons shifting to a random pattern during and after delivery of the stimulus train (Carlson et al., 2010; Walker et al., 2010). Inhibition of neuronal activity was also obtained in in vitro (Beurrier et al., 2001; Magarinos-Ascone et al., 2002) and in vivo studies. In rats, Tai et al. (2003) observed a significant decrease in firing rate or even the inhibition of most neurons during the stimulation, combined with a decrease in CoI mRNA levels. In non human primates, a substantial decrease in overall firing rate was also shown (Meissner et al., 2005). According to the authors, this decrease in mean firing rate can be accounted for by a pause in firing lasting several milliseconds after each pulse and resulting from the resetting of the firing probability of STN neurons to almost zero by the stimulus pulse (Carlson et al., 2010; Meissner et al., 2005). As the firing probability returned to baseline values 7 ms after the onset of the electrical stimulus, the overall decrease in mean firing rate resulted from the repetition of a dynamic process with a frequency of 130 Hz (inter stimulus interval 7.7ms) allowing the neuron to fire with its baseline firing rate only for a very short period. None of these studies addressed the issue of the mechanisms giving rise to this observed inhibition, but they clearly demonstrated that this phenomenon could not be due to a depolarization block of STN neurons as it was initially supposed. Another hypothesis can be put forward to account for this partial or total inhibition of STN neurons activity. STN neurons are glutamatergic, so the observed inhibition may result from the stimulation of extrinsic sources of synaptic inputs. The release of GABA following excitation of the GPe, the main GABAergic afferents in STN, is clearly one possible mechanism (Meissner et al., 2005; Tai et al., 2003) potentially accounting for these findings, including the short duration of inhibition observed after a single stimulus (Filali et al., 2004). Synaptic inhibitory processes of this type have major implications for the therapeutic mechanisms of STN-HFS as, unlike lesions and functional inactivation, they do not completely block the transmission of information through the STN. HFS seems to inhibit the activity of a clear majority of STN neurons, but some neurons in animal models of PD (Tai et al., 2003) and in patients (Walker et al., 2010) responded to stimulation by an increase in activity (Fig. 2D).These apparently conflicting findings are not necessarily inconsistent, as inhibition of the cell body does not preclude simultaneous excitation of the axon or even excitation of the cell body together with the inhibition of spontaneous firing. Indeed, computational modeling has shown that, despite the suppression of somatic neuronal activity during HFS, axonal stimulation may still occur within the STN at relatively high stimulation frequencies (McIntyre et al., 2004). This theoretical model is supported by the results of in vivo and in vitro studies. Using an enzyme-linked glutamate sensor, Lee et al. (2007) showed that HFS increased the extracellular concentration of glutamate in the STN of anesthetized rats, providing support for the notion that HFS can activate afferent axons of the STN. Glutamate within the STN may initially be excitatory. However, the post-synaptic effects of glutamate receptor activation are mediated by various glutamate receptors, including the AMPA and kaïnate ionotropic receptors. These receptors are rapidly desensitized in the presence of glutamate.

The prolonged increase in glutamate concentration induced by STN-HFS may eventually desensitize local AMPA/kaïnate receptors, thereby preventing any further spontaneous activity of STN neurons, despite continued electrical stimulation. However, it does not prevent the direct activation of the neuronal membrane. Consistent with these data and the hypothesized coexistence of simultaneous excitation and inhibition mechanisms within the STN level, Garcia et al. (2003) showed, in an in vitro study, that HFS has a dual effect at therapeutically relevant frequencies (80-185Hz); it entirely abolishes all types of spontaneous activity within the STN and generates a robust pattern of recurrent bursts of spikes, with each spike being time locked to a stimulus pulse, thus reflecting direct activation of the axon and back-firing of the soma (Fig. 2E and F). This HFS driven discharge of STN neurons has not been reported in vivo, but is fully consistent with earlier reports of antidromic activation elicited by HFS in the nuclei anatomically connected to the STN (Li et al., 2010; Maurice et al., 2003). It also provides an additional line of evidence that information transmission via the trans-subthalamic pathway is not completely blocked during STN-HFS.

