Effects of High-Frequency Stimulation in the Internal Globus Pallidus on the Activity of Thalamic Neurons in the Awake Monkey

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Anderson, Marjorie E., Nadia Postupna, and Mark Ruffo. Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. J Neurophysiol 89: 1150–1160, 2003; 10.1152/jn.00475.2002. The reduction in symptoms of Parkinson’s disease produced by high-frequency stimulation (HFS) in the internal globus pallidus (GPi) has been proposed to be due to stimulus-induced inactivation of pallidal neurons and resulting disinhibition of thalamic neurons. We tested this in awake Macaca fascicularis by stimulating between pairs of electrodes inserted into GPi under electrophysiological control and recording the responses evoked in thalamic neurons. HFS produced a reduction, not an increase, in discharge frequency during the stimulus train in 77% of the responsive thalamic neurons. Only 16% of the responsive cells showed an increase in discharge during stimulation and, for some of these, stimulation at a similar intensity produced contralateral muscle contraction, a probable sign of current spread to the internal capsule. The few thalamic neurons studied during bursting had a reduction in burst frequency and duration during HFS. We conclude that high-frequency stimulation within GPi does not necessarily facilitate thalamic discharge, and it may act, instead, to interrupt abnormal patterns of thalamic discharge associated with parkinsonian symptoms.

INTRODUCTION

High-frequency stimulation (HFS) within the internal globus pallidus (GPi), the subthalamic nucleus (STN), or the ventrolateral thalamus has become a treatment of choice for the drug-resistant symptoms of Parkinson’s disease (Alegret et al. 2001; Ashby et al. 1998; Benabid et al. 1994; Benazzouz et al. 1993; Boraud et al. 1996; Brown et al. 1999; Gross et al. 1997; Krack et al. 1998a,b; Limousin et al. 1995a,b; Pahwa et al. 1997; Pollak et al. 1996; Siegfried and Lippitz 1994; Valdeolmilla et al. 2001, 2002). Benazzouz et al. (1993) have also reported a reduction in rigidity and bradykinesia during stimulation of STN in monkeys after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration, and the same group (Boraud et al. 1996) has reported that HFS in GPi also reduces rigidity and bradykinesia in the same monkey model. This effect is achieved through electrodes implanted in either GPi or STN that are activated with continuous trains of biphasic stimuli delivered at frequencies in excess of 100 Hz. The symptomatic relief during stimulation is reported to approximate or exceed that provided by pallidotomy, in which a lesion is made in the posterolateral GPi (Ashby et al. 1998; Brown et al. 1999). Thus the paradox exists that symptoms are relieved when neurons are destroyed in GPi or when electrical stimuli are delivered repeatedly in the same region.

The mechanisms by which HFS in either GPi or STN may lead to symptomatic relief are unknown. It is hypothesized that either direct stimulation within GPi or stimulation within the primary known source of excitatory input to GPi, the STN, reduces the activity of the GPi inhibitory output neurons and thus increases the activity of thalamic target neurons by disinhibition. The reduction of activity at the site of stimulation—GPi or STN—is proposed to occur 1) because of a depolarization block of voltage-gated currents in neuronal elements in the stimulated structure (Benazzouz et al. 1995; Beurrier et al. 2001; Burbaud et al. 1994) or 2) because of activation of presynaptic axons that have an inhibitory action on the neurons in GPi or STN (Benazzouz et al. 1995; Boraud et al. 1996; Wu et al. 2001).

To test the hypothesis that HFS in GPi or STN results in a facilitation of thalamocortical neurons, one could record from neurons in basal ganglia-receiving areas of the thalamus during stimulation. One study has attempted to record the effect of stimulation in STN on neurons in the ventrolateral nucleus of anesthetized rats and has reported excitation in 16 of 19 thalamic cells studied (Benazzouz et al. 2000). In reality, however, their conclusions were based on the change in activity after the stimulus train had ended, since stimulus artifacts obscured the neuronal activity during the stimulus train.

