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Reviews

Latest View on the Mechanism of Action of Deep Brain Stimulation

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Abstract: How does deep brain stimulation (DBS) applied at high frequency (100 Hz and above, HFS) in diverse points of cortico-basal ganglia thalamo-cortical loops alleviate symptoms of neurological disorders such as Parkinson's disease, dystonia, and obsessive compulsive disorders? Do the effects of HFS stem solely or even largely from local effects on the stimulated brain structure or are they also mediated by actions of HFS on distal structures? Indeed, HFS as an extracellular stimulation is expected to activate subsets of both afferent and efferent axons, leading to antidromic spikes that collide with ongoing spontaneous ones and orthodromic spikes that evoke synaptic responses in target neurons. The present review suggests that HFS interfere with spontaneous pathological patterns by introducing a regular activity in several nodal points of the network. Therefore, the best site of implantation of the HFS electrode may be in a region where the HFS-driven activity spreads to most of the identified, dysrhythmic, neuronal populations without causing additional side effects. This should help tackling the most difficult issue namely, how does the regular HFS-driven activity that dampens the spontaneous pathological one, restore neuronal processing along cortico-basal ganglia-thalamo-cortical loops? © 2008 Movement Disorder Society

Key words: DBS; electrophysiology; antidromic spikes; Parkinson; dystonia; OCD

Deep brain stimulation at high frequency (HFS) has the potential to provide substantial benefit for various neurologic and neuropsychiatric diseases. HFS is an intracerebral, extracellular stimulation consisting of short pulses (in the order of 100 μs) regularly applied at a frequency of at least 100 Hz over a period of several years. First observed to alleviate tremor in ventral thalamus and pallidum,[1] HFS is now widely used in ventral thalamus for essential tremor,[2] in the internal pallidal segment (GPi) or subthalamic nucleus (STN) for Parkinson's disease (PD),[3–5] in the GPi for generalized dystonia,[6,7] and more recently for other diseases such as treatment-resistant obsessive compulsive disorder (OCD),[8,9] Tourette syndrome,[10,11] and depression.[12] Sites of stimulation are located inside the cortico-basal ganglia-thalamo-cortical loops, in motor or limbic regions, depending on the clinical signs.

Two major and nonexclusive explanations have been proposed for the effect of HFS: (1) it silences stimulated neurons and (2) it introduces a new activity in the network. The first theory stems from the observation that, functionally, HFS produces the same effect as a lesion of the stimulated area. The second hypothesis proposes that HFS injects in a point of the circuit a HFS-driven activity that propagates and consequently modifies the pathological spontaneous activity in many nuclei. The clarification of the mechanisms of action of HFS is imperative to avoid implanting electrodes in regions having a low impact on clinical signs and/or leading to activation of undesirable regions and incapacitating side effects. In this review, we focus on results obtained within the last 4 years from multiunit and single cell electrophysiological recordings.

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MECHANISMS OF STN-HFS IN THE CASE OF PARKINSON'S DISEASE

Increased synchronization and the appearance of pathological oscillations in the activity patterns of populations of STN and GP neurons but also in motor cortical networks are salient aspects of Parkinsonism. Pathological synchronization has been observed in human PD patients,[13] 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys[14] and rodents with 6-hydroxydopamine (6-OHDA) lesions,[15] suggesting functional alterations in the basal ganglia network. In particular, increased coherence in the β-band (13–30 Hz) is correlated with the severity of symptoms in humans.[16–18]

Mechanisms of STN-HFS have long been reduced to a lesion-like or inhibition hypothesis until biochemical, metabolic, and electrophysiological data in experimental models and patients together with modeling studies[19–23] provided consistent evidence in favor of an activation.

Basal ganglia are made up of different neuronal populations scattered in five different nuclei (see Fig. 1): caudate and putamen (striatum in rodents), globus pallidus (external and internal), subthalamic nucleus (STN), and substantia nigra pars reticulata (SNr) and compacta (SNc). The degeneration of the dopaminergic neurons of the SNc and the consequent loss of dopamine in the striatum leads to "typical" PD. STN neurons occupy a strategic position as they are the only glutamatergic neurons of the basal ganglia network, receive afferents from motor-related cortical areas, project to all nuclei of the basal ganglia (though to a lesser extent to striatum), and are reciprocally connected with GPe and brainstem neurons of the pedunculopontine nucleus (PPN).[25] Therefore, STN stimulation may activate diverse pathways and have widespread effects.