These observations highlight the multiplicity of effects recorded at local level, which may differ considerably according to the experimental conditions. The electrical field generated by the clinical DBS electrode has been extensively modeled (Butson & McIntyre, 2006; 2008; Miocinovic et al., 2009). Estimation of the current density surrounding a microelectrode tip is more challenging, but currents in the range of 50 to 500 μA are used, yielding a current density one to two orders of magnitude greater than those obtained with a DBS electrode. The particular neural element activated depends on current density (Rattay & Aberham, 1993), so extrapolation from the effects of a microelectrode to DBS electrode stimulation may be erroneous. Furthermore, despite the major contribution of computational models to our understanding of how and where neural elements are affected by stimulation pulses, these models remain of limited value for predicting the full extent of the effects induced by DBS, as they do not take into account the intranuclear organization of connection fibers. Depending on the spatial arrangement of fiber paths and intranuclear connections, neurons located well beyond the limit of the efficient stimulating current may be influenced by fibers activated by the stimulating electrode. Finally, detailed knowledge of the organization of intranuclear fiber paths, the precise location of the electrode and the electric field it generates must be taken into account when trying to understand the mechanisms of action of STN-HFS.

2.2.2 Effects at distal level

By activating axons, STN-HFS may generate widespread and heterogeneous distal effects. Experimental support for this hypothesis is provided by the observation that therapeutic stimulation of the STN in PD patients and animal models of the disease induces a change in the activity of BG structures anatomically connected to the STN, including its main direct target structures, the SNr (Benazzouz et al., 1995; Boulet et al., 2006; Burbaud et al., 1994; Degos et al., 2005; Galati et al., 2006; Maltete et al., 2007; Maurice et al., 2003; Shi et al., 2006; Tai et al., 2003; Windels et al., 2000, 2003) and GPi (Burbaud et al., 1994; Hahn et al., 2008; Hashimoto et al., 2003; Kita et al., 2005; Reese et al., 2008; Shi et al., 2006; Stefani et al., 2005), GPe (Hahn et al., 2008; Hashimoto et al., 2003; Kita et al., 2005; Windels et al., 2000, 2003), striatum (Bruet et al., 2001; Hilker et al., 2003; Lee et al., 2006 ; Meissner et al., 2001, 2002; Strafella et al., 2003), cortex (Butson & McIntyre, 2008; Fraix et al., 2008; Kuriakose et al., 2009) and thalamus (Benazzouz et al., 2000; Dorval et al., 2008).

As already observed for local effects, the effects of STN-HFS on distal structures appear contradictory. The first electrophysiological studies on anesthetized rats focused on the activity of the principal BG output nuclei, the SNr and EP. They reported a decrease of neuronal activity and firing rate in these structures after (Benazzouz et al., 1995, 2000) or during (Burbaud et al., 1994) application of STN-HFS. Others recordings acquired in normal or parkinsonian animals and in humans confirmed and extended these initial findings (Kita et al., 2005; Maltete et al., 2007; Maurice et al., 2003; Tai et al., 2003).This inhibition was initially thought to result from the suppression of STN cell activity (Benazzouz et al., 1995, 2000). However, it is actually more likely to result from the activation of GABAergic inputs as it is blocked by the local iontophoretic application of bicucculine, a $GABA_A$ receptor antagonist (Maurice et al., 2003)and as STN-HFS induces GABA release in the SNr (Boulet et al., 2006; Tai et al., 2003; Windels et al., 2000, 2003) (Fig. 3A). Lesions of the GP completely abolished this increase in GABA concentration in the SNr, then suggesting that GP GABAergic neurons constitute a major source of GABA in the SNr and that the activation of the GABAergic pallido-nigral pathway by HFS-STN contributes to the effects of this treatment (Windels et al., 2005) (Fig. 3B).This activation may occur in different ways, given the connections of the GP (Kita, 2007): a synaptic activation of the pallido-nigral neurons via the glutamatergic subthalamo-pallidal projections, an axon reflex resulting from antidromic activation of the pallidal neurons projecting to both the STN and the SNr and/or a direct stimulation of the pallido-nigral axons in the STN.

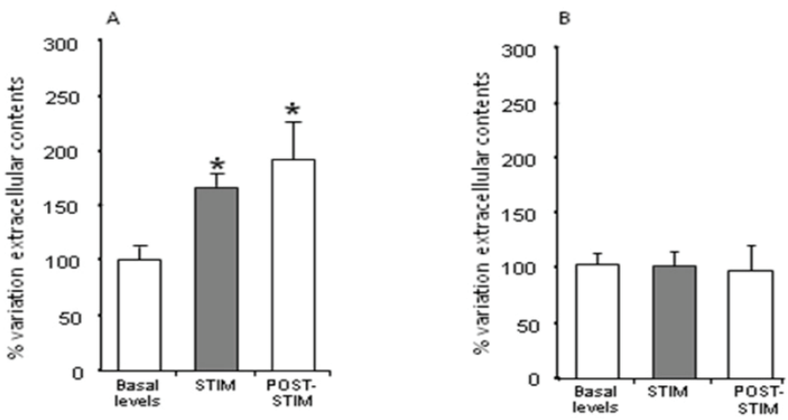

Fig. 3. Extracellular GABA levels determined before, during and after 1 hour STN-HFS in the ipsilateral SNr of 6-OHDA (A) or ibotenic acid GP plus SNc lesioned rats (B). Modified from Windels et al. (2005).