We have recorded the change in activity of thalamic neurons during trains of high-frequency stimuli applied between microelectrodes inserted under electrophysiological guidance into GPi of monkeys. By use of a spike-sorting system, we were able to distinguish stimulus artifacts from thalamic neuronal spikes and record activity during the HFS. Our results indicate that the primary effect of HFS using this technique is inhibition, not facilitation, of target thalamic neurons. These results have been reported in preliminary form (Postupna et al. 2001).

METHODS

Data were obtained from two juvenile male monkeys (M. fascicularis; initial weight 3.4 and 4.0 kg). All animal procedures were approved by the University of Washington Animal Care Committee and were in accordance with the Guiding Principles in the Care and Use of Animals in Research. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Use of Animals (American Physiological Society 2000). Animals were on food restriction during the week, with full rations on the weekend. Water was available in their cages at all times. One animal (monkey D) had received a prior infusion of MPTP into the left putamen via a cannula attached to an implanted osmotic minipump, but his symptoms were not severe enough to evaluate their response to HFS. The other animal was intact.

Surgical procedures

Using standard surgical techniques (Anderson 1978), two circular Ciflex chambers (Crist, Hagerstown, MD) were implanted over craniotomies. One, at a 45° angle from the sagittal plane, allowed access to the GP, and the second, angled from posterior to anterior at a 30° angle from the coronal plane, allowed access to the thalamus. Nylon tubes were also implanted anterior and posterior to the chambers to accommodate stabilization bars.

Stimulation in the GP

The general location of the GP was first mapped with tungsten electrodes driven by a hydraulic microdrive. The defining characteristics of GP were neurons with high-frequency discharge generally not interrupted by pauses of 0.5 s or longer that were deep to neurons with similar frequency, but significant pauses. GP neurons were sometimes preceded in the track by a short region with intermediate, steady discharge rates characteristic of border cells (DeLong 1971).

After mapping, insulated tungsten or platinum–iridium electrodes were inserted for HFS. Tungsten electrodes (8 mil) were insulated with a polyamide sleeve (Micro–ML tubing) along the shaft and with multiple layers of epoxylite over the taper. Epoxylite was ground from the tip and the tips were plated with particulate iron to give a final impedance of approximately 5 to 20 KΩ. Platinum–iridium electrodes, used for one stimulus pair, were glass insulated. Two electrodes, separated mediolaterally or anterior–posteriorly by 2 mm, were held in a screw-driven minimicrodrive and lowered in tandem while recording from each. An implantation depth was chosen at which high-frequency discharge, typical of GP activity, could be recorded from each electrode. These electrodes were then left in place for 4–5 days to allow stimulation while recording from thalamic neurons at different sites. Similar electrodes were reinserted, again under electrophysiological guidance, after a lapse of ≥2 days, at the same or nearby chamber locations.

Trains of constant current biphasic stimuli were applied between the two pallidal electrodes. The standard stimulus protocol used a train of 100 biphasic pulses, 0.2 ms duration for each phase, 120 Hz, applied at a stimulus intensity of 300 μA. In some cases, trains of 10, 50, or 1,000 pulses were applied, lower intensity pulses (50 to 200 μA) were tested, or the duration of each phase of the stimulus pulse was reduced to 0.1 ms.

Stimulus trains were most commonly triggered when the animal positioned its hand in the central hold zone to initiate a trial in the behavioral task (see following text). To assure that changes in activity were not simply due to task conditions, the stimulus trigger was sometimes switched to 200 ms following the GO tone used to trigger movement. If the animal was not working well, stimulus trains could be triggered manually by the experimenters.

As a test of the possibility that stimulus artifacts might be occluding sufficient neuronal spikes to produce the results described below, we sometimes disconnected the stimulus leads from the electrodes and left them hanging nearby, but disconnected. This produced a stimulus artifact, although its configuration and duration were not identical to those seen when the leads were connected. We will refer to this as FAKE stimulation.

Behavioral task

Monkeys were trained to make center-out arm movements across the surface of a digitizing pad (Turner and Anderson 1997). A lightweight splint that crossed the wrist and held the pick-up for the digitizing pad allowed measurement of hand position in x and y coordinates. Target locations were displayed to the animal via a one-way mirrorized sheet of plexiglass that displayed targets on an overhead computer monitor as virtual images in the plane of the digitizing pad. After holding his hand over a central circular target (hold home) zone for a variable period, a tone triggered movement of the right hand to one of the eight peripheral targets that was illuminated either coincident with the trigger tone (random) or for a brief period 1 to 3 s prior to the trigger tone (random precued).