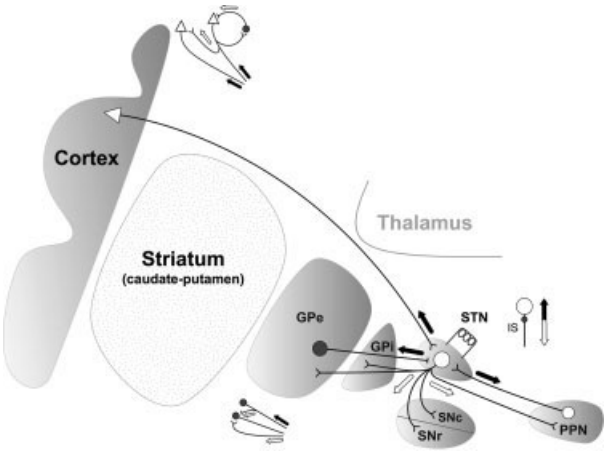

FIG. 1. STN and the basal ganglia network STN-HFS preferentially activates axons thus generating spikes that propagate in the antidromic (toward STN, motor cortex, GPe and PPN somas) and orthodromic (toward GPe, GPi, SNr, SNc, PPN) directions. Passing fibers can also be activated. As a result, basal ganglia nuclei such as SN and GP together with motor cortical areas are directly affected by STN-HFS. The striatum is mainly indirectly affected via the modulation of dopaminergic SNc neurons and cortical afferents. When antidromic spikes propagate back to a structure, they may invade somas and axon collaterals and thus activate other projection neurons and local interneurons when they exist. Insets show simplified cortical[24] (top) and GPe (bottom) networks. ▩, neuronal populations directly affected by STN-DBS; □, neuronal populations indirectly affected by STN-DBS; ⟶, antidromic activation of axons, ⟹, orthodromic activation of axons; ⊸, GABAergic neuron; ⊸, glutamatergic neuron.

Preparations, Parameters of Stimulation, and Excitation of Neural Elements

Different types of preparations have been used to study HFS mechanisms from anesthetized in vivo models of PD to in vitro slices. Recordings have been performed in patients as well. Each preparation has its own advantages and pitfalls, but their combination should allow understanding HFS mechanisms as long as we are aware of the limitations of the technique used. In this review, HFS refers to high frequency stimulations in vivo and in vitro.

The question of the mechanisms of action of HFS relies on the analysis of what does a high frequency and long duration stimulation of neuronal elements (HFS is applied for years). Electrophysiologists are used to study potential changes in response to single stimulations but here the question is far more complex mainly for technical reasons as recordings have to be maintained for minutes or hours and spikes identified among artifacts. If all studies on HFS mechanisms test high frequency (100–180 Hz) stimuli, they rarely apply them for long durations. Considering synaptic plasticity (potentiation or depression) that usually occurs in synaptic transmission after tetanic stimulation,[26] ultrashort (ms, s) and long (days, years) duration stimulations could evoke very different responses. Even though some of the symptoms are immediately improved,[27] when describing the electrophysiological effects of STN-HFS one must keep in mind whether it is a short- or a long-term effect. To compare results from different studies, intensity of stimulation is not as informative as charge density ($\mu C/cm^2$/phase).[28] This parameter depends on the diameter of the stimulation electrode or contact and is not always available from papers. For this reason, the value of current intensity is not mentioned. All protocols use short pulses (60–200 μs) of stimulation. Since cell bodies and axons have different chronaxies (chronaxy is the shortest duration of an effective electrical stimulus having a strength equal to twice the minimum strength required for exci-

tation), this value is used to determine which neural elements are excited by HFS. Cell bodies have chronaxies in the 1- to 10-ms range, large myelinated fibers have chronaxies in the 30- to 200-μs range, and small myelinated fibers have chronaxies in the 200- to 700-μs range.[29] For example, chronaxies for tremor reduction by HFS were estimated to be ~65 μs for thalamic and around 75 μs for pallidal stimulation,[30] suggesting that HFS targets large myelinated axons.

Is STN-HFS Noxious to STN Neurons?

Before analyzing the electrophysiological effect of STN-HFS, the first point to verify is the extent of STN lesion due to the chronic presence of the electrode and chronic application of HF stimulation. The classical Medtronic electrode was implanted in one STN in control or MPTP-treated monkeys, and the stimulation continuously applied for 7 months (pulses at 130 Hz, 60-μs duration). Cell counts performed in Nissl-stained coronal sections of the STN showed that the STN having the implant had only 5% difference in total cell number when compared with the side that did not have the implant.[31] Therefore, the chronically implanted electrode does not induce local degenerescence and the beneficial effects of STN-HFS are not mediated by a lesion of the STN as already suggested by human postmortem studies, which indicate little tissue damage associated with chronic HFS.[32]

Does STN-HFS Lock the Electrophysiological Activity of STN Neurons to Harmonics of the Stimulation Frequency?

