Internal Globus Pallidus Discharge Is Nearly Suppressed during Levodopa-Induced Dyskinesias

Stella M. Papa, MD,* Robert Desimone, PhD,† Mario Fiorani, MD,† and Edward H. Oldfield, MD*

The functional status of the globus pallidus internal segment (GPi) plays a key role in mediating the effects of antiparkinsonian drugs. During long-term levodopa therapy, patients develop abnormal movements, dyskinesias, the pathophysiological basis of which is poorly understood. We recorded single cells in the GPi of parkinsonian monkeys continuously through the "off" and "on" states, and 10 to 15 minutes later during "on with or without dyskinesias," depending on two doses of levodopa. The transition from the "off" to the "on" state was characterized by a decrease (most cells), no change, or an increase in firing rate of individual cells. During dyskinesias, firing rates declined profoundly in almost all cells, with decrements as low as 97% in individual cells. These changes occurred only when dyskinesias were present. The difference in GPi activity between "on" and "on with dyskinesias" suggests that normal motor function in Parkinson's disease critically depends on fine tuning of the basal ganglia output. Dyskinesias result from an imbalanced low GPi discharge, a circumstance that may be susceptible to development of new therapeutic approaches.

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Parkinson's disease is associated with profound cell loss in the pars compacta of the substantia nigra that results in severe dopamine depletion. To date, replacement therapy with levodopa is the most effective treatment. However, after several years of benefit, the efficacy of treatment deteriorates because of the development of motor complications.[1] Motor fluctuations, on–off phenomena, and dyskinesias usually accompany long-term levodopa therapy.[2,3] The mechanism by which providing dopamine to a denervated striatum produces abnormal movements, combined with the expected reversal of parkinsonian features, remains unknown.

According to the current knowledge of the functional anatomy of the basal ganglia,[4,5] after dopamine denervation, striatal cells that project directly to the globus pallidus internal segment (GPi) become hypoactive. Conversely, because of the excitatory or inhibitory action of dopamine on different populations of striatal cells,[6] projections to the external segment of the globus pallidus (GPe) are overactive. The overinhibition of GPe neurons through the indirect γ-aminobutyric acid (GABA)ergic striatal output leads to hypoactivity in the GPe output, which also is GABAergic and projects to the subthalamic nucleus (STN). Release of the STN results in overactivity of the glutamatergic STN projection to the GPi.[7] Thus, in the parkinsonian state, excessive excitatory input from the STN (indirect pathway), combined with disinhibition through the direct striatal projection, results in overactivity of the GPi.

Dopamine replacement by levodopa is thought to normalize GPi activity by its action through the direct and indirect striatal output pathways. Consistent with this concept, neurophysiological studies in parkinsonian monkeys,[8,9] and patients during pallidotomy,[10] show a reduction in the GPi activity with dopamine agonists or levodopa. If the antiparkinsonian effects of levodopa are mediated by decreased activity in the GPi, then levodopa-induced dyskinesias might result from excessively reduced activity of the GPi. There is evidence both for and against this hypothesis. On the one hand, hemiballismus is typically seen with STN vascular lesions[11] (presumably strongly reducing activity in GPi). In addition, subthalamotomy produces dyskinesias in normal and parkinsonian monkeys.[12–14] On the other hand, pallidotomy selective for GPi greatly ameliorates levodopa-induced dyskinesias.[15–17] Resolution

From the *Surgical Neurology Branch, National Institute of Neurological Diseases and Stroke, and †Laboratory of Neurophysiology, National Institute of Mental Health, National Institutes of Health, Bethesda, MD.

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Address correspondence to Dr Papa, Department of Neurology, Emory University, 6000 WMRB, Atlanta, GA 30322.

of this conundrum requires knowledge of the activity of the GPi cells during dyskinesias.

