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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

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Abstract—Electrophysiological recordings were made in anaesthetized rats to investigate the mode of function of high-frequency stimulation of the subthalamic nucleus used as a therapeutic approach for Parkinson's disease. High-frequency electrical stimulation of the subthalamic nucleus (130 Hz) induced a net decrease in activity of all cells recorded around the site of stimulation in the subthalamic nucleus. It also caused an inhibition of the majority of neurons recorded in the substantia nigra pars reticulata in normal rats (94%) and in rats with 6-hydroxydopamine lesions of the substantia nigra pars compacta (90%) or with ibotenic acid lesions of the globus pallidus (79.5%). The majority of cells recorded in the ventrolateral nucleus of the thalamus responded with an increase in their activity (84%).

These results show that high-frequency stimulation of the subthalamic nucleus induces a reduction of the excitatory glutamatergic output from the subthalamic nucleus which results in deactivation of substantia nigra pars reticulata neurons. The reduction in tonic inhibitory drive of nigral neurons induces a disinhibition of activity in the ventrolateral motor thalamic nucleus, which should result in activation of the motor cortical system. © 2000 IBRO. Published by Elsevier Science Ltd. All rights reserved.

Key words: Parkinson's disease, basal ganglia, globus pallidus, electrophysiology, electrical stimulation.

The subthalamic nucleus (STN) has been demonstrated to play a major role in the control of movements by exerting a glutamatergic excitatory influence on the output structures of the basal ganglia.[47,49] In experimental parkinsonism, electrophysiological studies have shown that degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) induces disorganization of STN neuronal activity, expressed by the changes in the firing rate and/or the firing pattern, in rats[15,25,26] and monkeys.[13,39] This abnormal STN activity provokes an increase in firing rate and a change in firing pattern of the internal part of the globus pallidus (GPi) neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys[13,18] and in the substantia nigra pars reticulata (SNr) of rats rendered hemiparkinsonian by unilateral injection of 6-hydroxydopamine (6-OHDA).[15,40] According to the generally accepted functional organization of the basal ganglia,[1,2] this change in the firing activity of output structures of the system is supposed to induce an increase in the tonic inhibitory influence exerted by these structures on the activity of motor thalamic nuclei, resulting in deactivation of motor cortical areas. From these data, the STN has been identified as a potential target for neurosurgical procedures used in therapy for Parkinson's disease. STN lesions have been shown to induce an improvement in parkinsonian motor symptoms accompanied by the appearance of abnormal movements and multiple deficits in attentional tasks.[3–5,12] In order to avoid these side-effects, we have replaced ablative lesions by high-frequency stimulation (HFS), which had been used in the ventral intermediate nucleus of the thalamus to replace thalamotomy in the treatment of tremor.[6,7] We have shown that HFS of the STN alleviates akinesia, rigidity and tremor in parkinsonian monkeys,[8,9,20] and in patients suffering from a severe form of Parkinson's disease.[29,34–36] The threshold of current intensity inducing positive effects does not induce side-effects.[8,9,20,34,37] In addition, we have observed that when the stimulation is stopped, the positive effect can be maintained for seconds to minutes, but is always reversible.[8,9]

It is clear now that STN HFS can reverse parkinsonian motor symptoms, but its basic mechanism is still obscure. In a preliminary study performed on normal rats,[11] we have shown that repeated single shocks applied to the STN induced increased activity in SNr neurons. In contrast, STN HFS (130 Hz) induced a net decrease in firing rate in SNr and entopeduncular nucleus (EP) neurons, and an increase in globus pallidus (GP) neuronal activity. The present work was aimed at a better understanding of the mode of function involved in the inhibitory effect of STN HFS, and on its consequences on various structures of the basal ganglia in normal and pathological conditions. We report here the results of the following experiments: (i) responses of SNr neurons to STN HFS in normal rats and in the 6-OHDA rat model of parkinsonism; (ii) responses of SNr neurons to STN HFS in rats with ibotenic acid lesion of the GP in order to investigate the role of the GP as a potential step in inducing SNr inhibition by its GABAergic efferents after being activated during STN HFS;[11] (iii) the effect of STN HFS on its

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Abbreviations: EP, entopeduncular nucleus; GP, globus pallidus; GPi, internal part of the globus pallidus; HFS, high-frequency stimulation; ISIH, interspike interval histogram; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6-OHDA, 6-hydroxydopamine; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; TH, tyrosine hydroxylase; VL, ventrolateral nucleus of the thalamus; VM, ventromedial nucleus of the thalamus.