Studies of the effect of STN-HFS locally on STN neurons gave the most controversial data. This probably results from the difficulty to separate the very short latency evoked spikes from the stimulation artifacts or as we will see later on the difference between cell body and axonal activity in some conditions. Benazzouz's group recorded inhibition of STN neurons during STN-HFS in 6-OHDA rats[33] but recently described that this inhibition only lasted 4 ms after each stimulus when the interval between two stimuli was fixed at 7.7 ms (130 Hz).[34] In patients, STN-HFS of short durations decreased STN neurons activity[35] and changed the firing pattern of some STN neurons.[36] Mechanisms underlying these observations have not been identified.

In slices, STN activity is very low when compared with that in vivo and does not show the pathological alterations resulting from dopamine depletion probably because the basal ganglia network is absent in coronal slices. Slices have however the advantage of allowing intracellular recordings and precise analysis of the correspondence between stimuli and spikes. In our experiments, STN spontaneous spikes disappeared during STN-HFS and were replaced by spikes evoked by and locked to stimuli (Fig. 2A). The STN firing pattern under HFS consisted of trains of evoked spikes in the γ-range frequency.[22,40] Interestingly, the fixed latency of HFS-driven spikes (close to 0 ms), the presence of the initial segment-somatodendritic (IS-SD) break in some of the recordings (Fig. 2A right), and the lack of effect of blockers of synaptic transmission, all strongly suggested that HFS directly activated the STN neuronal membrane at the level of their cell body, initial segment or first Ranvier node (Fig. 1A, inset STN). HFS-evoked spikes by colliding with orthodromic, spontaneous ones that had a lower frequency in slices, suppressed STN spontaneous activity in the activated STN neurons. Once HFS is turned off, STN neurons become silent during several seconds for two reasons: they are no longer excited by the electrical stimuli and their intrinsic voltage-dependent currents, in particular the persistent Na^+ current, are blocked.[41] Then, after a variable delay, this blockade resumes and the STN neuronal membrane can again autogenerate spikes and display its characteristic pacemaker activity.

One possible explanation for the controversial results obtained in vivo and in vitro is that action potentials evoked in axons by local HFS, inefficiently invade cell bodies in the antidromic direction due to geometric ratio. HFS would therefore lead to active axons and silent somas.[42,43] Since extracellular microelectrode recordings are biased toward recording action potentials from cell bodies rather than axons, this would result in the appearance of decreased activity within the stimulated structure though efferent axons are excited (see discussion in Ref. 39). In contrast, intracellular or juxtacellular recordings record axonal spikes evoked at the level of the initial segment (IS spikes, Fig. 2A middle) and higher intensities of stimulation would compensate for the geometric ratio.

Does STN-HFS Antidromically Activate Afferent Neurons to the STN?

A stimulation applied in a nucleus may activate afferent axons and give rise to antidromically propagating spikes. Antidromic propagation refers to the propagation of axonal spikes from their point of initiation close to the stimulating electrode, toward cell bodies, i.e., in the direction opposite to physiological spikes that propagate in the orthodromic direction toward