Neuronal recording

The activity of neurons in the thalamus was recorded extracellularly using tungsten microelectrodes similar to those described above, but with a slightly smaller shaft diameter (5 mil). Signals were amplified, and all waveforms that passed a threshold were saved digitally (Multichannel Acquisition Processor, Plexon). One or more spikes were discriminated from a single electrode using a dual time/window digital discriminator (RASPUTIN, Plexon), with an additional discriminator used to detect stimulus artifacts. For monkey D, some data were digitized off-line from VCR-based taped data. Isolation of individual spikes and artifact waveforms was reevaluated and corrected off-line using principal component analysis and visualization of the selected waveforms (Off-line Sort Program, Plexon). Figure 1 illustrates action potentials recorded from monkeys G (Fig. 1, A and B) and D (Fig. 1, C and D). Note that both large (Fig. 1B) and small (Fig. 1D) spikes could be detected between artifacts in the stimulus train.

Data analysis

Firing patterns and discharge rates during fixed peristimulus time periods were determined from PLEXON-generated files using NEX software (Plexon). Statistical comparison of mean firing rate during stimulation to mean firing rate before and after stimulation trains was done with one-way ANOVA and Tukey post hoc tests (Systat 9). A P value ≤ 0.005 was considered significant.

Histology

Marking lesions were made at known depths in selected tracks by passing DC current (10–30 μA for 10–30 s) through the microelectrode.

After recording was completed, animals were anesthetized deeply with pentobarbital sodium and killed by transcardiac perfusion with saline followed by fixation with 4% phosphate-buffered paraformaldehyde. Following fixation the brains were blocked, postfixed, cryoprotected with sucrose, frozen, and cut into 50-μm-thick sections. In monkey D, the tissue was cut in the parasagittal plane to facilitate location of thalamic recording tracks. In monkey G, a coronal plane of sectioning was used to facilitate location of GP simulating tracks.

RESULTS

Eighty-four cells (55 in monkey D and 29 in monkey G) were studied in the two animals during trains of high-intensity HFS. Based on the histological reconstructions, together with the type of activity recorded at different depths, 73 of these were determined to be in the thalamus at locations shown in Fig. 2.
Effects on thalamic neurons of GP-HFS INHIBITION. A reduction in activity was the predominant stimulus-evoked effect in cells that showed a change in activity during stimulation. Figure 3A shows an example of such a response. In this case, the firing rate dropped abruptly from a mean rate of 18.2 Hz prior to stimulation to a rate of 6.7 Hz during the stimulus train (Fig. 3A). The reduction was sustained throughout the stimulus train, and firing returned to approximately the prestimulus rate when the stimulus train ended. When the pulse duration was reduced from 0.2 to 0.1 ms for each phase, the inhibition disappeared (Fig. 3B). Figure 3C, in which FAKE stimuli were applied to the disconnected stimulus cables, shows that the stimulus-induced inhibition shown in Fig. 3A was not simply due to occlusion of spikes by stimulus artifacts. Although there is a significant \( P < 0.001 \) reduction in detected spike rate during FAKE stimulation (10.7 Hz during stimulation compared with 14.9 Hz during an equivalent time period prior to or 14.7 Hz following stimulation), this reduction (27%) was far less than the 63% reduction elicited by real stimulation with stimulus trains of the same 0.2 ms duration pulses.

To distinguish true stimulus-evoked inhibition from an apparent reduction in discharge that might be due to occlusion of spikes by the stimulus artifact, we compared the percentage reduction in discharge rate for statistically inhibited cells to the percentage of the interstimulus interval duration that was occupied by the saturated stimulus artifact during the same stimulus trials. Figure 4 shows this comparison for both true stimulation (Fig. 4, A and C) and for the cells in which we also used FAKE stimulation (Fig. 4, B and D). The saturated artifact during true stimulation occupied at most 30% and generally <20% of the interstimulus interval (Fig. 4C). True stimulation produced a much larger reduction in mean discharge rate, on the other hand, ranging from 24 to 95% of the prestimulus rate (Fig. 4A). For cells studied when the stimulus leads were disconnected, there was a measured reduction in discharge rate of \( \sim 30\% \) (Fig. 4B), comparable to the portion of the interstimulus interval that was occupied by the saturated artifact (Fig. 4D). Thus the measured reduction in discharge is real and not just a consequence of occlusion of spikes by saturated stimulus artifacts.