To address this issue, we used single cell recording of the firing of GPi cells in parkinsonian monkeys that developed dyskinesias after chronic levodopa treatment. To avoid the risks associated with pooling activity from different functional groups of cells in the different states, we recorded from individual cells continuously during a period in which animals passed through all states, parkinsonism, its reversal, and the exhibition of dyskinesias with levodopa administration. Subsequently, to better link the changes found in GPi activity during dyskinesias, a second set of experiments was performed by using a lower dose of levodopa that, although producing an "on" response of similar magnitude, did not elicit dyskinesias.

Materials and Methods

Subject Preparation

Monkeys (*Macaca mulatta*) were studied in accordance with the NIH *Guide for the Care and Use of Laboratory Animals.* They were rendered parkinsonian by systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[18] Subsequently, they were treated chronically with oral carbidopa/levodopa (Sinemet 25/100 mg; 25 mg of carbidopa/100 mg of levodopa)[18] until development of marked dyskinesias.[19] Doses of levodopa to elicit reproducible antiparkinsonian and dyskinetic responses were systematically examined with levodopa methyl ester plus benserazide dissolved in saline and given subcutaneously. Thus, levodopa doses that consistently produced dyskinesias ("peak dose" dyskinesias) were identified for each monkey ("high doses," 125–200 mg). In a similar manner, doses that reversed parkinsonian disability without producing dyskinesias were determined in animals that did not have an "all or none" response ("low doses," 50–100 mg). Four monkeys were selected for this study. Motor behavior scores are shown in the Table.

Table. Motor Behavioral Assessment

		Levodopa High Dose		Levodopa Low Dose	
Monkeys	Off	On	Dyskinesias	On	Dyskinesias
1	6	0	7	0.5	0
2	6.5	0	6	1.5	0
3	10	0	14	2	0
4	9	0	10	1	0

Parkinsonian disability ("off" and "on" states) and dyskinesias were scored by using a standardized motor disability scale for MPTP-treated monkeys.[18] Scores for each dose of levodopa are the average of three evaluations performed before surgery. The timing of these evaluations was the same as that used later for data collection during recording of the activity of GPi cells ("off" state, baseline; "on" state, at the onset of levodopa effects 20 minutes after the subcutaneous injection; dyskinesias, 10–15 minutes after entering the "on" state).

MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; GPi = internal segment of the globus pallidus.

Surgical Procedures

Before surgery, the animals were anesthetized with sodium pentobarbital, placed in a plastic and aluminum stereotaxic frame, and scanned by using magnetic resonance imaging. The coordinates of the GPi were then used to place the recording chamber (18 mm diameter) during the subsequent implant surgery under anesthesia with isoflurane.

For mapping purposes, the recording chambers were positioned at a 60° angle in the coronal plane to allow the path of the electrode to pass through the putamen, the GPe, and the GPi, following a dorsolateral–ventromedial trajectory. A post for holding the head was also surgically implanted.

Recording Techniques

A week after surgery, animals were seated in a chair with a head-restraining device for recording sessions. Tungsten microelectrodes (Micro Probe, Gaithersburg, MD) of 1 to 2 MΩ impedance were lowered with a hydraulic microdrive through a guide cannula passing a grid placed at the bottom of the recording chamber. Amplified and filtered electrical signals were displayed on an oscilloscope and a computerized system (Datawave). Rate histograms were displayed on line. Data were stored for off-line analyses. By using several penetrations, the entire area corresponding to the GPi was mapped.[20]

Drug Experiments

The experiments always started in the morning with recording in the "off" state (baseline of parkinsonian disability), for which the oral levodopa (animals received daily treatment with Sinemet 25/100 mg) was withdrawn on experiment days. After storing data for the "off" state, levodopa was injected at the doses previously determined. The activity of the same cell was monitored until the animal passed to the "on" state (reversal of parkinsonian disability), usually 20 minutes after the injection, and for the following 10 to 15 minutes, when peak dose dyskinesias did or did not appear, depending on the dose of levodopa given in each experiment.