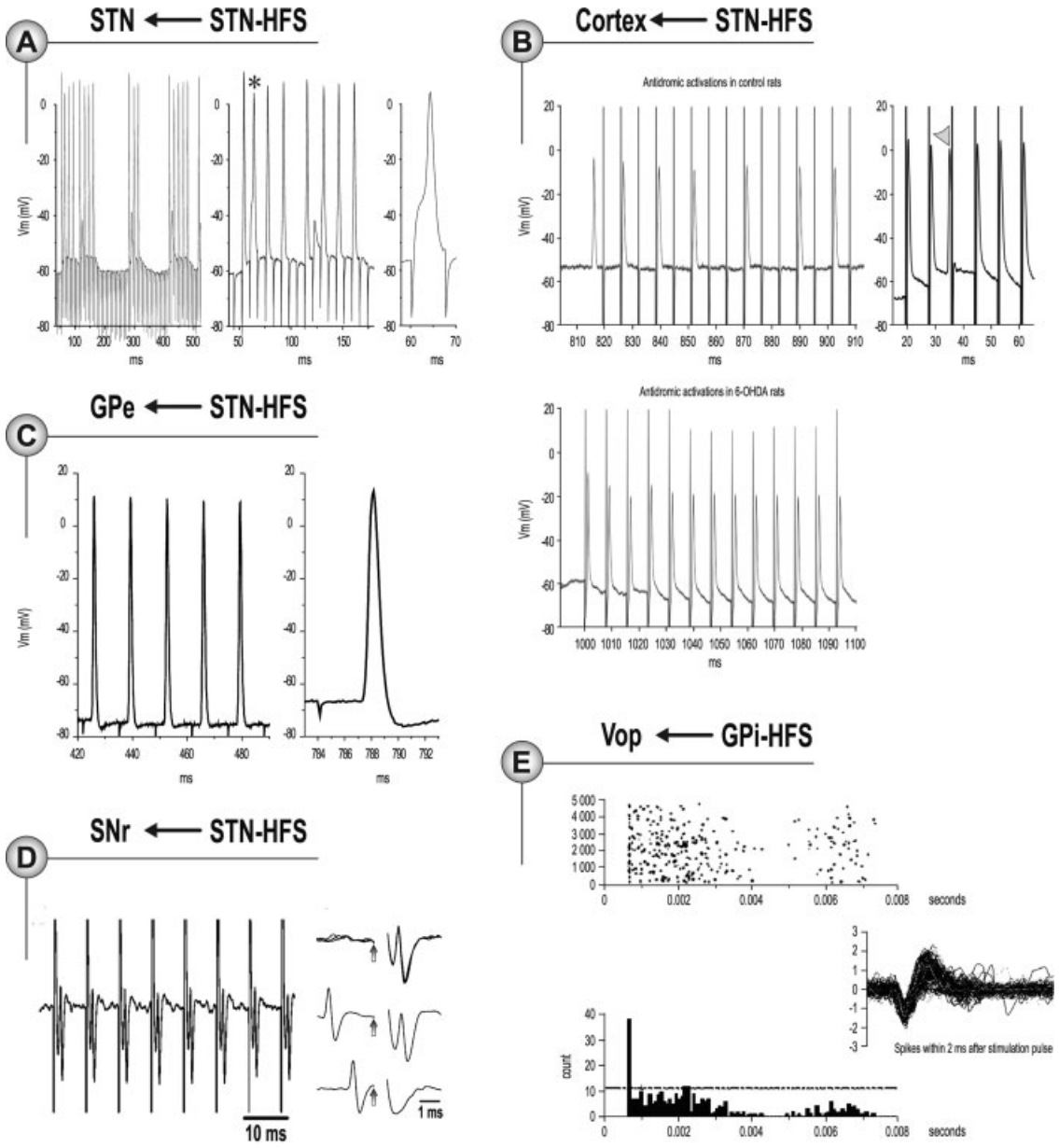

FIG. 2. HFS-driven antidromic spikes. (**A**) Local activation of STN neurons in response to STN-HFS (note IS spike at t = 120 ms, middle and IS-SD break, right) (Garcia et al., unpublished figure) and antidromic invasion of (**B**) motor cortical neurons in response to STN-HFS (arrow head indicates collision, right),[37] (**C**) GPe neurons in response to STN-HFS (Ammari et al., unpublished data), (**D**) SNr neurons in response to STN-HFS (note collision, bottom trace, right),[38] and (**E**) Vop thalamic neurons in response to GPi-HFS (poststimulus raster plot, top, histogram, bottom, antidromic spikes, right).[39]

axon terminals. STN-HFS thus evokes antidromic spikes in cortico-STN and GP-STN axons (see Fig. 1). But antidromic excitation of cortical and GP neurons may not be very efficient. For example, whereas the fast conducting branches in the highly myelinated brainstem region follow HFS, the slower conducting fibers in the poorly myelinated thalamic region fail to transmit consecutive antidromic spikes and maintain a steady low-frequency (6–12 Hz) spike output during the stimulation.[43]

Because of this low probability of antidromic invasion of somas, antidromic spikes are usually evoked in a subset of afferent neurons only. So, a subset of layer V/VI neurons of motor cortex that project to STN[44] displayed antidromic spikes (latency around 2 ms) whose frequency decreased with time to a steady state