As illustrated for another neuron in Fig. 5, activity was suppressed for the duration of the stimulus train. For this cell, the onset of inhibition was rapid at the beginning of the stimulus train and, after rebounding a bit within the first half second (Fig. 5, A and B), was sustained, with a firing rate of approximately 5 Hz through the duration of stimulus trains of either 100 (Fig. 5A) or 1,000 pulses (Fig. 5B).

Inhibition during stimulus trains initiated when the hand reached the hold home zone sometimes seemed to be followed by poststimulus facilitation. This is illustrated in Fig. 6A and B for another neuron during stimulus trains with intensities of 300 and 100 \( \mu A \), respectively. In reality, however, the apparent poststimulus facilitation was often a task-related increase in

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**FIG. 1.** Spike-sorting. A: action potential (red) from a single neuron is distinguished from the saturated stimulus artifacts (blue) and the background noise and stimulus decay (green). B: a scroll of sorted signals shows that the action potential can be detected during the stimulus train. The waveforms are expanded in time 4 times compared with the time base for the entire scroll. C: action potentials of two neurons (red and black) are distinguished from the stimulus artifacts and the background noise and stimulus decay. D: scroll of sorted spikes shows that the large spike was silenced during the stimulus train, but the small black spike was not and was detectable during the train.
activity, such as that shown for the same neuron in Fig. 6C, in which a weak (50 μA) short-duration (10-pulse) stimulus train triggered 200 ms after the GO tone failed to interrupt the movement-related increase in activity.

Movement-associated discharge could be suppressed, however, with stronger stimuli. Figure 6, D and E, show complete initial suppression of perimovement activity during 100 μA stimuli applied in 10- or 100-pulse trains. Complete suppression was not sustained throughout the long perimovement stimulus train with the 100-μA stimulus intensity, however (Fig. 6E), and the recovery during the latter three-quarters of the perimovement stimulus train was greater than that during a train of the same stimulus intensity applied while the hand was held in the hold zone (Fig. 6B).

As shown in Table 1, the standard stimulus protocol produced inhibition in 33 (46%) of the 73 total thalamic neurons studied, 19/44 (43%) in monkey D and 14/29 (48%) in monkey G. Of the 43 thalamic neurons with any stimulus-evoked change in discharge, inhibition was the response in 77%.

FACILITATION. Only 7 of 43 thalamic cells that responded to the standard stimulus protocol were excited by the stimulation (16%). As shown in the example of Fig. 7A, bipolar stimulation between two microelectrodes usually evoked an initial phasic burst of activity, followed by a more extended facilitation. The stimulus-evoked facilitation of another neuron, illustrated in Fig. 7B, was elicited by stimulation through a concentric bipolar electrode that was too large to allow neuronal recording to guide its placement in GPi. Stimulation through this electrode at this depth and intensity (300 μA) also evoked movement of the shoulder. Because the stimulus-evoked overt movement was typical of that evoked by stimulation within the internal capsule, it is likely that there was a direct action of the stimulus on the internal capsule. Because the response pattern—initial phasic activation followed by a sustained increase—is similar to that observed for thalamic neurons excited by HFS through microelectrodes positioned in GPi under electrophysiological guidance, it brings up the possibility that facilitation such as that illustrated in Fig. 7A also was due to stimulus spread to the internal capsule.

Changes in burst discharges

Three thalamic neurons in monkey D, all recorded after MPTP treatment, were bursting at the time that HFS was tested. In each of these, the number of bursts and the spikes/burst both were reduced during HFS. As illustrated in Fig. 8, bursts of two to five spikes occurred during the period prior to the 100-pulse stimulus train. During the 833-ms stimulation period, bursts occurred less frequently and never had more than two spikes/burst. Single spikes or doublets did occur approximately one or two times during each 833-ms stimulus period, however. After stimulation, longer bursts resumed.