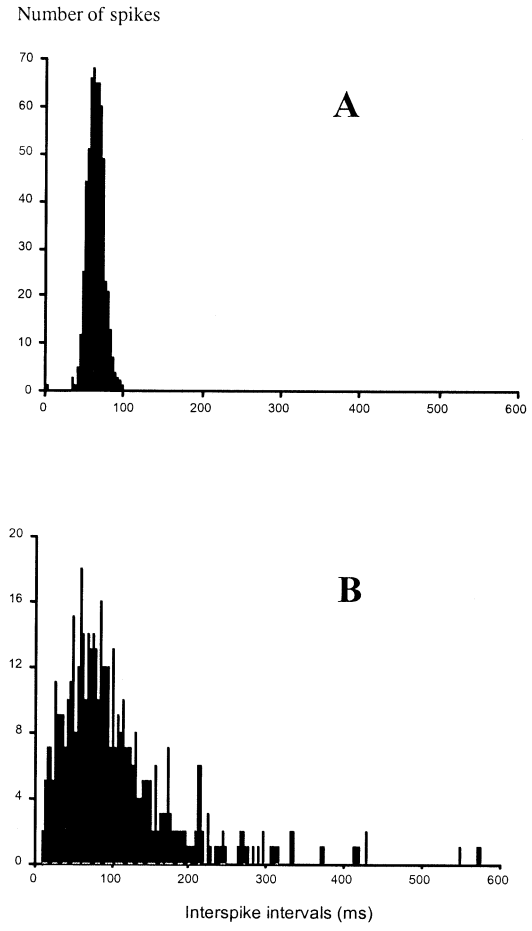

Fig. 1. ISIHs (bin width 4 ms, $n = 1000$ spikes) illustrating the firing pattern of two different STN neurons. (A) Regular or slightly irregular pattern. (B) Irregular firing pattern, including burst activity.

own neuronal activity in order to substantiate the hypothesis of local inhibition by HFS; and (iv) the effect of STN HFS on the activity of the ventrolateral nucleus of the thalamus (VL), which is known to receive direct GABAergic projections from the output structures of the basal ganglia.

EXPERIMENTAL PROCEDURES

The experiments were carried out in adult male Wistar rats ($n = 35$) weighing 270–350 g. They were kept under artificial conditions of light, temperature and humidity, with food and water available *ad libitum*. All animal experiments were carried out in accordance with the UK Animals (Scientific Procedures) Act, 1986 and associated guidelines, and the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Substantia nigra pars compacta and globus pallidus lesions

Rats were anaesthetized with chloral hydrate (400 mg/kg, i.p.) and mounted in a stereotaxic frame. Drugs were injected using a stainless steel cannula connected via a polyethylene catheter to a Hamilton microsyringe which was controlled by an infusion pump.

Lesions were made in SNc dopaminergic neurons by unilateral stereotaxic injection of 8 μg 6-OHDA (Sigma, Paris, France) dissolved in 4 μl saline supplemented with 1% ascorbic acid. The injection was performed in the SNc according to the coordinates of the rat brain atlas of Paxinos and Watson[44] (A 3.7, L 2.2, H 7.5) at a rate of 0.5 μl/min. All rats were tested for rotational behaviour induced by apomorphine injection (0.05 mg/kg, s.c.) two weeks post-surgery. This behavioural test was used as an index of dopamine depletion,[27] and only rats showing consistent turning towards the side contralateral to the lesion at more than 20 turns per 5 min were used for electrophysiological recordings, which were carried out three to four weeks after SNc 6-OHDA injection.

Lesions were made in the GP by microinjection of ibotenic acid (Sigma, Paris, France; 50 nmol/ml in 0.1 M sodium phosphate buffer, pH 7.4) into two dorsoventral sites of the GP (A −1.0 mm, L 3.2 mm, D 6.0 and 6.75 mm). For each site, 0.3 μl was infused at a rate of 0.25 μl/min. Electrophysiological recordings were carried out three to four weeks after ibotenic acid injection into the GP.

