Microstimulation-Induced Inhibition of Neuronal Firing in Human Globus Pallidus

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Dostrovsky, J. O., R. Levy, J. P. Wu, W. D. Hutchison, R. R. Tasker, and A. M. Lozano. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J Neurophysiol 84: 570–574, 2000. Neurosurgical treatment of Parkinson’s disease (PD) frequently employs chronic high-frequency deep brain stimulation (DBS) within the internal segment of globus pallidus (GPi) and can very effectively reduce L-dopa-induced dyskinesias and bradykinesias, but the mechanisms are unknown. The present study examined the effects of microstimulation in GPi on the activity of neurons close to the stimulation site. Recordings were made from GPi using two fixed or independently controlled microelectrodes, with the electrode tips usually ∼250 or >600 μm apart in PD patients undergoing stereotactic exploration to localize the optimal site for placement of a lesion or DBS electrode. The spontaneous activity of nearly all of the cells (22/23) recorded in GPi in three patients was inhibited by microstimulation at currents typically <10 μA (0.15-ms pulses at 5 Hz). The inhibition had a duration of 10–25 ms at threshold. These findings suggest that microstimulation within GPi preferentially excites the axon terminals of striatal and/or external pallidal neurons causing release of GABA and inhibition of GPi neurons.

INTRODUCTION

In the treatment of movement disorders such as Parkinson’s disease (PD), essential tremor, and dystonia, chronic “deep brain stimulation” (DBS) is now a common alternative to making a lesion (Gross et al. 1997; Koller et al. 1997; Krack et al. 1997; Kumar et al. 1998). DBS is used in motor thalamus, globus pallidus internus (GPi), and the subthalamic nucleus (STN). In all three regions therapeutic effectiveness occurs only at high stimulation frequencies (130–185 Hz) and, surprisingly, making lesions in similar regions produces similar effects (Lozano et al. 1998). It is therefore thought that DBS probably leads to inactivation or reduction of neural activity in the region stimulated, possibly by depolarization block (Burbaud et al. 1994) or release of GABA (Boraud et al. 1996), although there is no direct evidence for this.

The GPi is the major output nucleus of the basal ganglia. GPi neurons project to thalamus and brain stem where they produce inhibition by releasing GABA (Parent and Hazrati 199a,b). The main inputs to the GPi are also GABAergic, originating in the caudate and putamen and globus pallidus externus (GPe), but it also receives an excitatory glutamatergic input from the STN (Parent and Hazrati 1995a,b; Shink and Smith 1995). Thus, stimulating in the GPi potentially activates the axons of the projection neurons and/or the axons of the afferent inputs to the nucleus. In both cases orthodromic and antidromic action potentials would be evoked. The clinically observed effects could thus be caused by activation of afferent inputs onto GPi neurons. In the monkey, Boraud et al. (1996) reported that stimulation within GPi at therapeutic intensities resulted in decreased firing rate but not block of activity; they proposed that activation of GABAergic afferents within GPi leads to the inhibition.

To gain a better understanding of the mechanisms underlying the effects of DBS in human GPi, we examined the effects of microstimulation through one microelectrode on the neuronal activity recorded from a second microelectrode. Some of the findings reported here were briefly reported in Dostrovsky et al. (1999).

METHODS

The observations reported in the present study were made in three awake PD patients undergoing functional stereotactic surgery for the treatment of their movement disorder. Patients were off medications for 12 h at the time of the recordings. The methods used are described in detail in Lozano et al. (1996). Very briefly, under local anesthesia a stereotactic frame was applied to the patient’s head and then a burr hole was made in the skull and a guide tube aimed at the radiologically determined target was inserted. Pairs of platinum-plated tungsten microelectrodes (25-μm exposed tips), whose tips were at the same depth but separated laterally by ∼250 μm (except in one patient where they were >600 μm apart and independently driven), were driven through the GPi. Recordings of neural activity were obtained simultaneously from both electrodes. Recordings and stimulation were performed with two Guideline 3000 system amplifiers (Axon Instruments). Biphasic monopolar electrical stimulation (0.15 ms; 2–100 μA pulses, relative to guide tube) was performed through one electrode while single neuron recordings were obtained from the other electrode. The recordings from both electrodes were stored on magnetic tape. Off-line analysis of the digitized recordings were performed with a CED1401 data acquisition system and Spike2 software. Most of the neurons encountered in GPi fired at high rates of over 50 Hz and were classified as high-frequency discharge (HFD) cells (Hutchison et al. 1994). Recording sites were localized to GPi on the basis of physiological landmarks, including the optic tract and capsule (Lozano et al. 1996). The GPi is a large nucleus extending for a depth of approximately 10 mm along the axis of the electrode track, approximately 8 mm in the anterior–posterior axis, 10 mm in the superior posterior axis, and 7 mm in the mediolateral axis. All pro-
RESULTS

The effects of microstimulation were examined on 23 HFD neurons (mean firing rate 91 Hz). Single-pulse low-intensity stimuli delivered within GPi were found to inhibit the neuronal activity in all but one of the HFD neurons. Figure 1 shows examples of the stimulation effects in two neurons. Figure 1A shows the marked inhibition occurring following stimulation at 50 μA at a distance of 610 μm. Figure 1B shows the marked, but not total, depression of firing during a 300-Hz train. Figure 1C shows an example of stimulation effects on an HFD tremor cell; stimulation at 8 μA produced only very slight inhibition, but increasing the stimulation to 40 μA resulted in much more potent inhibition that was, however, not further increased by increasing the current to 80 μA. For 13 of the neurons that were tested with 250-μm–spaced tips, currents of 4 or 5 μA were used and found to be effective in producing inhibition (the remaining two neurons were tested only with 8 μA, and one of these was inhibited). In six of these cases the effects of 2-μA stimulation was tested but not found to produce discernible inhibition. The remaining eight neurons were recorded with electrodes separated by at least 600 μm. Most of these were tested only with higher currents, but in two cases currents of 5 or 15 μA were tested and found to be effective (Fig. 2, A and B).