Special care must be taken to insure that the apparent reduction in bursts was not just a result of occlusion of spikes by the stimulus artifact. (There would be a higher probability that one spike of a clustered high-frequency burst would be occluded by a stimulus artifact than would a single spike.)
bursts shown here, however, were too long to have occlusion with stimulus artifact as the sole explanation for the reduction in burst discharge during stimulation.

Anatomical distribution of stimulation-induced effects

As shown in Fig. 2, almost all of the thalamic neurons studied were in the ventral thalamus, primarily in VA and VLo. Cells whose activity was reduced during stimulation (red squares) generally were intermixed with cells that showed no response (green circles), although there sometimes seemed to be some clustering.

When the activity of multiple neurons was recorded simultaneously through the same electrode, the cells could show the same or different responses to stimulation in GPi. Figure 9A shows the activity of two such nearby neurons, both of which were inhibited during the stimulus train. Figure 9B, on the other hand, shows the activity of one cell that was inhibited and a second cell, recorded at the same time from the same electrode, that was unaffected during the stimulus train. The difference in the effect on these two cells studied with the same stimulus artifact also argues against the possibility that the reduction in activity during the stimulus train is simply due to occlusion of spikes by the stimulus artifact.
Stimulating microelectrodes were positioned under electrophysiological control. In all cases, both electrodes were positioned at sites of high-frequency discharge (HFD) activity characteristic of GP. This was typically 2–4 mm below the first cells with HFD, usually with significant pauses, and ≥1 mm above the point at which the cellular activity decreased, probably indicative of the internal capsule or the optic tract on the 45° lateral–medial angled tracks. On occasion, regular, intermediate frequency activity typical of “border cells” (DeLong 1971) was encountered above the implantation point at a position consistent with the internal medullary lamina or deep to it at a point consistent with the substantia innominata. Visually responsive fiber-type activity was occasionally encountered 2.5- to 3-mm deep to the final position of the stimulating microelectrodes. Because GPe, in which HFD would first have been encountered, usually has a thickness of <2 mm using this trajectory, and because the optic tract can be encountered deep to lateral portions of GPi, we were confident that both electrodes in each pair were consistently in GPi.

Histological sections of stimulus sites are shown in Fig. 10. In monkey D, sections were cut in the parasagittal plane to optimize identification of the locations at which thalamic neurons were studied. This meant that the sections cut across the trajectory of the pallidal stimulation electrodes. Figure 10, A and B, show electrode penetrations in the GP in two of these parasagittal sections. White arrowheads point to two sites of intense gliosis that would be consistent with positions at which stimuli were applied over the course of the several days that the electrodes were left in place. Figure 10D shows the rostrocaudal and mediolateral arrangement of each of the four electrode pairs, with electrode positions (indicated by matched symbols) separated by 2 mm in the anterior–posterior or medial–lateral plane. In this animal, 1 μl of dextran–rodamine was injected at the position denoted by the open circle in Fig. 10D. This location, which was in the middle of the stimulating electrode positions used to study most thalamic neurons in this animal, is marked by the black arrow in the parasagittal section of Fig. 10B. It is clearly well positioned in GPe.

Sections were cut in the coronal plane in monkey G to optimize identification of the site of GPi stimulation (Fig. 10C). For the last experimental session only, glass-covered electrodes were used for the pair of stimulating electrodes. Passage of current between these electrodes caused the glass to shatter for about 5 mm from the tip up the shaft of each electrode. Figure 10C, which shows the resulting lesion, demonstrates that the tips of the electrodes must have been in GPi. These electrodes were pair 1, as illustrated in Fig. 10E. This pair and pair 3, both of which had at least one electrode at the same anterior plane, were at the locations from which most of the thalamic cells were studied in monkey G (Table 1).