However, as shown by electrophysiological studies in rodents (Maurice et al., 2003; Tai et al., 2003), primates (Hashimoto et al., 2003; Kita et al., 2005) and PD patients (Hahn et al., 2008) and by functional MRI (Jech et al., 2006) and PET (Hershey et al., 2003; Perlmutter et al., 2002) studies in humans, STN-HFS can also increase the activity and the mean firing rate of basal ganglia output nuclei and the GPe. These excitatory effects, probably resulting from activation of the subthalamo-nigral and subthalamo-pallidal pathway, are not surprising as those axons are primarily glutamatergic (Kita & Kitai, 1987). The significant increase in extracellular glutamate concentration in the GP (Fig. 4A) and SNr (Fig. 4B) observed during

prolonged STN HFS in microdialysis studies (Boulet et al., 2006; Tai et al., 2003; Windels et al., 2000, 2003) and the latencies of the excitatory responses evoked in nigral cells by STN-HFS (Maurice et al., 2003) are consistent with this hypothesis. Nevertheless, the effect of STN-HFS on the excitatory influence of the trans-subthalamic pathway on SNr cells appears to be dependent on the stimulation intensity used. Indeed, increasing HFS intensity facilitates excitatory responses, as low-intensity HFS induces principally an inhibition in SNr cells and an increase in extracellular GABA concentration, whereas higher HFS induces excitation and an increase in extracellular glutamate concentration (Boulet et al., 2006; Maurice et al., 2003; Tai et al., 2003).

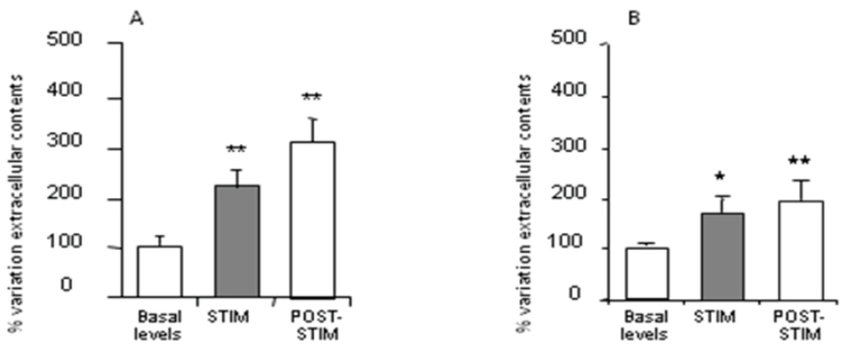

Fig. 4. Extracellular Glutamate levels determined before, during and after 1 hour STN-HFS in the GP (A) and SNr (B) ipsilateral to STN-HFS in normal (A) and 6-OHDA (B) rats. A, modified from Windels et al. (2000). B, modified from Boulet et al. (2006).

Finally, intracerebral microdialysis studies in rats have indicated that extracellular levels of both glutamate and GABA increase in the GPe and SNr during STN-HFS, suggesting a role for excitatory and inhibitory elements of the basal ganglia circuitry in the mode of action of STN-HFS (Windels et al., 2000, 2003). These results confirm the findings of electrophysiological studies showing that in anesthetized rats, the spontaneous firing of SNr cells either increases or decreases in the overall population of SNr cells (Degos et al., 2005). Similarly, almost equal numbers of excitatory and inhibitory responses were found in the SNr in a treadmill-locomotion task under behaviorally effective STN stimulation (Shi et al., 2006). In both cases, STN-HFS regularized the firing pattern of SNr cells (Degos et al., 2005) by subtle effects on both the inhibitory and excitatory BG pathways. STN-HFS preserves the inhibitory influence of the striatonigral pathway and, depending on its intensity, decreases or abolishes the excitatory influence of trans-subthalamic pathways on SNr cells. Thus, by decreasing the relative efficiency of the trans-subthalamic circuits, the STN-HFS introduces a bias between the direct and indirect trans-striatal circuits and restores the balance between the inhibitory and excitatory influences of the striatum and the STN, respectively, on SNr cells.