Electrophysiology

Electrophysiological recordings of the effects of STN HFS were carried out in urethane-anaesthetized rats using the same dosage (1.3 g/kg, i.p.) and the same protocol. Animals were placed in a stereotaxic frame, and the skull overlying the stimulated and recorded structures was removed. A concentric stimulating bipolar electrode (tip diameter 200 μm) was inserted stereotaxically into the STN obliquely at an angle of 12°, in the rostrocaudal direction when recordings were made in the SNr and STN, and caudorostrally when recordings were made in the VL. Stimuli were delivered by a WPI accupulser and stimulus isolation units (Word Precision Instruments, Aston, UK), which gave rectangular pulses. The stimulation parameters used in this study were: frequency 130 Hz, pulse width 60 μs, intensities 10–1000 μA, train duration 5 s. In order to avoid the artefacts of stimulation, spike discharges were not counted during the 5-s stimulation periods. Recordings were carried out before and after the application of STN HFS. Extracellular single-unit recordings were performed using glass micropipettes containing 1% Pontamine Sky Blue in 3.0 mol/l NaCl (impedance 5–15 MΩ). Recorded structures were targeted using the stereotaxic coordinates of the rat brain atlas of Paxinos and Watson:[44] SNr (A 3.2–4.2, L 2.2–2.5, H 7.5–8.5), STN (A 5, L 2.3, H 7.5–8.2), VL (A 6.7–7.2, L 2–2.5, H 5.5–6.5). The extracellular spikes were amplified, bandpass-filtered (300–3000 Hz) using a DAM-80 preamplifier (WPI, UK), displayed on an oscilloscope and stored in a computer equipped with the brainwave system (Datawave Technologies, Longmont, USA). During off-line analysis, this system allowed us to generate the spontaneous firing histograms and interspike interval histograms. Only neuronal activities with a signal-to-noise ratio >3:1 and stable discharge were investigated. For each structure, recorded cells were identified according to the pattern of discharge described in the literature and confirmed by histological verification of the recording sites. The baseline firing of each tested neuron was recorded for 2–3 min before STN electrical stimulation was applied.

Data analysis

Firing rate histograms, interspike interval histograms (ISIHs), the response period (around the time of the change in the firing rate) and the after-effect period (once the basal level of firing rate was recovered) were calculated. The cells were considered as responsive or not responsive to STN HFS on the basis of their firing rate change with respect to the control prestimulation period. Neurons showing a firing rate increase or decrease by more than 20% from the mean frequency of the prestimulation period were considered as responsive.

According to the ISIH, the firing patterns were divided into two different groups. (1) The first group is called the regular firing pattern, including a slightly irregular pattern, with an ISIH characterized by symmetrical or nearly symmetrical distributions of the interspike intervals (Fig. 1A). (2) The second group concerned the irregular firing pattern, including burst activity. In this group, the ISIH was characterized by a random and asymmetrical distribution of the interspike intervals (Fig. 1B). Visual inspection of digital neuronal activity displays was a useful complement for the analysis of the discharge patterns of the units.

Results are presented as mean ± S.D. Student's *t*-test and the chi-squared test were used to determine the statistical significance of the data.

Histology and immunohistochemistry

At the end of each recording session, the last recording site was marked by electrophoretic injection of Pontamine Sky Blue through the micropipette (−20 μA for 15 min). Rats were then deeply anaesthetized and perfused transcardially with saline (0.9%), followed by the fixative 4% paraformaldehyde in 0.1 M phosphate-buffered saline