The concentric macroelectrode used for stimulation in one session was inserted, again along the 45° angled track, at the location indicated by the filled circle (position 4) in Fig. 10E. This was the electrode from which shoulder movement was produced by stimulation, and the cell whose activity is illustrated in Fig. 7B was excited. Muscle contraction (of the face) was also evoked by stimulation at 300 μA through one of the microelectrode pairs in GPe, the second pair placed at position 3 (triangles). Another neuron, located rostrally in the thalamus,
was excited by this stimulus pair. Again, it is possible that this excitation was, in fact, due to spread to thalamic-destined axons in the internal capsule.

**Responses of neurons deep to the thalamus**

On some occasions in monkey D the recording electrode track extended deep to the thalamus, sometimes into the GP. The two lateral planes of Fig. 2A from this animal show that several of these deep neurons also were inhibited during stimulation (red squares). Two of these cells, in the most lateral plane, had average discharge rates in excess of 40 spikes/s and probably were in the GP. This indicates that stimulation in GPi also did reduce the discharge of some nearby GP somata.

**DISCUSSION**

The major finding of this study is that high-frequency bipolar stimulation through microelectrodes placed in the internal segment of the GP produced inhibition, not facilitation, of most thalamic neurons affected by the stimulus. Only a small fraction of the thalamic neurons with stimulus-evoked responses was facilitated and, in some of those cases, there was evidence that the stimulus position used for those trials actually resulted in stimulus spread to the internal capsule. These findings are in contrast to the predictions that thalamic activity would be disinhibited during HFS in GPi.

**Detection of action potentials during the stimulus train**

High-intensity stimuli applied in close proximity to a high-impedance recording electrode produce significant stimulus artifacts that can preclude examination during the stimulus train. Some prior studies have dealt with this either by reducing stimulus intensity (Dostrovsky et al. 2000) or by using the discharge immediately following stimulation to imply what happened during the stimulus train (Benazzouz et al. 1995, 2000; Beurrier et al. 2001).

In the present study, stimulus artifacts and neuronal action potentials were sorted by a spike-sorting system that allowed us to examine changes in discharge during the high-frequency stimulus train, even with stimulus intensities of 300 μA or greater. Although neuronal spikes that occurred coincident with the stimulus artifact certainly were lost because of amplifier saturation, several findings indicated that occlusion between the stimulus artifact and neuronal spikes could not account for the marked reduction in neuronal activity during the stimulus train. 1) The percentage reduction in discharge during true stimulation usually was much greater than the

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<th>Stimulus Pair</th>
<th>Cells Inhibited</th>
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<th>Cells Excited</th>
<th>Cells not Affected</th>
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Values in parentheses are percentages. * Spread = stimulation also caused a contraction of contralateral muscles.
percentage of the interstimulus interval occupied by the stimulus artifact. 2) When the activity of two thalamic neurons was recorded simultaneously by the same electrode and during the same stimulus train, the activity of one sometimes remained high at the same time that the activity of the other was almost completely suppressed. 3) On occasions in which the leads to the stimulating electrodes were disconnected, but left hanging close enough to the recording electrode to cause a significant stimulus artifact, the measured discharge rates of sorted spikes decreased only slightly and much less than measured during real stimulation. 4) A few neurons did show an increase in discharge, and many showed no change of activity during stimulus trains. Thus we believe that the measured reductions in thalamic neuronal activity during stimulation were real and not just due to occlusion of spikes by stimulus artifacts.

Comparison to other electrophysiological studies of HFS in GPi

No published studies have examined the effect of HFS in GPi on the activity of thalamic neurons, but some have examined the activity of nearby neurons in GPi in awake monkeys with MPTP-induced parkinsonian symptoms or in awake humans with Parkinson’s disease. Boraud et al. (1996) reported that bipolar stimulation through concentric macroelectrodes inserted stereotaxically into the head of GPi of monkeys made parkinsonian with MPTP produced a reduction of discharge of GPi neurons. The reduction was not as complete as we found in the thalamus, but the pallidal discharge was reduced from the abnormally high rate after MPTP without stimulation to one that was comparable to the rate recorded prior to administration of MPTP (approx 80 spikes/s). In the Boraud et al. study, spikes were detected with a discriminator, using care to be sure that the stimulus artifact did not result in loss of spikes. Since only the discriminator output was shown, however, it is difficult to evaluate the relative size or configuration of the artifacts compared with the spikes. Usually the stimulus artifact generated by a 90-μs, 350-μA stimulus current applied within approximately 2–3 mm of the recording site (as illustrated in their paper) would be large and, when applied at a frequency of 120 Hz, could produce artifacts that could occlude spikes and contribute significantly to the apparent reduction of GPi neuronal discharge rate that they described.