Given the ability of STN-HFS to stimulate axons, antidromically in particular, and the fact that the STN receives major inputs from the cortex and thalamus (Kita & Kitai, 1994), neuron activation and changes in excitability in deep cortical layers were expected, together with the damping of oscillation in the local field potentials observed during STN-HFS (Butson & McIntyre, 2008; Eusebio et al., 2009; Fraix et al., 2008; Jech et al., 2006; Kuriakose et al., 2009).

However, this cannot entirely account for the relationships between cortical antidromic activation and the impact of STN-HFS on cortical oscillations. This basis of relationships remains to be established, as STN stimulation may also affect the thalamo-cortical oscillators via antidromic activation of the thalamo-STN neurons and orthodromic activation of the subthalamo-cortical projections (Degos et al., 2008).

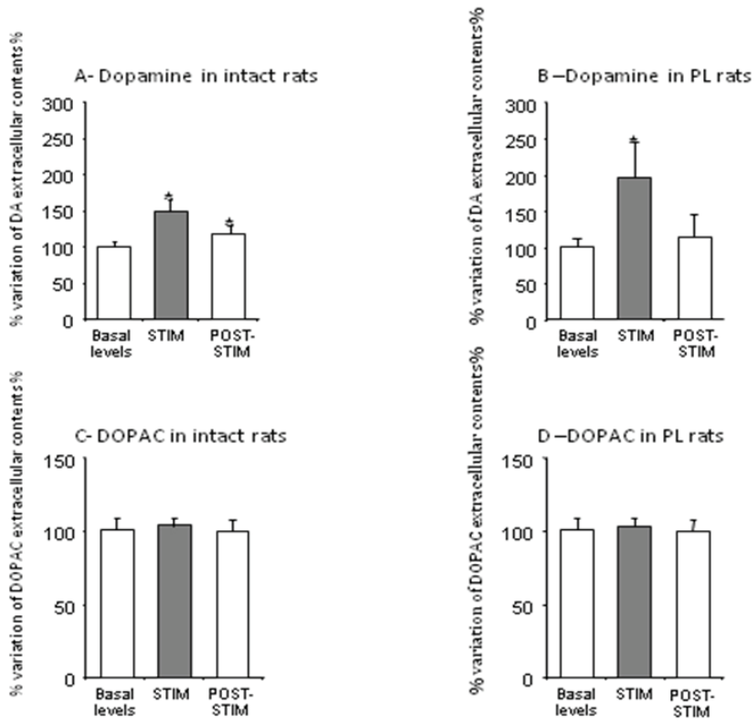

Fig. 5. Extracellular Dopamine (A and B) and DOPAC (C and D) levels determined before, during and after 1 hour STN-HFS in striatum of normal (A and C) and 6-OHDA (B and D) rats. Modified from Bruet et al. (2001).

Finally, variations in the extracellular concentrations of DA and its metabolites have been reported in the striatum of normal (Fig. 5A and C) and parkinsonian animals (Fig. 5B and D) during STN-HFS (Bruet et al., 2001; Meissner et al., 2001, 2002; Zhao et al., 2009). As STN sends direct projections to the striatum (Nakano et al., 1990) and STN-HFS improves all motor symptoms and allows a considerable reduction of dopaminergic medication in parkinsonian patients, it has been suggested that the therapeutic action of STN-HFS may depend partly on changes in striatal DA transmission. Unfortunately, these changes have not been confirmed in PD patients (Abosch et al., 2003; Hilker et al., 2003; Strafella et al., 2003) However, these human studies were carried out on parkinsonian patients on long-term L-Dopa treatment. The effects of this treatment on neuronal plasticity may account for the discrepancies between human and animal studies. The interactions between L-Dopa treatment and STN-SHF will be discussed below.

Over and above the multiple consequences of STN-HFS on distal BG structures, the way in which all these effects contribute to the therapeutic action of STN-HFS remains a key unanswered question.

2.3 Therapeutic effects of STN-HFS and functional considerations

An understanding of the therapeutic mechanisms of STN-HFS requires consideration not only of the local or distal changes in activity in the stimulated area, but also an evaluation of the changes in activity throughout the connected network. A detailed understanding of the neuronal mechanisms underlying the PD motor symptoms corrected by STN-HFS is required to obtain a complete answer to this question. PD is known to be associated with various changes in neuronal activity within the BG network, but the precise role of these changes in the expression of motor symptoms remains a matter of debate. Many possible hypothetical mechanisms of action of therapeutic STN-HFS have been put forward.