Changes in motor behavior, such as blinking, rapid movements of the eyes, and stretching of the legs, clearly indicated when the animal turned "on." Dyskinesias in the freely moving limbs or oral dyskinesias could clearly be seen during the experiment. Overall, the recording of a single cell was maintained for 40 to 50 minutes. To eliminate the potential influence of voluntary movements on firing rates, data were collected in the absence of voluntary movements for 2 to 5 minutes in each state: "off" (before levodopa injection), "on" (20 minutes after levodopa injection), and "on with or without dyskinesias" (10 to 15 minutes after turning "on").

Histology

To localize the recording area at the end of the study, a dye (Pontamine sky blue) was injected into the brain through a cannula placed with its tip at the same coordinates as the tip of the recording electrode. Then, the animal was killed immediately with sodium pentobarbital. After transcardial perfusion with formalin, the brain was removed and blocked in the stereotaxic frame. Sections were stained and examined for verification of the electrode site.

Data Analysis

Raw data were processed first by an event detection and extraction analysis to isolate spikes of single cells. Analysis of variance (ANOVA) followed by the post hoc Fisher's PLSD (protected least significant difference) test, when the ANOVA indicated significance, was used to compare firing rates of a single cell in the three states ("off," "on," and "on with or without dyskinesias"). A two-factor ANOVA was performed to compare firing rates of cells between each state in both groups of treatment (high and low dose of levodopa). Data are presented as mean ± SEM values.

Results

Changes in the Firing Rate of GPi Cells from the "Off" to the "On" State

Approximately one of three experiments could be completed because of the inability to hold the recording of a single cell for 40 to 50 minutes. Fourteen GPi cells were studied under the effects of the "levodopa high dose"; 10 cells were studied under the effects of the "levodopa low dose." Because the activity changes that occurred in association with the transition from the "off" to "on" state did not differ between the two groups of cells, they will be considered together here.

The average firing rate of 24 GPi cells during the "off" state was 46.2 ± 5 Hz (data are shown separately in Figs 1A and 2A). The advanced parkinsonism of these monkeys produced a severe and consistent "off" state throughout the experiment mornings when parkinsonian disability scores remained the same as those taken before initiating the experiments (see Table).

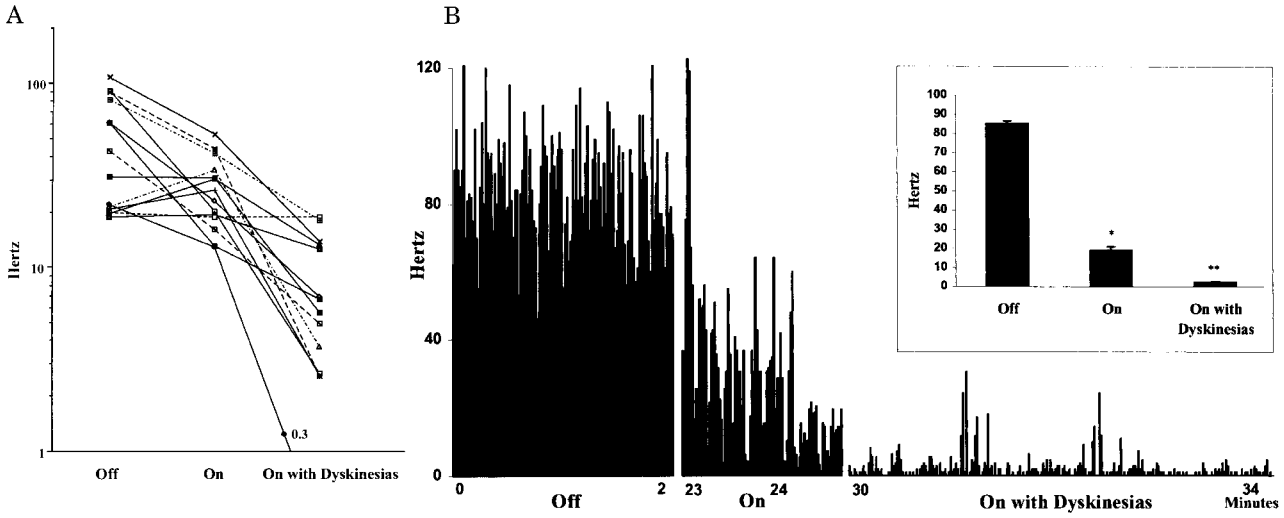
About 20 to 25 minutes after injection of levodopa, the firing rates of cells began to change, although data storage was not reinitiated until there were clinical signs that the animal had turned "on." The average firing rates declined from 46.2 ± 5 Hz during the "off" state to 26.3 ± 2.2 Hz during the "on" state, a 43% decline in rate; $p < 0.0005$ (paired t test). Analysis of rate performed in each cell showed a significant decrease ($p < 0.0001$, ANOVA) from "off" to "on" states in 17 GPi cells (n = 24; see Figs 1A and 2A). These cells reduced their firing frequency from "off" to "on" by 23% to 79%. Four cells did not change their firing rate and the other three increased it by 26% to 60% ($p < 0.01$).