Dostrovsky et al. (2000) and Wu et al. (2001) also reported that monopolar stimulation in humans through a microelectrode in GPi produced a reduction in the discharge of GPi neurons during the stimulus train. In this study, the activity of GP neurons was recorded within 250–600 μm of a second microelectrode used for monopolar stimulation. Stimuli were generally of low intensity (<20 μA) and low frequency (<50 Hz), although examples were given of profound depression of GPi discharge when stimuli of 300 Hz and 100 μA were applied.

We also found several cells deep to the thalamus that were inhibited by stimulation in GPi, although most did not have the high-frequency discharge typical of GP and may have been more posterior and medial, some in the hypothalamus. Despite the potential decrease in the discharge of somata in GP during stimulation in GPi, however, we still saw profound inhibition of most thalamic neurons during stimulation.

In other neurophysiological studies of the effects of HFS, stimuli have been applied in STN, the primary source of excitatory input to GPi. Benabid’s group (Benazzouz et al. 1995, 2000) reported that HFS through concentric macroelectrodes in STN of anesthetized rats reduced the activity of most neurons studied in STN and in SNr, a target of excitatory axons from STN. They reported that the discharge of thalamic neurons was increased by stimulation, consistent with a decrease in the activity of inhibitory basal

![FIG. 9. Effects of HFS on the discharge of two nearby cells recorded concurrently through the same electrode. A: both nearby cells are inhibited by HFS. B: two other nearby cells, one of which (cell 1) is inhibited and the other (cell 2) which is not significantly affected.](http://jn.physiology.org/)
ganglia output from SNr or the entopeduncular nucleus, the rodent homologue of GPi. The conclusions of this study, however, were based on activity immediately following cessation of the stimulus train because stimulus artifacts obscured effects during stimulation. Likewise, the report that voltage-gated currents in STN neurons studied in the slice are transiently blocked by HFS in STN was based on the absence of neuronal activity after the stimulus train (Beurrier et al. 2001).

Possible reasons for the difference between the hypothesized increase and the measured decrease in thalamic discharge during HFS

DIFFERENCE IN STIMULATING ELECTRODE LOCATION. In humans, HFS is applied through macroelectrode contacts arranged linearly along an angled anterior-to-posterior trajectory. Stimulation may be bipolar between two contacts, usually with a center-to-center separation of 3 mm, or monopolarly versus the pulse generator. Different stimulation configurations are tested after implantation and the one that best reduces symptomatology is chosen. The maximum extent of GPi in humans along the trajectory usually used is 9 mm (see Fig. 1 in Wu et al. 2001). This should be sufficient to insure that two macroelectrode contacts used for bipolar stimulation could both be in GPi, but it does not guarantee that they are. In fact, monopolar stimulation in GPe can produce effects on akinesia that are opposite to those produced when the electrode is in GPi. Reports from two groups (Bejjani et al. 1997; Krack et al. 1998a; Yelnik et al. 2000) indicated that monopolar stimulation in GPe produces an improvement in akinesia but may also produce dyskinesias, whereas stimulation in GPi worsens akinesia but stops drug-induced dyskinesias. Thus it is possible that the site of effective stimulation in the current study, which was confirmed to be in GPi, would have worsened, rather than decreased parkinsonian bradykinesia.

ELEMENTS ACTIVATED BY HFS. Determination of the elements activated by stimulation within the CNS is difficult. McIntyre and Grill (2000), who modeled the effect of mono- and bion-
sic stimulus pulses of different pulse durations applied in the vicinity of populations of intermingled model motoneurons and axons, determined that, for monopolar anodal stimulation, axons had a lower threshold, whereas the threshold was lower for the initial segment (cells) if monopolar cathodal stimulation was used. Symmetrical 0.2 ms duration biphasic pulses, such as those used in the present study (and in most clinical applications), showed less selectivity than did monophasic ones and excited both cells and fibers on alternate phases of the stimulus pulse.