In normal conditions, the SNr exerts tonic inhibition on premotor nuclei in the thalamus and brainstem. During the preparation and execution of goal-directed movements (Sato & Hikosaka, 2002), GABAergic striatonigral neurons phasically inhibit SNr neurons, thereby causing disinhibition of their premotor target nuclei (Chevalier & Deniau, 1990). This disinhibition process requires SNr neurons to display regular, tonic activity in resting conditions. It has been suggested that the trans-subthalamic pathway regulates the amplitude of movements and participates in the selection of motor programs through its contribution to the spatiotemporal shaping of the striatal inhibitory signal (Mink & Thach, 1993). Alterations of these two processes by interruption of DA transmission is thought to generate parasitic noise in motor networks and disrupt the spatiotemporal shaping of the disinhibition process, leading to inappropriate motor commands (Boraud et al., 2002; Chesselet & Delfs, 1996; Pessiglione et al., 2005). In PD patients and experimental models of the disease, hyperactivity of the STN and its targets has been identified as a possible mechanism underlying motor symptoms (Albin et al., 1989; Alexander et al., 1990). Together with the clinical observation that the lesioning or inactivation of the STN is effective against PD symptoms, this idea may account for the beneficial effects of STN-HFS in PD, with this treatment first suppressing output from the STN and then counteracting the overactivity of the BG output structures, thus restoring the functionality of the premotor target nuclei. However, STN-HFS also activates the axons of STN cells, and the mean firing rate of GPi neurons has been shown to increase or to remain constant (Hashimoto et al., 2003; Reese et al., 2008). These findings and the observations that the degeneration of SNc dopaminergic neurons primarily affects firing patterns rather than the firing rate of the STN and the BG output neurons (Tai et al., 2003; Wichmann et al., 1999) and that the mean firing rate of STN (Carlson et al., 2010) and thalamic neurons (Pessiglione et al., 2005) is unaffected in PD patients and experimental models of PD, respectively, calls into question the relevance of firing rate per se to the pathophysiology of PD and the mechanism of STN-HFS.

An alternative explanation for the efficacy of STN-HFS is that this procedure reshapes the spatiotemporal structure of neuronal discharge, regularizing the discharge patterns of the STN and BG output nuclei rather than modifying their firing rates. There is experimental evidence to support this view, with the demonstration that the neurons of the STN and basal ganglia output nuclei originally display bursting patterns of firing, with a more regular pattern of pauses imposed by STN-HFS (Carlson et al., 2010; Degos et al., 2005; Dorval et al., 2008; Maltete et al., 2007). Interestingly normalization of the firing pattern of SNr cells was observed whether the cells were inhibited or excited (Degos et al., 2005). This highlights the possible contribution of both inhibitory and excitatory synaptic events to the regularization by STN-HFS of spontaneous discharge and the transmission of cortical information in BG circuits. Local inactivation may decrease the transmission of cortical information via the trans-subthalamic circuits, and this probably helps to restore the balance between the

inhibitory striatal input and the excitatory STN input to BG output structures. By reshaping the firing of SNr cells into a tonic and regular pattern and restoring the balance between the trans-striatal and trans-subthalamic pathways, STN-HFS restores the functionality of the disinhibitory mechanisms by which the BG contribute to the organization of movement (Degos et al., 2005; Kravitz et al., 2010).

In conclusion, as a whole, the body of data obtained during STN-HFS does not support the classical view that the therapeutic effects of STN stimulation are mediated by the immediate inhibition of surrounding neurons. Instead, the available data are more consistent with the alternative hypothesis that STN-HFS synchronously activates the surrounding fibers, thereby normalizing or 'jamming' the pathological activity in the BG-thalamocortical network.