At the end of the experiments, animals were immediately returned to their home cages and reevaluated for parkinsonian disability and dyskinesias during the "on" state. Because responses to subcutaneous administrations of levodopa were very consistent, the behavioral scores were always similar to the previous evaluations (see Table).

Changes in the Firing Rate of GPi Cells with Levodopa-Induced Dyskinesias

The appearance of levodopa-induced dyskinesias was associated with profound changes in the activity of GPi

*Fig 1. Levodopa high-dose condition. (A) Firing rates of each of the 14 globus pallidus internal segment (GPi) neurons recorded continuously through the states of "off," "on," and "on with dyskinesias." Each point in the curves represents the average of the firing rate of a single cell during 2 to 5 minutes. From "off" to "on," firing rates decrease in eight cells (p < 0.0001), are unchanged in three cells, and increase in three cells (p < 0.01). From "on" to "on with dyskinesias," firing rates decline by 33% to 97% in 13 cells (p < 0.0001). Error bars are omitted for clarity. (B) Typical firing rates of a single GPi neuron recorded in the levodopa high-dose condition. Two- to 4-minute intervals of recording were analyzed in each state. Histograms display the rates with a binwidth of 1 second. The bar graph shows the averaged firing rate of this cell in each state. *,**p < 0.0001, vs "off" and "on" states, respectively. The average firing rate of this cell (2.5 Hz) declines by 87% during dyskinesias.*