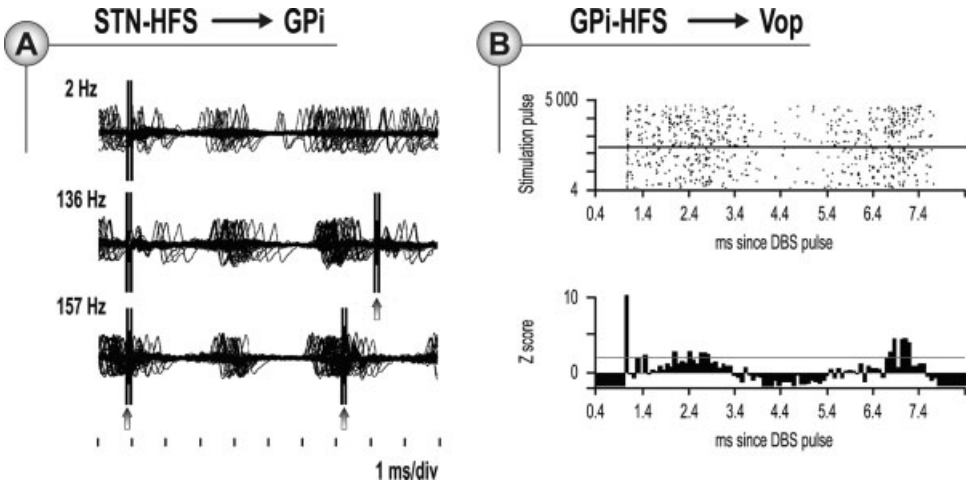

FIG. 3. HFS-driven orthodromic responses. Orthodromic responses of (**A**) GPi neurons in response to STN-HFS (complex sequence of excitation-inhibition-excitation),[23] (**B**) Vop thalamic neurons in response to GPi-HFS (antidromic activation followed by a complex sequence of excitation-inhibition-excitation, poststimulus raster, top, and histogram, bottom).[39]

at around 40 Hz in response to 120 Hz STN stimulation[37] (Fig. 2B). Recordings of short latency evoked potentials over the motor cortex during STN-HFS also indicated that cortico-STN axons were most likely activated.[45] As glutamatergic cortico-STN neurons give off many axon collaterals in deep and superficial layers[46] that contact other projection neurons and local GABAergic interneurons, antidromic invasion of a subset of neurons may retrogradely affect cortical circuits in complex ways (Fig. 1, inset cortex).[47]

STN-HFS in slices (130 Hz, 90 μs) evoked antidromic spikes in a subset of GPe neurons with a mean latency of around 2 ms (Fig. 2C) that collided with the ongoing activity in the recorded neurons. If antidromic spikes propagate in the complex network of local GABAergic collaterals that synapse onto other GP neurons, this may have consequences on the activity of neighboring GP neurons[48] (Fig. 1, inset GP).

STN-HFS also activates axons passing through and near the STN. Thus short STN-HFS (130 Hz, 60 μs, 30 s trains) in control rats in vivo antidromically activated a subpopulation of SNr neurons with a latency of around 1 ms,[38] probably as a result of the activation of ascending SNr axons. This decreased the spontaneous activity of the antidromically activated SNr neurons and inhibited other SNr neurons as shown in recordings[38] probably via the activation of the complex network of intranigral collaterals between GABAergic SNr cells.[49]

In conclusion, STN-HFS antidromically activates subsets of neurons in the different nuclei that send axons to or close to the stimulated site. In that context, STN-HFS probably also antidromically activates PPN neurons that project to STN.[50,51] Once evoked, antidromic axonal spikes propagate to their corresponding cell bodies at the stimulation frequency or its subharmonics. They may also propagate in recurrent axonal collaterals and activate synaptic transmission that impinges onto other projection neurons (GP, SNr) or local interneurons (see Fig. 1, insets cortex and GPe). The overall result on a network needs to know the probability of propagation of antidromic spikes in axonal branches[47] and how these spikes evoke synaptic responses at a long term.

Does STN-HFS Orthodromically Activate Target Neurons of the STN?

From their point of initiation, axonal spikes also propagate in the orthodromic direction toward axon terminals, i.e., along STN efferent axons (see Fig. 1). Do these spikes evoke postsynaptic responses? STN-HFS parameters that improved spontaneous movements and muscle tone (130, 210 μs, 25 s–5 min) in MPTP-treated monkeys evoked stimulus-locked double excitatory responses at latencies around 4 and 6 ms in the globus pallidus (GPe and GPi)[23] (Fig. 3A). It thus shifted the firing pattern of GPe and GPi neurons from irregular to stimulus-synchronized. The most probable mechanism underlying the earlier excitation is the orthodromic activation of STN efferent axons projecting to GP, the release of glutamate and the monosynaptic excitation of postsynaptic GPe or GPi neurons. In contrast, in control monkeys, bursts of 100 Hz stimuli (10 pulses) induced powerful excitatory responses in the GPe but inhibition in the GPi attributed to the activation of the disynaptic STN-GPe-GPi pathway.[52]