3. Possible interactions between STN-HFS and L-DOPA treatment

Until 1960, the only possible approach to the treatment of PD was surgery, because no effective pharmacological treatment was available. The accuracy of this prestereotactic neurosurgery left much to be desired. The discovery in 1960 that dopamine was severely depleted in the basal ganglia of the brains of PD patients provided a springboard for a novel pharmacological concept involving the replacement of a deficient neurotransmitter to treat a degenerative neurological disease. Levodopa, the precursor of dopamine in the catecholamine synthesis pathway, became the practical choice for the development of an oral pharmacological agent, because it crosses the blood brain barrier (for conversion to DA within the brain), whereas DA does not. L-Dopa is a highly effective pharmacological treatment and is now widely used. PD motor symptoms initially respond well to L-Dopa. Subsequently, however, the response to this pharmacological agent declines, mostly due to the occurrence of signs of resistance to treatment and various adverse events, including motor response complications such as wearing-off, 'on-off' fluctuations and L-DOPA-induced dyskinesia (Fahn, 1974; Marsden & Parkes, 1976). The severity of this problem has reignited interest in the surgical approach, which has been rendered all the more interesting by the enormous advances made in recent years in the fields of stereotactic surgery and brain imaging. The discovery that HFS can mimic, in a reversible and adjustable manner, the effects of functional target ablation has revived functional neurosurgery for the treatment of movement disorders, making it possible to target particular areas identified as important through basic neuroscience, such as the STN (Aziz et al., 1991; Benazzouz et al., 1993; Bergman et al., 1990). In the first patients with PD treated by STN-HFS in 1993 (Limousin et al., 1995b), L-Dopa-sensitive symptoms, such as tremor, rigidity and bradykinesia, improved significantly, making it possible to decrease the amount of L-Dopa administered by a mean of 55 % (Krack et al., 2003). Several thousands of patients worldwide have since been fitted with STN-HFS implants and have displayed marked improvements in their symptoms, making this method the reference surgical procedure for advanced PD. Surprisingly, the time course of improvement differs for different cardinal symptoms of PD after the initiation of STN-HFS. Rigidity and resting tremor decrease immediately, within a few seconds after the onset of STN stimulation. By contrast, the amelioration of akinesia and the induction of levodopa-mimicking dyskinesia by STN-HFS generally does not occur until a few minutes, hours or weeks (Krack et al., 2000). These observations, together with clinical observations that the clinical improvement due to STN-HFS is strongly correlated with improvements in parkinsonian signs in a preoperative levodopa challenge test, raise

questions about a possible delayed increase in DAergic transmission in the striatum due to the stimulation current. This hypothesis is supported by experimental data from in vivo microdialysis studies showing that STN-HFS increases the amounts of DA and its metabolites in the striatal extracellular compartment in normal and parkinsonian rats (Fig. 5A and B) (Bruet et al., 2001; Meissner et al., 2001, 2002) and monkeys (Zhao et al., 2009), probably through the direct or indirect activation of DAergic SNc neurons. These neurochemical results seem to be consistent with previous electrophysiological and anatomical studies showing a large increase in neural firing in the SNc DAergic neurons of 6-OHDA-treated rats immediately after the start of STN-HFS (Benazzouz et al., 2000) and the existence of moderate numbers of glutamatergic efferents from the STN projecting to the SNc with NMDA receptors located in their dendrites (Groenewegen & Berendse, 1990). Furthermore, the increase in SNc DAergic neuron activity may be induced by the indirect disinhibition of GABAergic SNr neurons. This hypothesis is supported by electrophysiological data demonstrating that SNc neurons are massively under the control of GABAergic collaterals from the SNr (Grace & Bunney, 1979), SNr neurons being inhibited by STN-HFS (Benazzouz et al., 1995; Kita et al., 2005; Maltete et al., 2007; Maurice et al., 2003; Tai et al., 2003).The increase of striatal extracellular concentrations of DA and its metabolites observed in animal models of PD may result from a direct effect of glutamate on SNc DA neurons mediated by NMDA receptors and/or a polysynaptic pathway (Bruet et al., 2001).