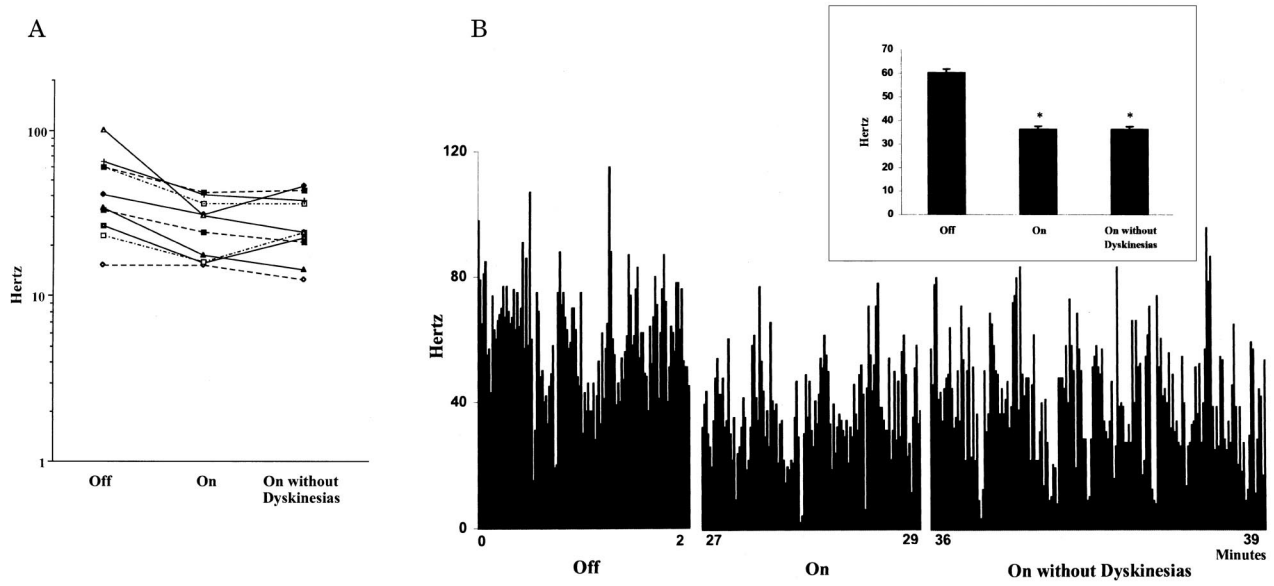


*Fig 2. Levodopa low-dose condition. (A) Firing rates of each of 10 globus pallidus internal segment (GPi) neurons recorded continuously through the states of "off," "on," and "on without dyskinesias" (10–15 minutes after the "on" onset). Each point in the curves represents the average of the firing rate of a single cell during 2 to 5 minutes. From "off" to "on," the firing rates decrease in nine cells ($p < 0.0001$) and are unchanged in one cell. From "on" to "on without dyskinesias," firing rates are unchanged in five cells, increase in three cells ($p < 0.005$), and slightly decrease in two cells ($p < 0.01$). Error bars are omitted for clarity. (B) Typical firing rates of a single GPi neuron recorded in the levodopa low-dose condition. Two- to 3-minute intervals of recording analyzed in each state. Histograms display the rates with a binwidth of 1 second. The bar graph shows the averaged firing rate of this cell in each state. *$p < 0.0001$, vs the "off" state. No changes of the firing rate between the "on" and "on without dyskinesias" states occurred.*

cells (see Fig 1B). On average, the firing rate declined to 7.6 ± 1.5 Hz during the period of dyskinesias, compared with 26 ± 3.1 Hz during the preceding "on" state, before dyskinesias started, a 71% decline in rate ($p < 0.0001$, paired t test). Tests performed on each cell individually showed that 13 of the 14 cells had a significant decline ($p < 0.0001$, ANOVA) in firing rate during dyskinesias (see Fig 1A). The activity that had already reduced at the "on" onset in eight cells declined an additional 49% to 97% when dyskinesias started. The firing rates that were unchanged at the "on" onset in three cells decreased in two of them by 33% and 83% during dyskinesias and remained unchanged in the third cell. Three cells that increased their firing rate at the "on" onset decreased it by 57% to 92% with dyskinesias. These decrements were similar among monkeys regardless of the severity of dyskinesias.

Changes in the Firing Rate of GPi Cells with a Levodopa Response Without Dyskinesias

Although firing rates declined dramatically when dyskinesias started, it is possible that these effects were the result of the amount of time spent in the "on" state regardless of the presence of dyskinesias. To control for this possibility, the activity of 10 cells was recorded in the levodopa low-dose condition, which does not produce dyskinesias over the same interval (10–15 minutes) after the "on" state, as studied in the setting of levodopa-induced dyskinesias. In this condition, firing rate decrements during the transition from "off" to "on" state were the same as those found in the levodopa high-dose condition (see above).

The average firing rate of the cells was not significantly different between the "on" state (27 ± 3.4 Hz) and the "on without dyskinesias" (28 ± 3.7 Hz) 10 to 15 minutes after turning "on." Comparisons between the "on" state and "on without dyskinesias" in tests performed on each cell individually (see Fig 2A) showed that five cells had no significant change in firing rate (see Fig 2B), three cells increased it by 45 to 50% ($p < 0.005$, ANOVA), and two cells had an 18% to 20% decrease in firing rate ($p < 0.01$). Thus, the large decline in firing rate observed in the "on" state with dyskinesias correlates with the dyskinesias themselves, and is not simply a product of the time spent in the "on" state.