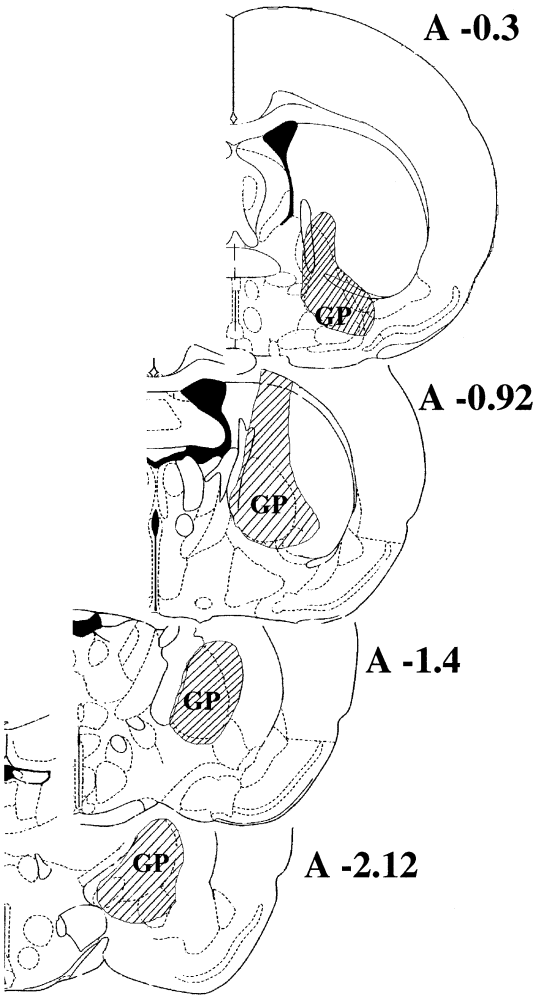

Fig. 2. Schematic reconstruction of ibotenic acid-induced lesion of the GP showing a representative example of the total lesion of the nucleus.

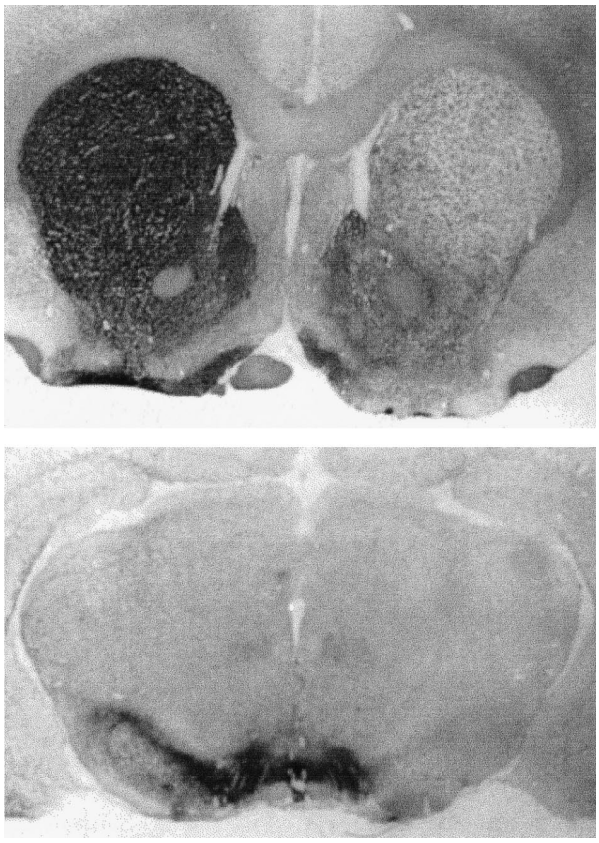

Fig. 3. Photomicrographs of TH-immunoreactive cells in the SNc (below) and fibers in the striatum (top) on the normal side (left) and on the 6-OHDA-injected side (right). Note the total lesion of TH cells induced by the injection of 6-OHDA into the SNc. Magnification: ×10.

(pH 7.4). The brains were removed, postfixed for 4 h in the same fixative, frozen in isopentane/liquid N_2 and cut into 40-μm frontal sections. Cresyl Violet staining was used to determine the location of Pontamine Sky Blue dots in each recorded structure and the tip of the stimulating electrode. The extent of the GP lesion was determined on the basis of pallidal cellular loss and reactional gliosis, also using Cresyl Violet staining. Only rats with a total lesion of the GP were used in this study (Fig. 2). As shown in Fig. 2, ibotenic acid injection ablated not only the GP but also a portion of the dorsolateral striatum. In 6-OHDA-injected rats, the extent of the SNc lesion was determined using immunohistochemical staining of tyrosine hydroxylase (TH), as described previously.[46] Representative examples of the total loss of TH-immunoreactive cells in the SNc and fibers in the striatum after 6-OHDA injection are shown in Fig. 3.