The current density produced at a given stimulus intensity would be lower near macroelectrodes than that near the microelectrodes used in the present study. Neuronal somata are thought to require a higher current density than axons to reach threshold (Ranck 1975), and it is possible that bipolar stimulation between two microelectrodes in the current study would more effectively stimulate GPi somata or initial segments, resulting in enhanced inhibition of thalamic targets, whereas stimulation with macroelectrodes used in humans or in animal studies would primarily excite inhibitory axons presynaptic to pallidal output neurons (Benazzouz et al. 1995; Boraud et al. 1996; Wu et al. 2001). We did use a concentric macroelectrode on one occasion to stimulate in GPi, but because of its size, we could not record the activity of single cells and confirm, by their discharge pattern, that the tip was in GPi. Stimulation through this electrode at its initial position did facilitate one thalamic neuron, but, at the standard stimulus intensity (300 μA), it also produced contraction of contralateral muscles. We interpreted this as an indication of stimulation of capsular fibers.

Chronaxy also is shorter for axons than for somata, and it is possible that the shorter pulse durations (as short as 60 μs) usually used for HFS in humans would preferentially activate inhibitory axons presynaptic to Gpi output cells, whereas the 200-μs pulses usually used in the present study would activate the somata of output neurons instead.

If GP-evoked inhibition of thalamic neurons were due to stimulus configuration, current density, or pulse duration, we would expect that, if we reduced the stimulus intensity or pulse duration to a point at which they favored excitation of inhibitory axons presynaptic to Gpi, the effect at the thalamus would switch from inhibition to facilitation (disinhibition). In fact, this never happened.

OTHER EVIDENCE THAT HFS MAY NOT REDUCE INHIBITORY PALLIDAL OUTPUT. Several other recent reports have brought into question the conclusion that HFS in Gpi or STN reduces the output of the structure stimulated. Windels et al. (2000) reported that HFS through concentric electrodes in the STN of anesthetized rats increased extracellular glutamate levels in both GP and SNr, which would be expected if excitatory STN neurons or their axons were activated, not inhibited. Hashimoto et al. (2001), who stimulated the STN of MPTP-treated monkeys through macroelectrodes, also found that, when the electrode was verified to be in STN, stimulation produced an increase in the mean discharge rate of GPi neurons. In this case, they also verified that the same stimulation increased purposeful contralateral limb movements. Furthermore, Baker et al. (2001), who had the opportunity to record in a human from thalamic neurons during HFS in Gpi, found no consistent changes in neuronal activity in Vop, the target of pallidal axons, during stimulation, although reductions in thalamic neuronal activity were noted after stimulation was stopped. Thus these reports support the conclusion of the present study that HFS in Gpi does not necessarily lead to decreased inhibitory pallidal output and facilitation of thalamic targets.

Other potential mechanisms by which HFS in Gpi or STN might reduce the symptoms of Parkinson’s disease

Hashimoto et al. (2001) also pointed out that clinically effective HFS in STN of MPTP-treated monkeys produced a more regular pattern of activity in Gpi. We also found that, when a few thalamic neurons were studied during bursting discharge, HFS in Gpi appeared to reduce the number of bursts and the number of spikes per burst. Although this was not a situation in which the monkey had parkinsonian symptoms that could be evaluated, it again brings up the possibility that the change in thalamic activity that leads to symptomatology is an abnormal pattern of activity, rather than a reduction in thalamic activity as a result of an increase in mean pallidal discharge rate. In fact, abnormal patterns of activity are common in pallidal neurons in both humans with Parkinson’s disease (Magnin et al. 2000; Zirh et al. 1998) and in the Gpi, SNr, and STN of MPTP-treated monkeys (Bergman et al. 1994; Wichmann et al. 1999). It may just be that the beneficial effects of HFS in STN, Gpi, or thalamus (and of pallidotomies) are primarily a consequence of the interruption of abnormal patterns of activity in corticothalamic circuits.

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