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A putative generalized model of the effects and mechanism of action of High Frequency Electrical Stimulation of the Central Nervous System

Alim-Louis BENABID, Bradley WALLACE, John MITROFANIS, Rong XIA, Brigitte PIALLAT, Stephan CHABARDES and François BERGER

INSERM U318, Université Joseph Fourier, CHU Albert Michallon, Grenoble Cedex 9, France

Abstract

High-frequency stimulation (HFS) of neural structures has been used since 1997 as an alternative to lesions in functional neurosurgery of movement disorders, and more recently, it has been applied to the treatment of epilepsies, obsessive-compulsive disorders, cluster headaches, and has other applications in experimental models, particularly for obesity. Although their clinical efficacy is not questioned, and that the effects most of the time parallel those of ablative techniques, leading to the concept of functional inhibition, the intimate mechanisms by which HFS induces excitation within fiber bundles and seems to inhibit cellular nuclei is still strongly debated. Principally due to the observation of long-term clinical effects over a period up to 15 years, it is clear that the mechanism is not due to a progressive lesion, as at every moment the interruption of stimulation reverses totally the effects. There is no current proof that long-term HFS is able to reset neural networks, or to induce profound modifications of the functional organization or of the synaptic connectivity.

To understand what is responsible for the immediate, reversible and adaptable effects of HFS, several mechanisms must be considered, which might be involved simultaneously or in sequence : i) Jamming of neural transmission through stimulated nuclei is one possibility, based on the principle that the regular imposed activity might drive the neurons to fire in a regular pattern, making it impossible to transmit more subtle messages, either normal or abnormal. Although it is difficult to prove this type of mechanism, it might account for the reports of increased activity following HFS in various structures. ii) Direct inhibition of spike initiation at the level of the membrane could be due to activation of inhibitory terminals, particularly gaba-ergic, or by a blockade of the voltage gated ion channels. iii) Recent data show that HFS decreases the production and release of low molecular weight proteic neurotransmitters, which could account for the functional inhibition while the efferent axon is still excited by the electrical stimulus. iv) Retrograde activation of upstream neuronal structures, as reported in the external pallidum during stimulation of STN, might be responsible of additional jamming-like effects due to collisions with descending spikes.

Due to the geometry of the chronic electrodes used in human patients, and to their size as compared to the size of the neural elements, the tentative model of the mechanisms of HFS must take into account possible simultaneous effects of stimulation on the presynaptic, synaptic, axonal, dendritic and post synaptic events, as well as on the fibers "de passage" involved in the vicinity of the stimulating electrodes. To this respect, modeling of the spatial distribution of voltages and currents appears to be of extreme importance.

A global model of the mechanism of HFS is proposed.

At the level of the somata and cell bodies, spike initiation is profoundly altered leading to a total suppression of spikes, as recorded in pallidal and subthalamic neurons of parkinsonian patients, possibly alterning with intensity driven spike activity, such as reported in STN on brain slices, using intracellular recordings. It seems from these studies that the presynaptic effects are not the determining events. The axonal efferents of the stimulated neurons, whatever happens at the level of the cell body, are more than probably excited. Therefore, the spikes which are initiated will travel along the axons down to the next synapse where they should initiate the release of neurotransmitter. However, recent data tend to prove that the synapse might not be able to function due to the shortage of neurotransmitter induced by the arrest of protein synthesis, transfer and release induced by HFS as shown by the use of protein molecular approaches. The fibers passing within the area and influenced by stimulation, but coming from neurons, whose cell bodies are situated at distance and not influenced by stimulation, are clearly stimulated and the spikes therefore initiated would trigger neurotransmitter release at their far target destination. This would account for the induction of clinical side effects, which are typically of excitatory type.

Key words : Deep brain stimulation ; mechanisms ; subthalamic nucleus ; Parkinson's disease ; high frequency.

Introduction

Surgery and pharmacology have always been the only therapeutic tools for neurodegenerative diseases. In the field of movement disorders, surgery came first (Albe-Fessard *et al.* 1963 ; Ohye *et al.* 1975), and was successful particularly on the tremor, which is the most spectacular, but not

always the most disabling, symptom of parkinson's disease (PD). The introduction of the treatment by the Dopamine precursor LevoDopa (Cotzias *et al.* 1967) was successful in compensating the loss of production of Dopamine by the degenerated Substantia Nigra pars compacta (SNc), and almost eradicated surgery. However, following long term high doses treatment with LevoDopa, dyskinesias and motor fluctuations appear. This recreated the need for reusing, in those circumstances, surgical procedures. However, their known complications (Matsumoto *et al.* 1976 ; Matsumoto *et al.* 1984 ; Tasker *et al.* 1997 ; Louw and Burchiel 1998 ; Tasker 1998), particularly when bilateral procedures were required, called for new methods to complement the therapeutical panel. The discovery (Benabid *et al.* 1987) that the effects of deep brain stimulation depend on the frequency, provided such an alternative. The beneficial effects of this method, its low morbidity, its adaptability and even its reversibility have made it over the last decade the treatment of choice of advanced forms of PD and have triggered its spreading over an increasingly large number of indications, even outside the field of movement disorders.

Paradoxical effects of high frequency stimulation

Electrical stimulation is usually associated to excitation of neural elements. Depolarization induced by cathodal stimulation triggers the opening of voltage dependent sodium channels and leads to the initiation of a spike, self-reproducing and propagated along the axon in a non-decremental manner. Repetition of the stimuli leads to an increased efficiency, due to temporal and spatial summations. This is not a linear phenomenon and the excitability of the membrane increases with frequency until an optimum above which excitability decreases again. Because of these excitatory effects, stimulation has been used as a tool to explore the functions of neural structures, in various circumstances and particularly during surgical procedures to help defining the target for ablative surgery.