RESULTS

Substantia nigra pars reticulata neurons

A total of 112 cells in the SNr were tested for STN high-frequency electrical stimulation. Forty-nine neurons were recorded in normal rats ($n = 10$), 29 in 6-OHDA-injected rats ($n = 6$) and 39 in rats ($n = 7$) with GP lesion. The proportions of SNr cells according to their responses to STN HFS are summarized in Table 1, and Fig. 3 illustrates representative examples of responses to STN HFS of the majority of tested cells in the SNr.

In normal rats, the spontaneous activity of recorded neurons in the SNr ($n = 49$) was characterized by a tonic regular or slightly irregular discharge pattern with a mean firing rate of 15.2 ± 6.1 spikes/s (mean ± S.D.). In rats with 6-OHDA SNc lesions, the discharge pattern of SNr neurons ($n = 29$) was obviously irregular and the mean firing rate (21.3 ± 7.4 spikes/s) was significantly higher (40%, Student's *t*-test, $P < 0.01$) than that obtained in normal rats. In rats with ibotenic acid lesions of the GP, the discharge pattern of SNr neurons ($n = 39$) was similar to that recorded in normal rats. The mean firing rate (15.5 ± 7.5 spikes/s) was also not significantly different from that of normal rats (Student's *t*-test, $P > 0.05$).

In normal rats, the large majority of cells tested in the SNr (46/49, 94%) showed a significant decrease in firing rates in response to STN HFS (Student's *t*-test, $P < 0.001$; Fig. 3A; 130 Hz frequency, 5 s train duration). The threshold of current intensity inducing this response was 300 μA. After stimulation was stopped, the firing rate did not return to its basal level of activity immediately, but an important after-effect was observed (Fig. 4A). The response duration varied from 50 to 120 s, with a mean of 84.41 ± 16.38 s. Three of 49 cells (6%) responded with a short period of excitation (8–10 s), followed by a decrease in neuronal activity with a response duration which varied from 50 to 160 s. The mean response duration was 88.22 ± 17.12 s.

In rats with SNc lesions, electrophysiological recordings were carried out three weeks after 6-OHDA injection. In the majority of SNr cells tested (90%, 26/29), STN HFS (130 Hz at 500 μA, lasting 5 s) induced the same effect as obtained in

Table 1. The proportions of cells recorded in the substantia nigra pars reticulata, the subthalamic nucleus and the ventrolateral nucleus of the thalamus according to the nature of their responses to high-frequency stimulation of the subthalamic nucleus

	Inhibition	Excitation	No response	Total number of cells
SNr, normal	46	3	0	49
SNr, 6-OHDA lesion	26	2	1	29
SNr, GP lesion	31	6	2	39
STN, normal	14	0	0	14
VL, normal	0	16	3	19

Note that these responses were recorded in normal rats for the SNr, STN and VL, and in rats with 6-OHDA lesions of the SNc or with ibotenic acid lesions of the GP for the SNr.

normal rats, i.e. an inhibitory response characterized by a low firing rate for 80–100 s before reaching spontaneous baseline activity (Fig. 4B), with a mean of 89.11 ± 6.21 s. The duration of the inhibitory response was not significantly different from that obtained in normal rats (Student's *t*-test, $P > 0.05$). Two of 29 cells tested (7%) showed excitation of their firing activity in response to STN HFS and one cell (3%) presented no response. The distribution of SNr neuronal responses in this group of rats is similar to that obtained in normal rats (chi-squared test, $\chi^2 = 4.82$, $P > 0.05$).

In rats with GP lesions, recordings were carried out three weeks after ibotenic acid injection into the GP. STN HFS induced a decrease in the firing rate in the majority of SNr neurons tested (79.5%, 31/39; Fig. 4C). After stimulation was stopped, the mean duration of inhibition was 44.36 ± 10.87 s, with a range between 20 and 80 s. The duration of the SNr inhibitory response to STN HFS was significantly smaller than that obtained in normal rats (Student's *t*-test, $P < 0.01$) and in rats with SNc 6-OHDA lesions (Student's *t*-test, $P < 0.01$). Six of 39 SNr cells tested (15.5%) showed excitation of their firing activity in response to STN HFS and two cells (5%) presented no response. The distribution of SNr neuronal responses in this group of rats was similar to that obtained in normal rats (chi-squared test, $\chi^2 = 4.85$, $P > 0.05$) and in 6-OHDA-injected rats (chi-squared test, $\chi^2 = 4.87$, $P > 0.05$).