Unfortunately, these findings and the hypothesis based on them were not confirmed by clinical studies investigating striatal DA release in PD patients by positron emission tomography (PET) with the ^{11}C-labeled reversible dopamine-D2/3-receptor ligand raclopride. Differences in raclopride binding between "on" and "off" STN-HFS conditions may reflect intervention-induced changes in endogenous transmitter release, because striatal raclopride binding levels are inversely related to DA levels in the synaptic cleft. The use of PET for assessing changes in synaptic DA levels in living humans is now a well established technique (Laruelle et al., 2000; Stoessl & Rivest, 1999). However, although STN-HFS proved highly effective in the patients tested, no significant differences in striatal raclopride binding were observed between the "on" and "off" conditions (Abosch et al., 2003; Hilker et al., 2003; Strafella et al., 2003). There are two probable reasons for the discrepancies between the results obtained for humans and animals: 1) clinical studies were performed on PD patients with chronic exposure to STN-HFS over a number of months whereas STN-HFS in animals reflects more acute effects; 2) the PD patients identified as candidates for STN-HFS have advanced disease and have been on chronic L-Dopa treatment for long periods of time, whereas the animals subjected to stimulation did not receive L-Dopa. Long-term dopatherapy induces a reorganization of the neuronal network, and all PD patients given STN-HFS have previously received L-Dopa treatment. Furthermore, STN-HFS has been reported to decrease motor fluctuations and levodopa-induced-dyskinesia (LID) in PD patients despite the continuation of levodopa treatment in most of these patients (Burchiel et al., 1999; Kumar et al., 1998; Limousin et al., 1998; Moro et al., 1999; Volkmann et al., 2001). It therefore makes more sense to consider the cumulative effects of L-Dopa plus STN-HFS, rather than the effects of STN-HFS alone. LID is thought to result from a combination of additional factors: the severity of dopaminergic brain lesions, as LID is not observed in normal individuals receiving therapeutic doses of levodopa, and the chronic pulsatile administration of high doses of levodopa, as LID is not observed in untreated patients and is more severe in patients treated with high doses of levodopa (Bejjani et al., 2000). As STN-

HFS allows two of these factors — high doses and the pulsatile administration of levodopa and dopaminergic agonists — to be significantly reduced, it would be interesting to determine whether the decrease in LID expression induced by STN-HFS reflects direct and specific functional effects of stimulation on the BG network or an indirect action associated with a decrease in the daily dose of levodopa. Indeed, paradoxically, given the decrease in LID observed after stimulation, STN-HFS may have a dyskinesia-inducing effect in some patients (Krack et al., 2003; Limousin et al., 1996; Volkmann et al., 2001) and in animal models of the disease (Boulet et al., 2006; Oueslati et al., 2007) if the voltage is increased, emphasizing the complex interactions between levodopa treatment and STN-HFS.

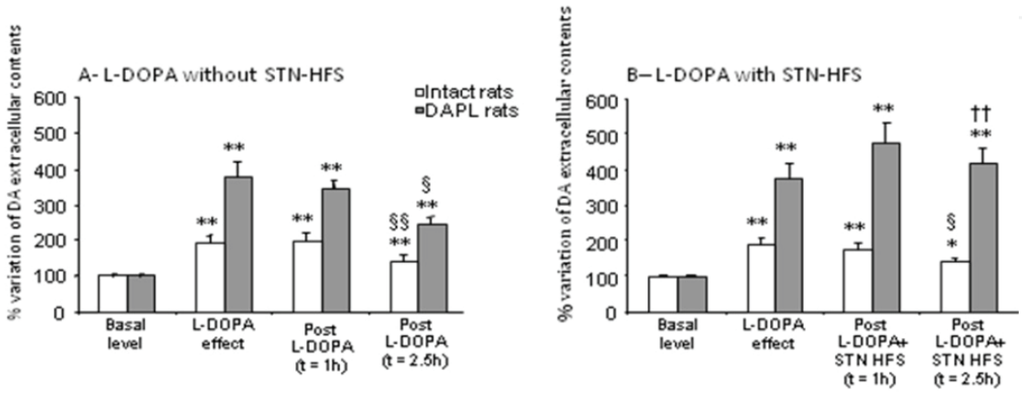

Fig. 6. Effects of L-DOPA alone (A) and L-DOPA plus STN-HFS (B) in extracellular concentration of dopamine in the striatum of normal and partially denervated rats. Modified from Lacombe et al. (2007). *p<0.05, **p<0.001: versus basal values; §: versus L-DOPA effect; †: versus no STN-HFS.

Several recent experimental studies have provided strong evidence that the striatum is a primary site of interaction between levodopa and STN-HFS (Gubellini et al., 2006; Lacombe et al., 2007; Oueslati et al., 2007). A microdialysis study on anesthetized rats with partial DA depletion showed that STN-HFS interacts synergically with levodopa-induced changes in striatal extracellular DA concentration, by stabilizing the levodopa-induced increase in striatal DA levels (Fig. 6A and B) (Lacombe et al., 2007). The authors suggested that this stabilization of striatal DA concentrations may be involved in the alleviation of levodopa-related motor fluctuations, such as the wearing-off phenomenon in particular (Nimura et al., 2005), as De la Fuente-Fernandez et al., (de la Fuente-Fernandez et al., 2001) showed that fluctuations in striatal synaptic DA concentrations precede the clinically apparent wearing-off phenomenon. Another study in 6-OHDA-treated awake rats demonstrated that STN-HFS did not alleviate and might even have prolonged LID and exacerbated LID-associated changes in the levels of several striatal markers, such as preproenkephalin (PPE) and preprodynorphin (PPDyn) mRNA (Oueslati et al., 2007). Despite the apparent difference in these results, STN-HFS potentiates the effects of levodopa rather than counteracting the modifications induced by dopaminergic treatment in both cases. This observation was supported by a behavioral study followed by in vitro patch-clamp electrophysiological recordings in brain slices of 6-OHDA-lesioned rats treated chronically with STN-HFS and dyskinesiogenic doses of L-Dopa. STN-HFS has been shown to abolish the striatal glutamatergic hyperactivity typical of parkinsonian rats and exacerbated by levodopa.