In all cases the inhibition was short-lived (15–25 ms at 50% recovery for stimulation intensities of 4–20 μA) and increased modestly with increasing currents to about 50 μA. Figure 2 shows examples of the effects of increasing stimulation current on the firing of eight neurons recorded during one dual-electrode penetration. In most cases recovery from inhibition following a single stimulus pulse was very rapid, but in a few cases was more prolonged (e.g., Fig. 2C). In 20 of the 22 neurons, the onset of inhibition was shorter than the duration of the stimulus artifact (usually about 0.5–1 ms in duration) and so could not be determined. However in one case the onset of inhibition occurred about 3 ms after the stimulus and in the other cell at about 4 ms. However, in this latter case, when the stimulation intensity was increased to 16 and 40 μA the onset paradoxically increased to over 10 ms. In one other cell, there was a period of increased excitability with a duration of about 10 ms occurring right after the inhibition (20–30 ms after the stimulus). In the cell depicted in Fig. 2A the cell firing is depressed at higher intensities except for a short period 30–75 ms after the stimulus. Figure 3 shows examples of effects of increasing the frequency of stimulation. As would be expected from the typical 20-ms inhibition duration, increasing the frequency of stimulation to about 50 Hz resulted in pronounced depression of firing. However, even at high rates of stimulation (e.g., at 300 Hz), some cells occasionally fired during the train, as shown in Fig. 1. Surprisingly, we found no evidence of decreasing inhibition to successive stimuli within trains (10 or 20 Hz, 3 s duration).

DISCUSSION

The present study revealed that most of the GPi neurons were inhibited by low-intensity stimuli delivered a few hundred microns away. The time course of this inhibition suggests that it is caused by synaptic release of an inhibitory transmitter. Since GPi is known to receive a large projection from GABAergic neurons in the putamen and GPe (Shink and Smith 1995), the present findings suggest that stimulation within GPi preferentially activates the axons and axon terminals of these GABAergic afferents, leading to release of GABA on the GPi HFD neurons; activation of collaterals of GPi neurons may also contribute to the inhibition. GPi
neurons are known to receive excitatory glutamatergic inputs from subthalamic neurons. We speculate that the reason we did not observe excitation following stimulation in GPi is that many more GABAergic afferents and synapses were activated than were glutamatergic ones, possibly due to higher excitability and/or increased number (Shink and Smith 1995), and that the inhibition therefore masked any underlying excitation. It is possible that the delayed inhibition or increased excitability for a short period after the end of the inhibition, which was observed in a few of the cells,
the currents that were found to be effective were too low to activate the soma or axons at distances of 250–600 μm. According to estimates in other brain regions, a stimulus of 10 μA would only be capable of exciting cell bodies that were <65 μm from the tip (Ranck 1975).

Our findings suggest that DBS would preferentially activate the inhibitory afferents in GPi leading to inhibition of the output neurons. Since the inhibition is so short-lasting, high-frequency stimulation would be needed to obtain optimal inhibition, as is the case clinically. However, our findings suggest that maximal effects would result at stimulation frequencies between 50 and 100 Hz whereas the clinical effects apparently are optimal only at frequencies over 130 Hz. Another caveat is that we do not know whether possible transmitter depletion or receptor desensitization may limit the effects following long-term continuous stimulation. Depolarization block of the output neurons cannot explain the inhibition observed in our studies since the neurons were not directly excited and were still capable of firing occasionally, even during high-frequency stimulation.

The currents used therapeutically in DBS are much larger, although, due to the much larger electrode tip surface area (5000× greater), the current density near the electrode tip in our studies is comparable. At 3mA, a current typically found to be effective (Ashby et al. 1998), large-diameter myelinated axons at distances up to 2.5 mm from the center of the electrode are probably excited (Ranck 1975). Thus it is likely that DBS stimulation will result not only in massive release of GABA onto most GPi neurons but will also directly excite the output axons of many GPi neurons, especially for electrode locations near the inferior border of GPi. Since the output neurons of the GPi regularly fire at peak frequencies over 200 Hz (i.e., interspike intervals of <5 ms; unpublished observations), direct excitation by high-frequency stimulation should lead to repetitive excitation rather than cause a block of firing. Thus the overall effect of DBS is probably a combination of inhibition of some output neurons and excitation of others. Although the excitatory effect will not result in decreased inhibition of the target neurons in thalamus and brain stem, it would eliminate any functionally relevant modulation (patterned output) and thus may be effective in preventing dyskinesia and tremor, which are probably dependent on patterned output. It is interesting that differential effects of DBS dependent on location within GPi have been reported (Bejjani et al. 1997; Krack et al. 1998). This may be related to the preferential activation of pallidal outflow axons with electrodes located at the base of GPi and inhibitory effects of neuronal somata at electrodes within GPi proper.

In summary, the present findings suggest that stimulation within GPi preferentially activates the GABAergic axon terminals of striatal and/or external pallidal neurons, thereby causing the release of GABA and postsynaptic inhibition of GPi neurons. Thus stimulation-evoked release of GABA within GPi may be one of the mechanisms involved in the therapeutic effects of pallidal DBS, which would explain why the effects are similar to pallidotomy. This proposal is supported by a report that injection of the GABA agonist muscimol into GPi in a PD patient resulted in decreased bradykinesia (Penn et al. 1998).
REFERENCES