Does STN-HFS similarly affect GP and SNr neurons? Deniau's group studied the spontaneous and evoked SNr activity before and during STN-HFS in control rats or rats treated with neuroleptics to block dopaminergic transmission. In control rats, STN-HFS (130 Hz, 60 μs, 30 s) evoked antidromic spikes and

inhibition as previously seen but also orthodromic spikes (excitation) in SNr neurons.[38] The short latency excitation is likely to result from the orthodromic activation of the excitatory STN-SNr glutamatergic axon terminals. In cataleptic rats, at parameters that reversed the catalepsy (130 Hz, 60–80 μs), STN-HFS regularized the pattern of discharge of SNr neurons as it significantly decreased the number of neurons exhibiting burst discharges and reduced the number of bursts emitted by bursting neurons.[63] In PD patients under surgical procedure, at parameters (130 Hz, 60 μs) that induce clinical improvement of rigidity and finger tapping, STN-HFS increased mean spike frequency of SNr neurons and evoked short latency (4 ms) excitatory responses. Autocorrelograms demonstrated the presence of a periodic spiking at 130 Hz. In parallel, the firing pattern changed from irregular to a "grouped" pattern consisting of groups of spikes separated by longer periods of pauses.[53] In another study in patients, STN-HFS (140 Hz, 60 μs) evoked in SNr neurons a three-phase sequence, inhibition (0–2 ms)-excitation (2–4 ms)-inhibition (4–7 ms) after the stimulation pulse. There was a 51% decrease in the percentage of the spikes contributing to bursts and a 70% decrease in the mean duration of bursting mode activity.[54]

Therefore, STN-HFS in some GP and SNr neurons replaces the "pathological" activity encoded by the basal ganglia during PD by a stimulus-driven firing pattern. This new activity would result, at least in part, from the activation of STN efferent fibers. The multiphasic pattern of the responses (alternated periods of excitation and inhibition) suggests a participation of polysynaptic responses. This has to be confirmed since HFS usually suppresses polysynaptic responses. At present, the mechanisms underlying the complex responses recorded in the target neurons of the STN in response to short-term STN-HFS or GP-HFS are not yet elucidated.

Does STN-HFS Protect the Remaining SNc Neurons and Amplify Levodopa Treatment?

The protection from degeneration of the remaining dopaminergic neurons by STN-HFS has been investigated in murine and primate models of PD. Temel et al.[55] injected 6-OHDA at four sites in both striatum of rats. During the phase of ongoing neurodegeneration in the SNc, half of the lesioned rats were treated with bilateral STN-HFS (pulse width at 60 μs, frequency at 130 Hz, 1 hour per day over a period of 3 months). This amount of STN modulation was sufficient to obtain a significant rescue of SNc dopaminergic neurons from cell death. Bilateral STN-HFS not only had a protective effect on the number of TH positive neurons but also on the total number of neurons in the SNc. It could be argued that this effect resulted from a nonidentical retrograde degeneration of SNc dopaminergic neurons in the different lesioned rats and thus did not result from STN-HFS. For this reason, to mimic the clinical situation and to be able to observe neuroprotection, Benabid's group performed a subacute model of MPTP treatment in primates and induced a symmetrical 50% reduction of Nissl-stained and TH positive cells in the two SNc. They applied a unilateral STN-HFS after MPTP treatment and compared the number of Nissl-stained and TH-positive SNc cells between each side of the brain in two animals, the non-HFS side serving as a control. They found around 20% more dopaminergic neurons in the SNc of the side that underwent HFS when compared with the non-HFS side. When the HFS electrode was located outside the STN, the difference between both sides was not significant.[31] Therefore STN-HFS may have offered neuroprotection to nigral dopaminergic neurons that would have degenerated as part of the disease process.

Several studies reported an excellent clinical outcome of STN-HFS in levodopa (L-dopa) responsive forms of Parkinson's disease,[56] and STN-HFS allows the discontinuation of L-dopa or equivalent treatment or large reductions in daily dose[57] in contrast to GPi-HFS. The question therefore aroused whether STN-HFS favors dopamine release in the striatum. Savasta's group tested this hypothesis by measuring the extracellular content of dopamine with HPLC and its metabolites in the striatum of rats that underwent a partial 6-OHDA lesion of one SNc.[58] After a delay of 3 weeks to allow the degeneration of 70% of dopaminergic nigrostriatal fibers in the dorsolateral part of the striatum, they implanted the stimulation electrode in the STN and the microdialysis probe in the striatum, both ipsilateral to the lesion. The i.p. injection of L-dopa (50 mg/kg) increased by around three times the content of extracellular dopamine in the lesioned striatum measured 1 hour after the injection. STN-HFS at clinical parameters (130 Hz, 60 μs, during 1 hour) amplified by around 100% this L-dopa-induced increase of dopamine during the stimulation period and for the following 2.5-hour after the end of stimulation. In contrast, in intact animals, L-dopa failed to enhance the extracellular dopamine levels during the stimulation period. This suggests that STN-HFS interacts in a synergistic manner with L-dopa but the