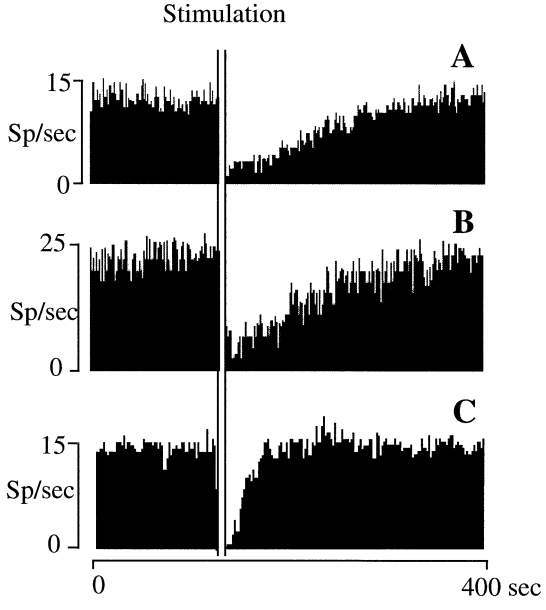

Fig. 4. Ratemeter records (number of spikes per 1-s period) showing representative examples of typical responses of identified SNr neurons to HFS (130 Hz; pulse width 60 μs, intensity 300 μA, train duration 5 s) of the STN in normal rats (A) and in rats with 6-OHDA-induced SNc lesions (B) or with ibotenic acid-induced GP lesions (C).

Effect of subthalamic nucleus stimulation on neuronal activity in this nucleus

A total of 14 cells in the STN was tested for STN electrical stimulation in normal rats ($n = 6$). Their distance to the stimulation site was, on average, 400 ± 150 μm. In all cells tested (Table 1), the application of HFS in the STN (130 Hz at 500 μA, lasting 5 s) induced a decrease in STN neuronal activity for 30–90 s after the stimulation was stopped (Fig. 5). The mean duration of this after-effect was 54.39 ± 11.27 s.

Effect of subthalamic nucleus stimulation on neuronal activity in the ventrolateral nucleus of the thalamus

The effect of STN HFS on VL neurons was tested in six normal rats. The spontaneous activity of VL neurons was characterized by burst firing pattern, sometimes with oscillations. The majority of VL cells tested (84%, 16/19) for STN stimulation responded with a significant increase in activity using the same stimulation parameters as described below (Fig. 6). After the stimulation was stopped, the VL cells tested showed more oscillations and the responding duration varied from 25 to 140 s, with a mean ± S.D. of 80.78 ± 20.32 s. Three of 19 cells (16%) showed no response to STN HFS.

DISCUSSION

In the present study, we showed that STN HFS induced (i) a significant decrease in STN neuronal activity, (ii) a significant decrease in firing rate of SNr neurons in intact animals and in rats with 6-OHDA-induced SNc lesions or with ibotenic acid

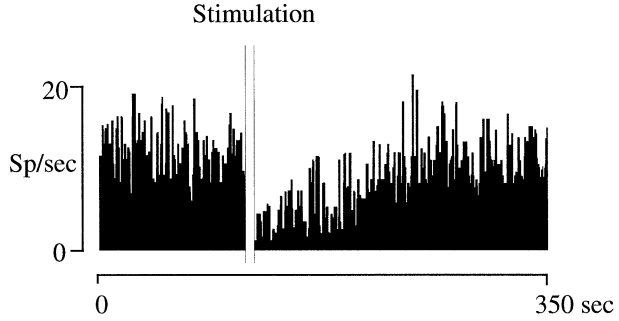

Fig. 5. Ratemeter records (number of spikes per 1-s period) showing the effect of HFS (130 Hz; pulse width 60 μs, intensity 300 μA, train duration 5 s) of the STN on its own neuronal activity in normal rats.