Intraoperative thalamic stimulation abolishes Parkinsonian rest tremor at frequencies above 100 Hz

We had observed during previous surgeries that using stimulation for exploration purposes, at low and high frequency, that high-frequency, (higher than 100 Hz), was able to stop the tremor while low frequency, (lower than 50 Hz) was not able to stop it or was even able to drive the tremor at frequencies around 5 to10 Hz. The paradox between excitation and the subsequent lesion-like effect was immediately apparent and the question of the mechanism of action of HFS was raised since the beginning. The easiest explanation, difficult to demonstrate, was that stimulation, above a certain frequency, disrupted, distorted, or altered the neuronal message and we called that "jamming". This was then used as an additional tool for locating the best site where to make the lesion of thalamotomy. The idea came quickly that this could be used permanently as a treatment, using the hardware which was available for the treatment, at low-frequency (30 to 60Hz) for intractable pain. Therefore, during the surgical treatment of a patient with essential tremor (Benabid *et al.* 1987), who had been treated some months ago by a thalamotomy on one side and who suffered from a disabling bilateralisation of his tremor, we performed for the first time the contralateral implantation of an electrode to deliver high-frequency stimulation (HFS) in his thalamic ventrointermedius nucleus (Vim).

Using this method in further patients, it was quickly demonstrated that deep brain stimulation (DBS) at high frequency (HF) could replace ablative stereotactic methods at large (Benabid *et al.* 1987 ; Benabid *et al.* 1991).

This empirically based concept was therefore applied, in addition to the thalamic target Vim for rest tremor and for postural essential tremor, but also to the other classical targets for PD, particularly to the internal Pallidum GPi (Siegfried and Lippitz 1994 ; Lozano *et al.* 1997 ; Krack *et al.* 1998 ; Volkmann *et al.* 1998), known for its specific effect on levodopa-induced dyskinesias and used in pallidotomies (Laitinen *et al.* 1992 ; Hariz and Hirabayashi 1997). The demonstration that the method was reliable and safe compared to lesioning methods, allowed its extension to new targets, theoretically designed from basic neuroscience, such as the subthalamic nucleus (STN) (Bergman *et al.* 1990 ; Pollak *et al.* 1993 ; Limousin *et al.* 1995 ; Limousin *et al.* 1998 ; Krack *et al.* 2003).

One may consider that, as a conclusion of this first period, one had established the empirical concept « HFS is equivalent to lesion », stating that HFS-DBS produced a functional inhibition mimicking the effects of lesion. This concept has currently the status of an axioma as it is verified in every circumstance where it is applied (not only in all 3 targets used for PD, but also in other clinical indications such as the posterior hypothalamus for cluster headaches (Franzini *et al.* 2003 ; Leone *et al.* 2003), or in experimental animals in the ventromedial hypothalamus (Chabardes 1999) from where changes in feeding behaviour can be induced), and still has to be demonstrated.

This concept has two consequences :

– Is it still valid in other indications ?
– Is this a new physiological concept ? And if so, what is its mechanism ?

Other Indications

Based on these clinically proven experiences, several other indications have been explored and are treated, either on the basis of the extension of the concept to targets having already proven their efficiency, or on the basis of theoretical expectations, drawn from experimental evidence. Besides the medical and therapeutic interest of this extension of the method to other diseases, the reproducibility of the lesion-like effect of HFS in different targets and various indications is an important feature, demonstrating the broad and general value of the concept. In addition, each new indication brings additional features which may help decoding the mechanism.

HF-DBS for Dystonia

Following the reports of improvement of dystonia by pallidotomy (Lozano *et al.* 1997), HFS has been tried in GPi where once again it mimics the effects of lesions created by pallidotomy (Coubes *et al.* 2000 ; Coubes *et al.* 2002 ; Detante *et al.* 2004). It is striking to observe that in this particular indication the similarities between the effects of HFS and lesion concern also the time course of clinical improvement. In PD, the effects of HFS are almost immediate (within seconds) and similarly reversible. In dystonia, these improvements are not seen before a rather longer delay of days if not weeks, and keep improving along time even over some years. This delayed time course is similar for HFS and for pallidotomies, proving that this is related to the nature of the cause of the dystonia rather than to the method of altering the function of GPi.

HF-DBS for Epilepsy

It has been known for long (Gale 1986) that cortical excitability may be modified by pharmacological and lesioning manipulations of the nigral system, leading to the concept of "Nigral Control of Epilepsy". Based on these observations, and on additionnal animal experiments (Vercueil *et al.* 1998 ; Bressand *et al.* 2002) we have implanted STN in several cases of intractable epilepsy with significant results (Benabid *et al.* 2002 ; Chabardes *et al.* 2002). Other data are being reported on the efficiency of direct stimulation of the amygdalo-hippocampic formation (Vonck *et al.* 2002) or even the epileptic focus itself (Velasco *et al.* 2001).

HF-DBS for Obsessive Compulsive Disorders (OCD)

The discredit of psychosurgery during the second half of the XXth century has deprived some psychiatric patients from a very useful therapy when all other treatments have failed. Capsulotomies and cingulotomies were still performed in rare institutions but their irreversible nature, added to misuse, and poor physiological basis, had raised concerns and had restricted its use. The reversibility of HF-DBS has reopened an opportunity. Psychosurgery was successful mostly in obsessive compulsive disorders (OCD). For this reason, DBS was used to replace lesions in the internal capsule in this indication (Nuttin *et al.* 1999). The reported results were encouraging, but the parameters used (high voltage, large pulse width) suggested that the neuronal structure involved was at distance from the real target, which could be, according to the current understanding of the physiology of the basal ganglia, in the area of the nucleus accumbens. Recent and preliminary data reporting results of HF-DBS of the nucleus accumbens are in agreement with this hypothesis (Sturm *et al.* 2003). HF-DBS of STN in 2 PD cases who had in addition traits of OCD showed that the improvement of the PD symptoms was paralleled by the improvement of the OCD symptoms, as evaluated with the Y-BOC rating scale (Mallet *et al.* 2002).