underlying mechanisms have not been elucidated. A simple explanation would be that STN-HFS acts by directly modulating the firing rate of the remaining dopaminergic neurones.[59,60]

Which of the STN-HFS-Induced Electrophysiological Effects Are Related to Clinical Efficacy?

Ideally, to test this question, we should specifically block one by one the identified responses to HFS and analyze the consequences on motor behavior. This experiment is difficult to perform. We will propose some hypotheses as follows: a therapeutic electrophysiological effect is likely to (i) reduce pathological patterns in the basal ganglia, (ii) be recorded from output nuclei of the basal ganglia whichever site of the cortico-basal ganglia-thalamo-cortical loops is stimulated (in the same animal models), and (iii) allow re-establishment of a control response of output GPi and SNr neurons to cortical stimulation (triphasic response).

We have seen that HFS introduces a stimulation-locked, complex activity in subsets of neurons from many sites of the basal ganglia network (STN, motor cortex, GPe, GPi, SNr), and thus decreases ongoing pathological activity in these neurons. This may also be valid for PPN and the good results obtained on axial motor signs with STN-HFS in association with PPN-HFS[61] may result from a change of PPN discharge pattern. Direct activation of passing fibers dorsal to the STN and in particular nigro-striatal and pallido-thalamic axons may also participate to the beneficial effect as the best position of the HFS electrode active contact is in the dorsal part of the STN.

To answer the second hypothesis, we can take the example of GPi-HFS and STN-HFS that both ameliorate clinical signs of PD. Do they have similar electrophysiological effects on GPi neurons in the primate model of PD? Bar-Gad et al.[62] recorded the activity of GPi neurons in MPTP-treated monkeys in response to microstimulations applied in GPi (135 Hz, 200 μs, 600–3000 trains of 10 stimuli separated by 500 ms). They reported a double excitation with latencies of 3 and 6 ms, separated by a short period of inhibition. Overall 70% of the GPi neurons displayed a locked activity, i.e., they lost their basic firing pattern and switched to a predicted, orderly discharge that was locked to the stimulus. These results show striking similarities with those recorded in GPi with STN-HFS in MPTP-treated monkeys[23] (see earlier).

The third point was shown in SNr where STN-HFS reversed to control the classical triphasic response to motor cortex stimulation[63] but the mechanisms have not been elucidated.

HFS FOR OTHER NEUROLOGICAL DISORDERS

HFS in Motor Cortico-Basal Ganglia-Thalamocortical Loop for Essential Tremor

HFS of ventral nuclei of the thalamus can dramatically relieve essential tremor in the majority of patients.[2,64] Essential tremor is thought to arise from dysfunction of the glutamatergic olivocerebellar pathway, which projects to ventral thalamic (VL) nuclei.[65] VL-HFS in rat brain slices silenced or suppressed the activity of thalamic relay neurons after a transient period of intense depolarization.[66] The authors hypothesized that VL-HFS introduced a functional deafferentation of stimulated neurons, thereby stopping tremor from propagating to thalamo-cortical loops. To test whether this depression of afferent synaptic transmission is selective, they stimulated at 5 Hz in two different loci within the VL to mimic afferent stimuli at tremor frequency. Both stimulations evoked excitatory postsynaptic potentials at 5 Hz in the recorded VL neuron. A concomitant short-duration HFS (125 Hz, for 10 s) in one locus or totally suppressed the 5 Hz EPSPs in the HFS-stimulated pathway but not in the nonstimulated one, suggesting that HFS selectively disrupts afferent synaptic transmission.[67] One of the underlying mechanisms could include the depression of excitatory glutamatergic transmission in the ventral thalamus by activation of the presynaptic A1 receptors. HFS releases ATP, the precursor of adenosine and local adenosine infusion suppresses tremor in the harmaline-treated mice.[68] However, these mechanisms have been identified during very short-term HFS (10 seconds) and may not sustain the long-term beneficial effects of VL-HFS.