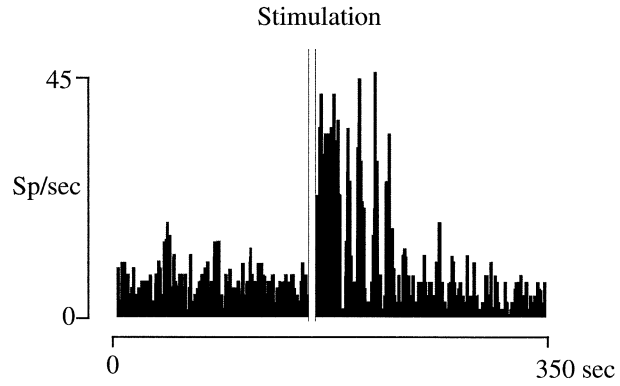

Fig. 6. Ratemeter records (number of spikes per 5-s period) showing examples of the typical response of neurons recorded in the VL to HFS (130 Hz; pulse width 60 μs, intensity 300 μA, train duration 5 s) of the STN in normal rats.

lesion of the GP, and (iii) a significant increase in the firing rate of the VL.

From the results of several studies carried out in primate models of parkinsonism and in patients suffering from severe Parkinson's disease, it is well established that STN HFS[8,9,20,21,29,34–36] produces the same effect as STN lesion,[3,12] i.e. the alleviation of parkinsonian symptoms. There is also evidence showing that abnormal increased activity and burst pattern in STN neurons are associated with the manifestations of parkinsonism,[13,25,26,39] while reduced activity leads to abnormal involuntary movements[15,17,23,46] in rats and monkeys. Muscimol injected into the STN of MPTP monkeys reduces local neuronal activity. This effect is followed by reduced akinesia, tremor and rigidity, as well as the emergence of dyskinesias in the contralateral limbs.[51] From these studies, it appears that inhibition of STN neuronal activity is one important way of suppressing parkinsonian symptoms.

The results of the present study demonstrate that, in the rat, STN HFS produces an inhibitory influence on its principal efferent structure, the SNr, which is the major output structure of the basal ganglia. In our previous preliminary study,[11] we showed that, in addition to SNr inhibition, STN HFS also induced suppression of activity in the EP (the equivalent of the GPi in monkey and human), which represents the second output structure of the system. This effect could be the consequence of the inhibition of STN neuronal activity induced by STN HFS. In fact, as revealed in our present work, when STN HFS was given, the firing rate of STN neurons decreased. Combining all electrophysiological and pharmacological data with those of the present study, we can postulate that HFS induces a direct inhibitory influence on the stimulated neurons, through an as yet unknown mechanism. There are several possibilities: one possibility could be that STN HFS induces a so-called depolarization block of STN cell activity, which suppresses their powerful glutamatergic excitatory effect on the basal ganglia output structures. This hypothesis is supported indirectly by the relationship between the responses of SNr cells and STN stimulation frequency. SNr cell activity is increased by single shocks and low-frequency (less than 60 Hz) STN stimulation, while it is strongly decreased by high-frequency (130 Hz) STN stimulation.[11] Similar results have been observed in our parkinsonian patients. Limousin *et al.*[34] showed that the clinical effect of STN stimulation on parkinsonian motor symptoms is dependent on frequency. Frequencies lower than 30 Hz are ineffective and those over 50 Hz are effective. In addition, this hypothesis is acceptable and supported by the inhibition of the subthalamic neurons recorded. These results are in good agreement with other electrophysiological studies using electrical[24] or pharmacological[47] stimulation of the STN. Microinjection of a GABA antagonist, bicuculline, into the STN induces an increase in firing rate of its efferent structures, while the GABA agonist, muscimol, induces the opposite effect. These results provide evidence for excitatory glutamatergic transmission in STN projections.[47] However, with regard to action potential production, it is difficult to explain that HFS works by a depolarization.[10]

Another possibility might be that STN HFS can disrupt one or more neural networks, or produce a net inhibition in the network either by preferential activation of inhibitory neurons or by the properties of the network itself when driven at high rates. For example, recent investigations have shown that the STN and GP are two tightly interconnected structures that control the output structures of the basal ganglia.[48] On the one hand, STN neurons send glutamatergic projections to the GP,[45,48] and GP GABAergic neurons send projections to the STN and also to the SNr and EP. On the other hand, in our previous work, we have shown that STN HFS induces an increase in GP neuronal activity in rats.[11]