HF-DBS for Cluster Headaches

Cluster headaches might be a devastating disease, occuring repeatedly in patients prone to this vascular dysregulation. PET-scan studies have shown that the episodes corresponded to a hyperactivity of the ipsilateral posterior hypothalamus (May *et al.* 1998). The implantation of this target with electrodes meant to inhibit this hyperactive area has demonstrated a striking, acute, reversible and ipsilateral effect of high-frequency stimulation (Franzini *et al.* 2003 ; Leone *et al.* 2003).

Future Applications : HFS for Obesity or Anorexia Nervosa ?

The VentroMedial Hypothalamus (VMH), and the Lateral Hypothalamus (LH) are structures involved in the control of feeding behaviour. Experimental data are available since several decades in dogs and cats, and demonstrate that lesion of the VMH or low frequency stimulation of LH induce hyperphagia and then obesity, while low frequency stimulation of VMH and lesion of LH induce the reverse behaviour leading to a cachectic state in rat experiments (Chabardes 1999). Lesions of the hypothalamus due to lipomas or secondary to surgical lesions (such as after surgery for craniopharyngiomas) may also induce malignant obesity. HF-DBS of VMH in rats induce hyperphagia while low frequency stimulation decreases the food intake of fasted rats.

These are experimental data, not yet usable as a basis for treatment, but they provide interesting clues about how HFS might work, in these normally functioning structures, where no abnormal bursting pattern or hyperactivity needs to be inactivated.

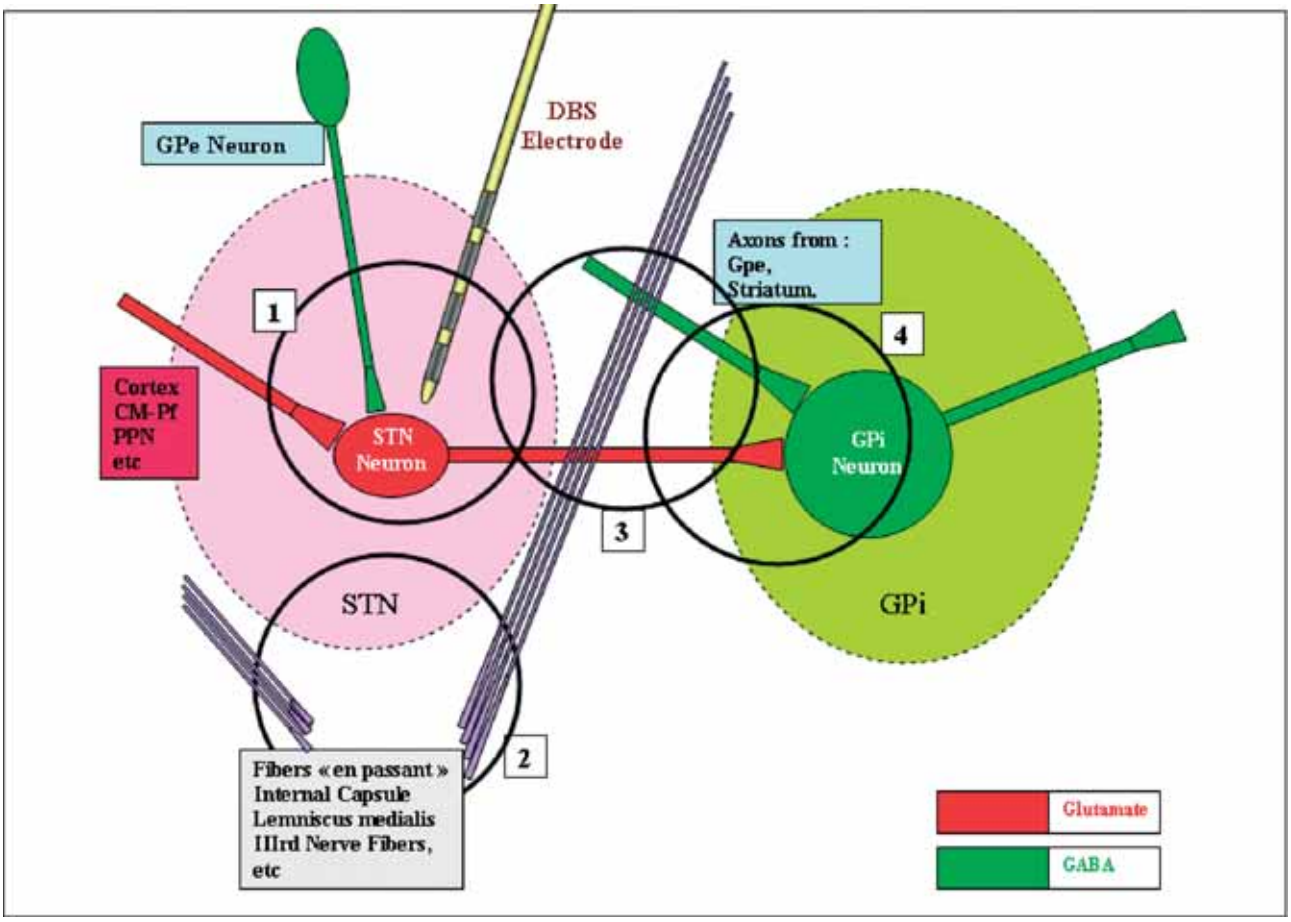

FIG. 1. — Schematic representation of the structures involved during STN stimulation.

Within STN nucleus, where the chronic DBS electrode is inserted, a STN neuron receives Gabaergic afferents from GPe and Glutamatergic afferents from the cortex, the CM-Pf and PPN nuclei, and emits Glutamatergic efferents to the target nuclei GPi (and SNr not represented here), which receives also terminals from other origins (such as GPe and the Striatum). Not directly related to this network, axons pass by these structures, constituting the Internal Capsule, the Lemniscus medialis, or lower and more medial, the fibers of the IIIrd nerve.