Comparison Between "On With Dyskinesias" and "On Without Dyskinesias"

Comparisons of the firing rate between cells recorded in the levodopa high-dose experiments (n = 14) and

those in the low-dose group (n = 10) demonstrated that there were no differences between the groups in the "off" or "on" states (46.3 ± 8.1 vs 46 ± 8.2 Hz and 26 ± 3.1 vs 27 ± 3.4 Hz, respectively). Activity of GPi cells was 73% lower in "on with dyskinesias" than in "on without dyskinesias" (7.6 ± 1.5 and 28 ± 3.7 Hz, respectively; $p < 0.001$, factorial ANOVA; Fig 3).

Recording Site

The histological analysis showed staining in the posterolateral region of the GPi in all monkeys. Thus, the recording sites, which were circumscribed to a few penetrations 1 mm apart, were within the sensory motor area of the GPi.

Discussion

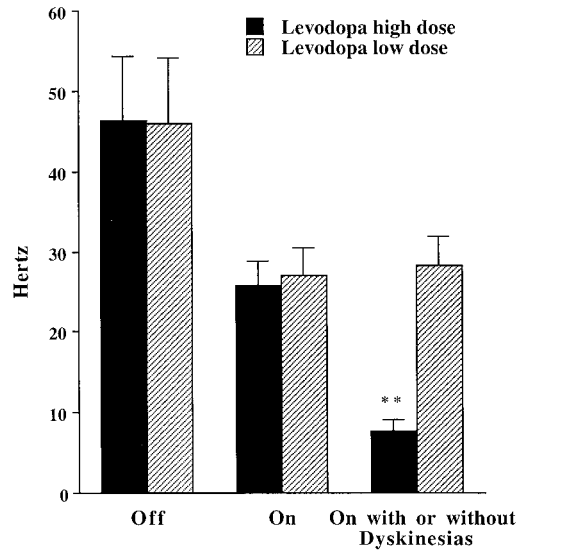
Continuous single cell recording in the GPi of parkinsonian monkeys revealed a profound reduction of firing rates during dyskinesias produced by levodopa. The firing frequencies, which had already declined by entering the "on" state, declined again in almost all cells simultaneously with the occurrence of dyskinesias, when the firing rate of some neurons declined to as slow as 3 to 5 Hz. The validity of these results also is based on aspects of the study design. To control for variability in the level of dopamine stimulation from session to session, as manifested by motor fluctuations,[21,22] levodopa was given subcutaneously and animals were selected based on exhibition of consistent dyskinetic responses to predetermined doses. Another important aspect of the methods of this study was the recording of individual cells as the animal passed through each state—"off", "on," and "on with dyskinesias." Fewer cells changing their firing rate in the opposite direction to most cells, which would have been missed with comparisons between the averaged activity of cell pools recorded separately in each state, could be distinguished here. This experimental setting, which combines consistency in behavioral responses to levodopa, the continuous recording of individual GPi neurons through each state, and the study of "on" and "on with dyskinesias" states separately in the same neurons permitted determination of the GPi activity that is specifically related to dyskinesias. Thus, these data demonstrate for the first time that levodopa-induced dyskinesias are associated with pronounced and massive decrease of the GPi firing.

The foregoing association is further supported by the observation that firing rates of GPi cells remain unchanged during the "on" state when dyskinesias do not occur. Responses to nondyskinetic doses of levodopa are accompanied by a reduction of firing frequencies at the "on" onset and no substantial changes thereafter. The difference between the two doses of levodopa cannot be attributed to a lower antiparkinsonian effect of the predetermined lower doses because, similarly to the higher doses, they produced a full "on" response (scores 0.5–2 were more related to others than motor parameters of the scale). Accordingly, the firing rates of GPi cells reduced to the same extent from "off" to "on" states with both levodopa doses.