Nevertheless, our results show that lesions of the GP induced a dramatic effect on the duration and recovery from the inhibition induced by STN HFS. From these results, we can postulate that the GP plays an important role in STN HFS-induced inhibition of SNr neuronal activity in intact animals and that a different mechanism, partially independent of GP, may be responsible for the SNr inhibition in animals with GP lesions. As it has been shown that anaesthetics can influence basal ganglia neuronal activities, the delay in recovery observed after STN HFS could be due to the possible interaction of anaesthesia and the effects of STN HFS. However, in our previous study, carried out on non-anaesthetized MPTP-treated monkeys, we have shown that STN HFS induced an improvement in parkinsonian motor symptoms and that after the stimulation was stopped this amelioration was maintained during seconds to minutes.[9] This after-effect was also observed in our operated parkinsonian patients (unpublished data). From these observations, we can postulate that the delay in recovery is a specific response to STN HFS.

According to the concept of motor circuit functional organization, motor nuclei of the thalamus [ventromedial nucleus (VM) and VL in the rat] are the last relay before the signals from the basal ganglia motor-regulating circuit enter the cortex. Inhibition of the two output structures in the system would induce a decrease in the inhibitory action on the motor thalamus and consequently an increase in the excitatory input to the cortex. The present study shows that STN HFS increased the firing rate of VL neurons. This result is consistent and in good agreement with our previous data showing that STN HFS induced an increase in VM neuronal activity in a frequency-dependent manner.[19] So far, in the absence of data showing the existence of direct projections from the STN to the VM/VL, the effects of STN HFS on these nuclei should be mediated by SNr and EP GABAergic inhibitory projections. According to the motor circuit concept, increased activity in motor thalamic nuclei has to result in an increase in neuronal activity in cortical areas. This hypothesis is confirmed by a positron emission tomography study, using regional cerebral blood flow measurements in

parkinsonian patients. Limousin *et al.*[33] have shown that STN HFS, which produced a significant improvement in movement performance, was accompanied by an increase in cortical activity of the supplementary motor area, dorsolateral prefrontal cortex and cingulate. These effects are similar to those observed after the administration of apomorphine. Jenkins *et al.*[28] have shown that impaired activation of these cortical areas was reversed when akinesia was treated with apomorphine. From the results of these studies, it appears that both STN HFS and apomorphine treatment result in the same normalization of the pattern of activation of non-primary motor cortical areas. Another similarity between STN HFS and apomorphine treatment was observed in the rat. In the present study, we show that STN HFS induced an inhibitory effect on recorded neurons in the STN, and a similar effect was observed after systemic injection of apomorphine in rats with 6-OHDA SNc lesions.[31] In addition to this evidence, other arguments reinforce the idea that HFS plays a direct inhibitory effect on STN neurons. Chronic HFS produces an effect analogous to that seen after lesions of several structures implicated in the pathophysiology of Parkinson's disease: (i) the STN, with evidence from primate models of parkinsonism (lesion,[3,12] HFS[8,9]) and from parkinsonian patients (lesion,[21] HFS[29,34–36]); (ii) the ventral intermediate nucleus of the thalamus (lesion,[41,42,50] HFS[6,7]); (iii) the parafascicular nucleus of the thalamus (lesion,[43] HFS[16]); and (iv) the GPi (lesion,[32,38] HFS[22,30]). Concerning the GPi, in addition to the similarities observed between the clinical effect induced by lesions and HFS, Boraud *et al.*[14] have shown that, during HFS, the improvement in parkinsonian motor symptoms was correlated to a significant decrease in the firing rate of GPi cells recorded in the stimulated area.

CONCLUSIONS

Our electrophysiological results show that HFS of the STN has an inhibitory influence on STN neurons, reducing excitatory output from the STN, which results in deactivation of the output nuclei of the basal ganglia. The reduction in tonic inhibitory drive of SNr and EP (GPi in monkey and human) neurons in response to STN HFS induces a disinhibition of activity in motor thalamic nuclei which results in activation of the motor cortical system. Moreover, in order to investigate the precise modifications in membrane properties of STN neurons in response to high-frequency electrical stimulation, intracellular electrophysiological techniques should be used.

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