1. Within the STN nucleus, at the level of the STN membrane, of axons impinging upon the stimulated neurons and their terminals.
2. Axons passing by the stimulated structure but coming from cell bodies which are far from the site of stimulation (such as the fibers of the internal capsule or the fibers of the IIIrd nerve).
3. Axons (subthalamo-pallidal, pallido- and striato-pallidal, and axons “en passant”).
4. Axons originating from the stimulated STN neurons and ending at the level of the subthalamo-pallidal (or nigral) synapse.

The review of these clinical and experimental situations demonstrates that HF-DBS can be a surgical tool, adaptable, reversible , because it consistently mimics lesions in various neural structures and it is applicable to several targets at the same time. Then how can we explain that stimulation can be a substitute for lesions ?

Mechanism of action of HF-DBS

The challenge is to solve the following paradox : How can stimulation produce the same clinical effects as lesions in various structures of the brain ? Actually, the facts are different depending on the frequency. HFS (more than 50 Hz, actually at about 130-185 Hz) mimics the effects of ablative procedures (considered as inhibitory) in neural somatic structures such as the thalamus (Vim, CM-Pf), the basal ganglia (GPi, STN) and the hypothalamus (VMH). On the contrary, during the surgical exploration, HFS as well as LFS excite neural fiber bundles, such as the optic tract (inducing flashes), the pyramidal tract (inducing contractions), the lemniscus medialis (inducing paresthesias), or the IIIrd nerve fibers (inducing mono-ocular deviations). When a chronic electrode (1.27 mm in diameter) bearing four contacts (1.5 mm long, separated from the next one by 0.5 mm), with a voltage of about 2 to 3 volts, which corresponds to 2 to 3 mAmp as the average impedance of the system is about 1000 Ohms, the area involved by the suprathreshold currents is not limited to a point and even in a homogeneous structure such as STN, comprises neuronal somata, of course, but also their dendritic fields, the corresponding synapses and the afferent fibers, as well as the efferent axons of the neurons. The different elements of the neurons respond differently to stimulation. Fibers have a lower threshold than the cell bodies, the orientation of the fibers is important depending on their

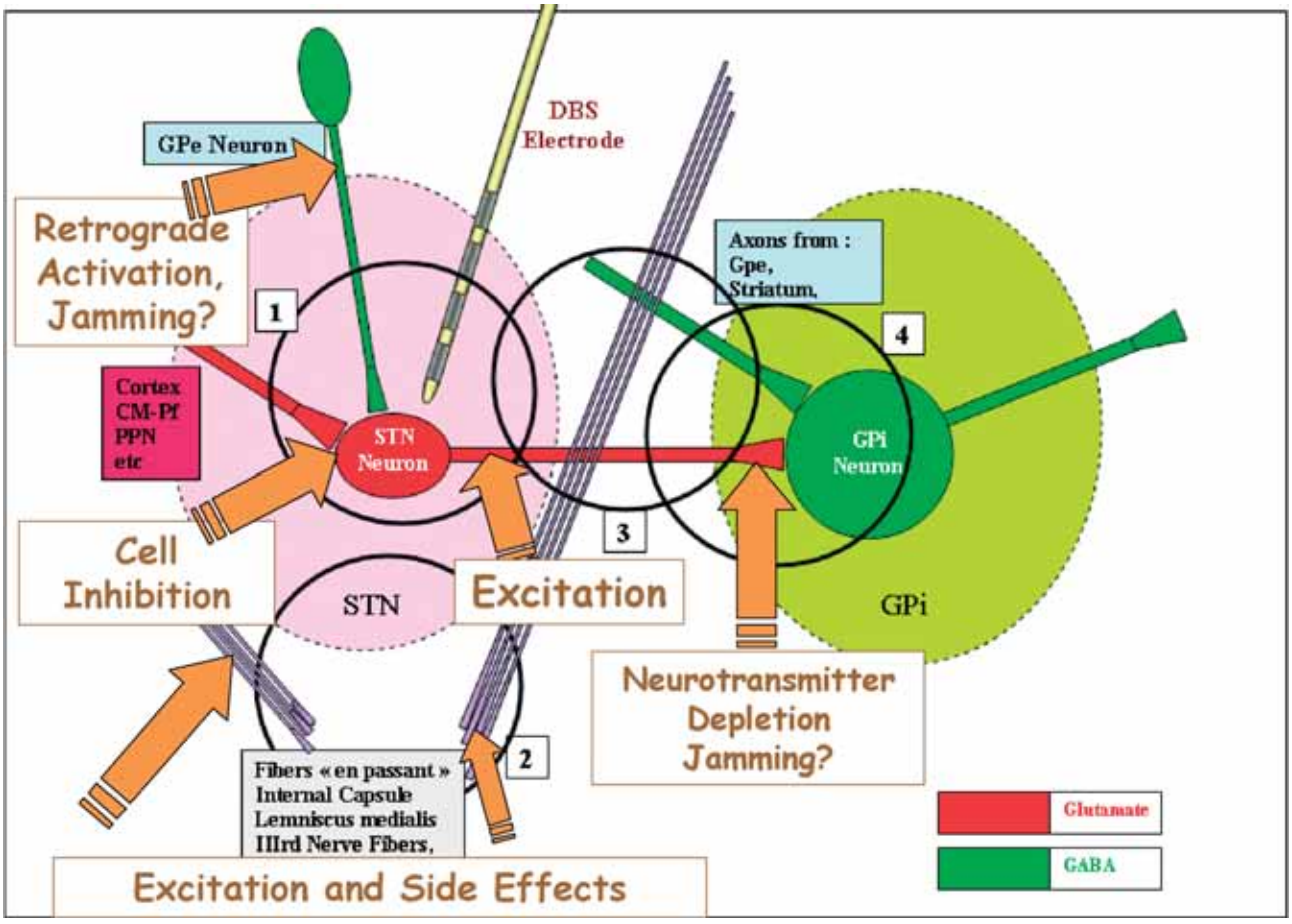

FIG. 2. — A global model of HFS induced functional inhibition.