Data were always collected in the absence of voluntary movements, permitting comparison of firing rates during "off," "on," and "on without dyskinesias" states with those during dyskinesias, which are involuntary movements. It is unlikely that the involuntary movements themselves influenced the firing rates, because voluntary movements increase the activity of GPi cells[23] as opposed to the activity decrements of the GPi cells that we observed during dyskinesias.

In agreement with previous reports,[8–10] the transition from "off" to "on" states was associated with a 50% reduction in the average firing rate of GPi cells. By following cells through the transition from one state to another, we determined that fewer cells did not change their rate in the "on" state and that the firing rate increased in a minority of cells. Hence, normalizing motor behavior in a parkinsonian setting can be attained by a reduction in the GPi discharge, but preservation of a certain level of firing activity seems to be required.

*Fig 3. Comparison of firing rates between the two groups of globus pallidus internal segment (GPi) neurons that were studied in the levodopa high-dose and low-dose conditions (n = 14 and 10, respectively). Averages of the firing rates are similar in both groups of cells during the "off" and "on" states, but they significantly differ 10 to 15 minutes after the onset of the "on" state, when dyskinesias do, or do not, occur ("on with dyskinesias" and "on" without dyskinesias" in cells recorded with levodopa high-dose and low-doses, respectively). **p < 0.001, factorial analysis of variance.*



According to current views of the basal ganglia functions,[24,25] the GPi discharge suppresses unwanted movements[26] and facilitates desired movements, most likely mediating the appropriate scaling of muscle activity.[27,28] Dyskinesias, then, derived from either spontaneous unwanted movements at rest or inappropriate muscular scaling during action may be explained by the loss of GPi inhibitory influences on the thalamocortical projections. Conceivably, in the uncomplicated "on" state (without dyskinesias) the maintenance of a certain level of firing rate in some GPi cells, or even the increase in certain others, may explain normal mobility with suppression of involuntary movements. In turn, a uniform and deep decline in GPi discharge may lead to dyskinesias. Therefore, normal motor function appears to depend on precisely balanced activity of GPi cells.

The present study provides physiological evidence for an imbalance of the GPi discharge associated with levodopa-induced dyskinesias. Nevertheless, an imbalance that results from very low firing rates of GPi neurons may seem incompatible with the clinical results of pallidotomy because it greatly reduces dyskinesias in parkinsonian patients.[16,17] It has been hypothesized that the overactive GPi discharge in the parkinsonian state results in a "noisy" disturbed input to the thalamocortical drive.[24] Likewise, the low GPi activity we found during dyskinesias might also be disturbed or "noisy" because it lacks the better organized and balanced activity that is present in "on without dyskinesias." Thus, the beneficial effect of pallidotomy on dyskinesias may result from eliminating the transmission of "noisy" signals through the thalamic relay to the cortex. However, what aspect of the low GPi discharge is "noisy" remains unknown, suggesting the need for further study of the complex neuronal firing patterns in the GPi.

Finally, the critical difference in the functional status of the GPi between the uncomplicated "on" state and "on with dyskinesias" provides the basis of therapeutic considerations. Drugs acting through other neurotransmitter systems, for instance, the glutamatergic,[29] may interfere with the effects of dopamine stimulation on the GPi output. Noteworthy is that glutamate antagonists combined with levodopa in MPTP parkinsonian monkeys substantially reduce dyskinesias while preserving the antiparkinsonian effects of levodopa.[18] Whether these drugs oppose the effects of dopamine at other basal ganglia regions to secondarily modify GPi activity or if they directly act on GPi neurons by blocking the glutamatergic subthalamic input, a "pharmacological pallidotomy,"[30] remains unknown. The present data encourage the development of drugs that counter excessive dopamine action and maintain a normal and balanced activity in the GPi as a treatment for advanced Parkinson's disease.

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