Surprisingly, this effect was paralleled by improvements in akinesia but not in LID (Gubellini et al., 2006). Although these experimental data seem at first sight to be consistent with the indirect improvement of LID by STN-HFS, a direct effect cannot be excluded, given the complexity of LID, which includes a number of phenomena, such as peak dose chorea, the on-off phenomenon, wearing-off fluctuations and off-period dystonia. The mechanisms underlying these types of LID are not well understood and, given the multiple effects of STN-HFS, it would not be surprising to find that STN-HFS has a direct effect on some types of LID, such as off-period dystonia, as suggested in a clinical study (Krack et al., 1999). By contrast, other types of LID, such as on-period dyskinesia, may be decreased essentially by the decrease in the daily dose of levodopa (Guridi et al., 2008) and still others, such as peak dose dyskinesia, may even increase, depending on stimulation status (Nutt et al., 2001). Thus, the improvement in LID mediated by chronic STN-HFS is probably multifactorial, resulting from both the stabilized functioning of the BG induced by STN-HFS and a decrease in the sensitization phenomenon caused by the chronic intermittent administration of high doses of levodopa (Bejjani et al., 2000).

4. Conclusions

The remarkable efficacy of STN stimulation for the treatment of PD is probably due to the nodal position of this nucleus, which concentrates connections with almost all the BG nuclei and the cerebral cortex into a small volume. In addition to local effects, STN-HFS generates system effects through the back-firing of afferent neurons and the activation of projection pathways from the stimulated nucleus. Clearly, when considered in the context of the total BG thalamo-cortical network, the combined effects of STN-HFS partly correct most of the defects in neural discharge thought to be responsible for the motor symptoms of PD. However, this correction is achieved through the imposition, by stimulation, of a particular pattern of activity on the network. The extent to whichsuch a controlled network retains the ability to encode information remains to be determined. Finally, many factors may influence the net effect of STN-HFS: the neurotransmitters released by the fibers stimulated, the intrinsic properties of the neurons, the axonal branching of the network. Thus, in contexts other than PD, an inability to limit the impact of stimulation to the stimulation site may be a disadvantage. This highlights the importance of defining a rationale for the choice of target in the broad range of neurological disorders for which HFS is a potential therapeutic tool.

5. References

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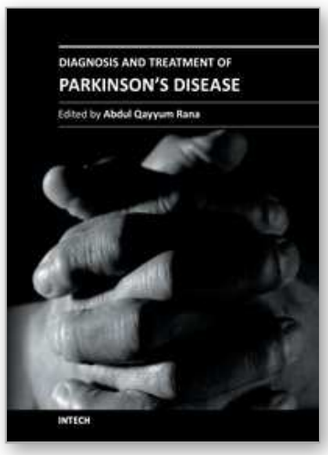

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Parkinson's disease is diagnosed by history and physical examination and there are no laboratory investigations available to aid the diagnosis of Parkinson's disease. Confirmation of diagnosis of Parkinson's disease thus remains a difficulty. This book brings forth an update of most recent developments made in terms of biomarkers and various imaging techniques with potential use for diagnosing Parkinson's disease. A detailed discussion about the differential diagnosis of Parkinson's disease also follows as Parkinson's disease may be difficult to differentiate from other mimicking conditions at times. As Parkinson's disease affects many systems of human body, a multimodality treatment of this condition is necessary to improve the quality of life of patients. This book provides detailed information on the currently available variety of treatments for Parkinson's disease including pharmacotherapy, physical therapy and surgical treatments of Parkinson's disease. Postoperative care of patients of Parkinson's disease has also been discussed in an organized manner in this text. Clinicians dealing with day to day problems caused by Parkinson's disease as well as other healthcare workers can use beneficial treatment outlines provided in this book.

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