Within STN nucleus, where the chronic DBS electrode is inserted, a STN neuron receives Gabaergic afferents from GPe and Glutamatergic afferents from the cortex, the CM-Pf and PPN nuclei, and emits Glutamatergic efferents to the target nuclei GPi (and SNr not represented here), which receives also terminals from other origins (such as GPe and the Striatum). Not directly related to this network, axons pass by these structures, constituting the Internal Capsule, the Lemniscus medialis, or lower and more medial, the fibers of the IIIrd nerve.

1. HFS inhibits spike initiation at the level of the STN membrane (Benazzouz *et al.* 1995 ; Beurrier *et al.* 2000 ; Welter *et al.* 2004) and decreases neurotransmitter (glutamate) synthesis and synaptic release (Xia *et al.* 2004 (unpublished data)).

Axons impinging upon the stimulated neurons and their terminals would be excited and would deliver an increased amount of their neurotransmitters. However, their postsynaptic effect (initiation of EPSPs by glutamate terminals coming from the cortex, the CM-Pf and PPN nuclei, or of IPSPs by GABA terminals coming from GPe) might be anihilated by the inhibition of the spike initiation at the level of the postsynaptic STN membrane by HFS.

2. Axons passing by the stimulated structure but coming from cell bodies which are far from the site of stimulation (such as the fibers of the internal capsule or the fibers of the IIIrd nerve), would be excited, therefore inducing remote side effects (gaze deviation, monocular deviation, muscular contractions, sensory paresthesias).

3. Axons (subthalamo-pallidal, pallido- and striato-pallidal, and axons “en passant”) are excited at low and at high frequency. The effect of HFS on these axons depends on their origin, whether or not their cell bodies are within the stimulated area.

4. Axons originating from the stimulated STN neurons are probably stimulated and generate spikes which are propagated to the subthalamo-pallidal (or nigral) synapse : however, at this level, the neurotransmitter cannot be released anymore, as its synthesis would have been inhibited at the level of the STN cell body (Schuske and Jorgensen 2004) (Xia *et al.* 2004 (unpublished data)). If this inhibition is unsufficient, the spikes which are not inhibited are propagated under a disrupted pattern of firing ; this would render the final neuronal message meaningless for the whole network (Hashimoto *et al.* 2003), in a global process which we have called “jamming”. Axons originating from GPe and/or the striatum may be excited when passing close to the stimulated area : they are Gabaergic and should participate to the inhibition of the target structures, GPi and SNr.

being parallel or perpendicular to the current lines. Stimulation might induce the silencing of the neuronal firing, the jamming of a network or of a feedback loop which would make the wrong message erased or meaningless, or the fatigue of synapses by depletion of the neurotransmitter. Several of these mechanisms could be involved altogether in the same structure or at different levels (Figure 1), which allows us to propose a tentative model for the mechanism (Figure 2). Do we have data from our observations or from the literature, to support or infirm these hypotheses ?

At the level of the cell body, there is now evidence that the neuronal firing is inhibited :

Recording of neuronal activity at the site of stimulation, in STN of anesthetized rats (Benazzouz *et al.* 1995 ; Benazzouz *et al.* 2000a ; Benazzouz *et al.* 2000b), as well as in rat brain slices (Beurrier *et al.* 2000) and during intraoperative recordings in human patients (Filali *et al.* 2004) show that following the period of stimulation, which is obliterated by the stimulation artifacts, there is a profound inhibition, over several hundred milliseconds. This inhibition is also observed in the target structures of STN, such as the entopeduncular nucleus (EP, equivalent in rats to the human internal pallidum) or in the substantia nigra pars reticulata (SNr), consistently with the hypothesis that HFS of STN has shut down temporarily its glutamate output, leading to the cessation of its excitatory drive on EP and SNr. We had observed a similar phenomenom in CM-Pf neurons in rats where the ventrobasal somatosensory complex of the thalamus was stimulated, although this happened at lower frequencies, around 60Hz. This post-stimulus inhibition however does not explain what happens during stimulation, which corresponds to the clinical situation, where HFS is chronically administered and during which the clinical benefit is observed.

Artifact suppression methods have been developed by different teams, allowing them to record the neuronal activity during the stimulation period, at the site of stimulation : this has been done in human patients during surgery for advanced Parkinson's disease, in the GPi (Dostrovsky *et al.* 2000 ; Dostrovsky and Lozano 2002), as well as in the STN (Welter *et al.* 2004) which show that spikes are not induced during HFS, as well as immediately after stimulation. This has been done also at the site of stimulation in STN on rat brain slices : in these experiments, a dual effect is observed (Garcia *et al.* 2003), associating the silencing of the soma membrane where no spontaneous activity is seen anymore, and the occurrence of burst, driven at higher frequency, and at the frequency or a multiple of the frequency of stimulation. The shape of these spikes making the bursts suggests that they are induced at the level of the axon efferent from the STN neuron cell body, and invading retrogradely the soma.

Actually, the stimulation field necessarily encompasses also the neighbouring axons, either originating within the stimulated structure (such as subthalamo-pallidal axons), or passing by it (such as in the F1 and F2 Forel fields, or in the internal capsule). Therefore, the spikes induced at this level will propagate along the excited axons, in both direction from the point they were created, retrogradely towards the soma as well as orthodromically towards the synapse. The propagation towards the soma might explain the results of Garcia et al. (Garcia *et al.* 2003) on rat brain slices, where the electrical silence of the soma membrane is interrupted by bursts of spikes driven at the frequency of stimulation, which might be due to this retrograde propagation to the cell body of axonal spikes initiated along the part of the STN axon leaving the nucleus and involved by the electrical field. The propagation towards the synapse should create at this level an increase of synaptic events, which in the case of the subthalamo-pallidal synapse should excite the pallidal neurons, no matters of what happened at the level of the STN soma. In this case, STN HFS should result in an excitation of the pallidal neurons, and not correspond to what is observed when a lesion is made either in STN (subthalamotomy) or in GPi (pallidotomy), which both induce a clinical improvement.