HFS in Motor Cortico-Basal Ganglia-Thalamocortical Loop for Dystonia

Neuronal activity is altered in basal ganglia and ventral thalamic nuclei in dystonia.[69] The firing pattern of GPi neurons known to be regular in monkeys[70] consists in patients of irregular grouped discharges with intermittent pauses and a third of the neurons discharge at the frequency of the electromyogram.[71,72] Neurons in ventral oralis posterior/intermediate nuclei of the thalamus (Vop/Vim) have a sustained activity at 130 to 150 Hz, organized in bursts lasting from 500 ms to 5 seconds and recurring at a frequency similar to that of dystonia frequency.[71]

GPi-HFS is currently used for primary generalized DYT-1 positive dystonia and idiopathic cervical dystonia.[7,73,74] In contrast to Parkinson's disease, the beneficial effects of HFS in dystonia are not immediate but progressive over weeks to months. However, recordings in patients can only be performed during the surgical procedure, i.e. at t_0, or in control animals, owing to the lack of reliable animal models of dystonia.

During short duration GPi-HFS, 50 to 70% of Vop neurons of the thalamus reduced their average discharge frequency with a delay of a few milliseconds in control monkeys[75] or dystonic patients,[39] suggesting that HFS activates GPi efferent axons that are GABAergic and inhibitory onto thalamic neurons (Fig. 3B). Moreover, 88% of Vop neurons were antidromically activated with 1-ms latency probably as a result of the activation of axons originating in Vop and passing in the vicinity of the GPi-HFS electrode (Fig. 2E).

HFS in Limbic Cortico-Basal Ganglia-Thalamocortical Loop for Obsessive Compulsive Disorder

Obsessive compulsive disorder has been consistently associated with metabolic hyperactivity in the caudate nucleus, medial thalamus, and orbitofrontal cortex in patients at rest.[76–78] Recently, a dramatic increase in neuronal activity of the ventral caudate nucleus was identified and correlated to the patients' self-evaluated obsessions.[79] HFS of the ventral anterior internal capsule,[80] accumbens,[8] or limbic STN[81] are therapeutic approaches for treatment-resistant OCD. HFS mechanisms were studied with imaging techniques in patients and electrophysiological techniques in control rats as robust animal models of OCD are lacking.

HFS of the accumbens (130 Hz, 200 μs, during 30 min) in control rats induced the inhibition of nearly all the recorded orbitofrontal neurons probably as a result of the antidromic activation of cortico-accumbens axons and other corticofugal axons.[24] The authors suggest that antidromic spikes propagate in axonal collaterals of cortical neurons and thus evoke inhibitory responses in neighboring neurons via GABAergic interneurons (Fig. 1, inset cortex). But this still has to be demonstrated as antidromic axonal spikes often inefficiently invade axon collaterals and somas.[43]

CONCLUSION

The studies explained so far have focused on the effects of STN-HFS at the site of stimulation or of the first order neurons immediately downstream (orthodromic effect) or upstream (antidromic effects) the STN and in resting conditions. This last point is of importance since results obtained at rest cannot be extrapolated to what may occur during the behavior.[82]

Electrical stimulation of a nucleus with short duration pulses (less than 1 ms) preferentially activates axons rather than somas.[29,83] This results in the generation of axonal spikes and the consequent antidromic and orthodromic activation of subsets of distant neurons that send axons to the stimulated structure or are synaptically connected to it (see Fig. 1).

HFS-driven antidromic spikes collide with spontaneous orthodromic ones leading to the blockade of ongoing (pathological) activity in subpopulations of basal ganglia neurons, as long as the orthodromically propagated, spontaneous activity has a lower frequency than the HFS-driven one. This dual effect has been clearly shown in the STN,[22] motor cortex,[37] GPe-GPi (Ammari et al. personal communication), and SNr[38] during STN-HFS, in ventral neurons of the thalamus during GPi-HFS[39] and suggested in the orbitofrontal cortex during accumbens-HFS.[24] An additional complication stems from the fact that activated axons also propagate spikes in the orthodromic direction and give rise to sustained neurotransmitter release.[84–86] How postsynaptic responses (glutamatergic or GABAergic) follow a high frequency and long duration stimulation such as HFS is a question that still remains open, as the electrophysiological studies performed so far have only focused on relatively short-term stimulations.[23,39,62,75] The overall consequence of HFS on stimulated networks appears to be the generation of a new regular activity, locked to the stimulation but in a complex way. We propose that this HFS-driven activity decreases spontaneous pathological patterns, exacerbates the responsiveness to L-dopa and reverses several markers to control,[58,87,88] yet preserves the transmission of cortical information.[63,81]

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