Recording at the level of pallidal neurons should provide interesting data to further understand what happens in this situation : this has been done in MPTP monkeys, chronically implanted with a human chronic DBS electrode 3387, connected to an implanted programmable pulse generator Soletra (Hashimoto *et al.* 2003). They observed, in conjunction with an improvement of the clinical status of the monkeys, shown by EMG recordings, an alteration of the spontaneous firing of pallidal neurons, made of a silencing of the spontaneous activity, interrupted by burst of spikes, which could be induced by the excitation of the axons coming from the effective stimulated area. These axons could be originating from STN neurons or could be passing axons projecting onto GPi neurons. Although this is not stated by the authors, the recorded activity might be either post-synaptic spikes generated by the GPi neurons, or could be field potentials generated by the presynaptic depolarisation of the terminals of these axons, without necessarily a synaptic transmission to pallidal neurons. This raises the crucial question of the events occurring at the synaptic level, downstream to the stimulated sites and structures.

At the level of axons, observation of the effect of stimulation during surgical exploration of the target and of its surroundings demonstrates that high frequency as well as low frequency stimulations excite these elements. The excitation of the fibers passing close to the site of stimulation induces the expected symptoms : paresthesias in the lemniscus medialis, muscular contractions in the internal capsule at the level of the pyramidal tract, conjugated eye deviation in the geniculate tract of the internal capsule, mono-ocular deviation in the fibers of the IIIrd cranial nerve. Therefore the axons efferent from the subthalamic neurons should be also excited. The induced spikes should therefore travel along the efferent axons and reach the synapses to the target structures, such as SNr or GPi. Recording in GPi during STN stimulation in monkeys shows increased activity (Hashimoto *et al.* 2003), but this could be due to activation of fibers close to the site of stimulation, which in the experimental situation of this paper (monkeys stimulated in STN with a

human chronic electrode) might overpass the STN nucleus. Anyway, this activity induced in GPi is linked to the stimulation and disturbs the spontaneous activity, which might create at this level a jamming. Microdialysis in the rat shows an increased release of glutamate, presumably coming from the STN. These data are difficult to interprete because the prolonged time course of the release outpasses by large the duration of the effects of STN stimulation. Moreover, the size of the probe as compared to the size of the investigated structure does not allow to consider these data as representative of the structure, and therefore does not make the microdialysis data reliable (Windels *et al.* 2003). However, axons originating from the STN neurons should be excited as well. They would be therefore responsible for the excitation of the target cells, in SNr as well as in GPi, provided that the spikes are able to induce a synaptic activity at this level. To check this, we have studied the effect of HFS on a prolactinoma cell line producing Prolactine in culture. The release of prolactine is decreased by HFS in a similar extent than by the addition of Dopamine, the prolactine inhibitor factor. Similar experiments were performed on the Neuronal-like Cell Line PC12 using a Long Oligonucleotide Microchip bearing 5000 rat gene on a Nylon film, with radioactive detection. These experiments show that HFS decreases transcription in 80% of the genes (Xia *et al.* 2004 (unpublished data)).

One may therefore assume that the synapses activated by the axons originating from neurons situated in the area of stimulation cannot release the expected neurotransmitter, making these neurons like “firing blanks” (Schuske and Jorgensen 2004) and creating a functional inhibition.

At the level of the cell body, the axon terminals coming from the afferent neurons, are mainly glutamatergic from the cortex, the parafascicularis nucleus and the pedunculopontine nucleus, but also GABAergic coming from the external Pallidum GPe. These two types of afferents might therefore be excited and deliver both glutamate and GABA, the last one being dominant in term of the final results. The hypothesis of the GABA action is the one suggested by Dostrovsky et al. (Dostrovsky *et al.* 2000 ; Dostrovsky and Lozano 2002). Moreover, the axons originating in GPe are retrogradely activated (Benazzouz *et al.* 1995), which could participate to either a jamming or an incoming additional inhibitory GABA input onto STN, participating to the STN inhibition.

On the basis of these considerations, we propose a global model explaining the major observations and supporting the concept of HFS induced functional inhibition (Figure 1 and 2). HFS at the level of a neuronal structure inhibits spike initiation at the membrane level and decreases neurotransmitter synthesis and synaptic release. Axons originating from the stimulated neurons could initiate and propagate spikes, which however would be inefficient at the synaptic level, considering the above described inhibition of the neurotransmitter production and release. If this inhibition were insufficient, the disrupted pattern of firing would render the final neuronal message meaningless for the whole network, in a global process which we have called “jamming”. Jamming was the mechanism we proposed at the time we observed this effect in Vim (Benabid *et al.* 1987 ; Benabid *et al.* 1991), where the bursting firing of kinaesthetic cells synchronous to tremor had suggested that HFS could obliterate this periodic bursting, therefore stopping tremor. It was difficult to demonstrate either experimentally or in the clinical human situation. Mathematical modelling however provides support for this hypothesis, the regularity of the firing suppressing the informational content of the neuronal message the variance of which becomes equal to zero (Mcintyre *et al.* 2004). However, one still has to understand how this could work at the cell body level and not at the axonal level. As a matter of fact, HFS delivered within bundles does not create an inhibition, which would result in a loss of function (anesthesia in the lemniscus medialis, motor deficit in the internal capsule, gaze paralysis, etc) : on the contrary, positive effects are induced such as paresthesias, muscular contractions, gaze deviation, which are consistent with an excitatory effect of HFS on fiber bundle. Axons impinging upon the stimulated neurons and their terminals would be excited and would deliver their neurotransmitters (provided their somata would be at sufficient distance to avoid inhibition of the neurotransmitter production), but their action might be inefficient because of the inhibition of the spike initiation at the level of the membrane by HFS. Axons passing by the stimulated structure but coming from cell bodies which are far from the site of stimulation, would be excited and would deliver an increased output of their neurotransmitters at the level of their target synapses, therefore inducing remote side effects.

The conclusion of this third part is that HF-DBS of basal ganglia is the current surgical alternative in the treatment of Parkinson’s Disease. It has already several applications to other diseases (dystonias, epilepsy, OCD, cluster headaches) and future indications are being investigated. In all cases, the effects of HFS of the various structures exhibit the same features as those observed following ablative surgery of the same targets. Its mechanisms are not fully understood but produce a phenomenom which is basically a Functional Inhibition, with multiple complex components, from the Gene to the Cell, from neuronal silencing to jamming of the neuronal message, including reduction of the synapse transmission.

The mechanism of high-frequency stimulation might be the combination of several phenomena including the above hypotheses as well as others. One may express this using the following formula :

Mechanism HFS *(*frequency*)* =
K_1*(*membrane inhibition*)* + K_2 *(*jamming*)* + K_3 *(*excitation of excitatory afferents*)*
+ K_4 *(*excitation of inhibitory afferents*)* + K_5 *(*excitation of efferents*)* + · · ·+ K_n *(*plasticity*)* + · · ·

where the K_i represent the coefficients which weight each possible sub-mechanisms according to their relative participation in the global mechanism of action, including the shut-down of glutamate, which may have consequences at the level of the neuroprotection (Piallat *et al.* 1996 ; Wallace 2004). Determination of these *Ki* coefficients is therefore the goal of the research in this domain. The physiology of electrical stimulation in general, or even at a larger scale, the biological effects of electricity might be revisited and further investigated.

REFERENCES

Albe-Fessard D., Arfel G., Guiot G. Activités électriques caractéristiques de quelques structures cérébrales chez l'homme. *Ann. Chir.*, 1963, **17** : 1185-1214.

Benabid A. L., Minotti L., Koudsie A., de Saint Martin A., Hirsch E. Antiepileptic effect of high-frequency stimulation of the subthalamic nucleus (corpus luysi) in a case of medically intractable epilepsy caused by focal dysplasia : a 30-month follow-up : technical case report. *Neurosurgery*, 2002, **50** : 1385-1391.

Benabid A. L. *et al.* Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet*, 1991, **337** : 401-406.

Benabid A. L., Pollak P., Louveau A., Henry S., de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the Vim thalamic nucleus for bilateral Parkinson disease. *Appl. Neurophysiol.*, 1987, **50** : 344-346.

Benazzouz A., Gao D., Ni Z., Benabid A. L. High frequency stimulation of the STN influences the activity of dopamine neurons in the rat. *Neuroreport*, 2000a, **11** : 1593-1596.

Benazzouz A. *et al.* Effect of high-frequency stimulation of the subthalamic nucleus on the neuronal activities of the substantia nigra pars reticulata and ventrolateral nucleus of the thalamus in the rat. *Neuroscience*, 2000b, **99** : 289-295.

Benazzouz A., Piallat B., Pollak P., Benabid A. L. Responses of substantial nigra reticulata and globus pallidus complex to high frequency stimulation of the subthalamic nucleus in rats : electrophysiological data. *Neurosci. Lett.*, 1995, **189** : 77-80.

Bergman H., Wichmann T., DeLong M. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science*, 1990, **249** : 1436-1438.

Beurrier C., Bioulac B., Hammond C. Slowly inactivating sodium current (I(NaP)) underlies single-spike activity in rat subthalamic neurons. *J. Neurophysiol.*, 2000, **83** : 1951-1957.

Bressand K. *et al.* Superior colliculus firing changes after lesion or electrical stimulation of the subthalamic nucleus in the rat. *Brain Res.*, 2002, **943** : 93-100.

Chabardes S. La stimulation aigüe et chronique à haute et basse fréquences des noyaux ventro-médian et latéral de l'hypothalamus chez le rat : effets sur le poids et la prise alimentaire. Université Joseph Fourier - Grenole I, Diplôme d'Etudes Approfondies (DEA), Sciences, 1999.

Chabardes S. *et al.* Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. *Epileptic Disord.*, 2002, **4 Suppl 3** : 83-93.

Cotzias G., Van Woert M., Schiffer L. Aromatic amino acids and modification of Parkinsonism. *N. Engl. J. Med.*, 1967, **276** : 374-379.

Coubes P., Roubertie A., Vayssiere N., Hemm S., Echenne B. Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. *Lancet*, 2000, **355** : 2220-2221.

Coubes P. *et al.* Deep brain stimulation for dystonia. Surgical technique. *Stereotact. Funct. Neurosurg.*, 2002, **78** : 183-191.

Detante O. *et al.* Globus pallidus internus stimulation in primary generalized dystonia : a H215O PET study. *Brain*, 2004, **127** : 1899-1908.

Dostrovsky J. O. *et al.* Microstimulation-induced inhibition of neuronal firing in human globus pallidus. *J. Neurophysiol.*, 2000, **84** : 570-574.

Dostrovsky J. O., Lozano A. M. Mechanisms of deep brain stimulation. *Mov. Disord.*, 2002, **17** : S63-68.

Filali M., Hutchison W. D., Palter V. N., Lozano A. M., Dostrovsky J. O. Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus. *Exp. Brain. Res.*, 2004, **156** : 274-281.

Franzini A., Ferroli P., Leone M., Broggi G. Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches : first reported series. *Neurosurgery*, 2003, **52** : 1095-1099.

Gale K. Role of the substantia nigra in GABA-mediated anticonvulsant actions. *Adv. Neurol.*, 1986, **44** : 343-364.

Garcia L., Audin J., D'Alessandro G., Bioulac B., Hammond C. Dual effect of high-frequency stimulation on subthalamic neuron activity. *J. Neurosci.*, 2003, **23** : 8743-8751.

Hariz M., Hirabayashi H. Is there a relationship between size and site of the stereotactic lesion and symptomatic results of pallidotomy and thalamotomy ? *Stereotact. Funct. Neurosurg.*, 1997, **69** : 28-45.

Hashimoto T., Elder C. M., Okun M. S., Patrick S. K., Vitek J. L. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *J. Neurosci.*, 2003, **23** : 1916-1923.

Krack P. *et al.* Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N. Engl. J. Med.*, 2003, **349** :

1925-1934.

KRACK P. *et al.* Subthalamic nucleus of internal pallidal stimulation in young onset Parkinson's disease. *Brain*, 1998, **121** : 451-457.

LAITINEN L., BERGENHEIM A., HARIZ M. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *J. Neurosurg.*, 1992, **76** : 53-61.

LEONE M., FRANZINI A., BROGGI G., BUSSONE G. Hypothalamic deep brain stimulation for intractable chronic cluster headache : a 3-year follow-up. *Neurol. Sci.*, 2003, **24 Suppl 2** : S143-145.

LIMOUSIN P. *et al.* Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N. Engl. J. Med.*, 1998, **339** : 1105-1111.

LIMOUSIN P. *et al.* Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet*, 1995, **345** : 91-95.

LOUW D., BURCHIEL K. J. Ablative therapy for movement disorders. Complications in the treatment of movement disorders. *Neurosurg. Clin. N. Am.*, 1998, **2** : 367-373.

LOZANO A. M. *et al.* Globus pallidus internus pallidotomy for generalized dystonia. *Mov. Disord.*, 1997, **12** : 865-870.

MALLET L. *et al.* Compulsions, Parkinson's disease, and stimulation. *Lancet*, 2002, **360** : 1302-1304.

MATSUMOTO K., ASANO T., BABA T., MIYAMOTO T., OHMOTO T. Long-term follow-up review of cases of Parkinson's disease after unilateral or bilateral thalamotomy. *Appl. Neurophysiol.*, 1976, **39** : 257-260.

MATSUMOTO K., SHICHIJO F., FUKAMI T. Long-term follow-up review of cases of Parkinson's disease after unilateral or bilateral thalamotomy. *J. Neurosurg.*, 1984, **60** : 1033-1044.

MAY A., BAHRA A., BUCHEL C., FRACKOWIAK R. S., GOADSBY P. J. Hypothalamic activation in cluster headache attacks. *Lancet*, 1998, **352** : 275-278.

MCINTYRE C. C., GRILL W. M., SHERMAN D. L., THAKOR N. V. Cellular effects of deep brain stimulation : model-based analysis of activation and inhibition. *J. Neurophysiol.*, 2004, **91** : 1457-1469.

NUTTIN B., COSYNS P., DEMEULEMEESTER H., GYBELS J., MEYERSON B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet*, 1999, **354** : 1526.

OHYE C., NAKAMURA R., FUKAMACHI A., NARABAYASHI H. Recording and stimulation of the ventralis intermedius nucleus of the human thalamus. *Confin. Neurol.*, 1975, **37** : 258.

PIALLAT B., BENAZZOUZ A., BENABID A. L. Subthalamic nucleus lesion in rats prevents dopaminergic nigral neuron degeneration after striatal 6-OHDA injection : behavioural and immunohistochemical studies. *Eur. J. Neurosci.*, 1996, **8** : 1408-1414.

POLLAK P. *et al.* Effets de la stimulation du noyau sous-thalamique dans la maladie de Parkinson. *Rev. Neurol. (Paris)*, 1993, **149** : 175-176.

SCHUSKE K., JORGENSEN E. M. Vesicular glutamate transporter - Shooting blanks. *Science*, 2004, **3004** : 1750-1752.

SIEGFRIED J., LIPPITZ B. Bilateral chronic electrostimulation of ventroposterolateral pallidum : a new therapeutic approach for alleviating all parkinsonian symptoms. *J. Neurosurg.*, 1994, **35** : 1126-1130.

STURM V. *et al.* The nucleus accumbens : a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. *J. Chem. Neuroanat.*, 2003, **26** : 293-299.

TASKER R. R. Deep brain stimulation is preferable to thalamotomy for tremor suppression. *Surg. Neurol.*, 1998, **49** : 145-153.

TASKER R. R. *et al.* Deep brain stimulation and thalamotomy for tremor compared. *Acta Neurochir. Suppl. (Wien)*, 1997, **68** : 49-53.

VELASCO F., VELASCO M., VELASCO A. L., MENEZ D., ROCHA L. Electrical stimulation for epilepsy : stimulation of hippocampal foci. *Stereotact. Funct. Neurosurg.*, 2001, **77** : 223-227.

VERCUEIL L. *et al.* High-frequency stimulation of the subthalamic nucleus suppresses absence seizures in the rat : comparison with neurotoxic lesions. *Epilepsy Res.*, 1998, **31** : 39-46.

VOLKMANN J. *et al.* Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. *Ann. Neurol.*, 1998, **44** : 953-961.

VONCK K., BOON P., ACHTEN E., DE REUCK J., CAEMAERT J. Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. *Ann. Neurol.*, 2002, **52** : 556-565.

WALLACE B. A. The neuroprotective effects of subthalamic nucleus (STN) suppression. Université Joseph Fourier - Grenoble I, Doctorat d'Université, Neurosciences, 2004.

WELTER M. L. *et al.* Effects of high-frequency stimulation on subthalamic neuronal activity in parkinsonian patients. *Arch. Neurol.*, 2004, **61** : 89-96.

WINDELS F. *et al.* Influence of the frequency parameter on extracellular glutamate and gamma-aminobutyric acid in substantia nigra and globus pallidus during electrical stimulation of subthalamic nucleus in rats. *J. Neurosci. Res.*, 2003, **72** : 259-267.

A.-L. BENABID,
INSERM U318,
Université Joseph Fourier,
CHU Albert Michallon, Pavillon B, BP 217,
F-38043 Grenoble Cedex 9 (France).
E-mail : Alim-Louis.Benabid@ujf-grenoble.fr.