Physiology of Hypokinetic and Hyperkinetic Movement Disorders: Model for Dyskinesia

Jerrold L. Vitek, MD, and Monique Giroux, MD

Although the basal ganglia have been implicated in the development of movement disorders since the 1940s, the exact role played by these structures has remained elusive. The development of the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-monkey model of parkinsonism, and the recent resurgence of surgical therapy for the treatment of hypokinetic and hyperkinetic movement disorders has, however, led to an improved understanding of the pathophysiological mechanisms that underlie their development. In this article, we review the functional organization and examine the changes in neuronal activity that occur in the basal ganglia thalamocortical 'motor' circuit in these disorders. An alternative to the classic 'rate' model for Parkinson's disease is presented that incorporates the observed changes in neuronal activity, as well as additional neuronal pathways that contribute to these changes. Based on studies in animal models and humans with hyperkinetic movement disorders, it is postulated that dyskinesias develop as the result of a combination of excessive reductions in the mean discharge rate, altered patterns and increased synchronization of neurons in the internal segment of the globus pallidus. It is further postulated that the particular type of involuntary movement which develops also depends on the relative change in neuronal activity in the direct, indirect and alternative pathways. Support for these postulates is examined, and models for drug-induced dyskinesia, hemiballismus and dystonia are proposed.

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Dyskinesias have been defined as excessive abnormal involuntary movements.[1] One of the more common dyskinesias is that which occurs secondary to long-term levodopa use in parkinsonian patients, termed levodopa-induced dyskinesia. Levodopa-induced dyskinesia falls into the category of hyperkinetic movement disorders, which also includes such disorders as hemiballismus and dystonia. Although different names are given to these movement disorders, all are typified by excessive involuntary movement. Many characteristics of the involuntary movements are similar in hyperkinetic disorders. An insight into the physiological basis underlying the development of drug-induced dyskinesias may be gained by examining the physiological changes that occur in dystonia and hemiballismus. By comparing these changes with those that occur in hypokinetic disorders [e.g. Parkinson's disease (PD)], in which the physiological changes that underlie their development are better understood, we may also gain a better understanding of the relationship between the physiological changes that occur and the type of abnormal movements which emerge.

The basal ganglia have been implicated in the development of movement disorders since the early studies by Meyers in the 1940s. Meyers attempted to alleviate the altered movements associated with PD and other movement disorders by destroying various portions of the basal ganglia.[2,3] Subsequent studies in animal models of these disorders employing molecular, anatomic,[4] physiologic,[5–8] pharmacologic[9,10] and metabolic techniques,[11–14] and, more recently, by electrophysiological recordings in the basal ganglia and thalamus in patients with movement disorders undergoing stereotactic surgical procedures,[15–21] have led to an improved understanding of basal ganglia thalamocortical circuitry. They have also led to an improved understanding of the relationship of changes in neuronal activity in this circuit to the development of hypo- and hyperkinetic movement disorders, and yielded new insights into the pathophysiological mechanisms that underlie the development of these disorders. These new insights support the concept that the basal ganglia play a key role in the development of hypo- and hyperkinetic movement disorders, and provide a solid scientific rationale for surgical intervention that was not present in earlier studies. In this article, we review the functional organization of basal ganglia thalamocortical circuitry, examine the changes in neuronal activity

From the Department of Neurology, Emory University School of Medicine, Atlanta, GA.

Address correspondence to Dr Vitek, Department of Neurology, Emory University School of Medicine, 1639 Pierce Drive, WMRB 6000, Atlanta, GA 30322.

that occur in the basal ganglia thalamocortical 'motor' circuit in hypo- and hyperkinetic movement disorders, and present a model for the dyskinesias (e.g. drug-induced dyskinesia, hemiballismus and dystonia) that incorporates these new insights.

Functional Organization of Basal Ganglia Thalamocortical Circuitry

The basal ganglia are viewed as components of multiple segregated circuits, including motor, oculomotor, associative and limbic circuits.[22] The motor circuit is implicated in the pathophysiology of both hypokinetic (e.g. PD) and hyperkinetic (e.g. drug-induced dyskinesia) movement disorders.[23] It takes origin from pre- and post-central sensorimotor fields, and engages specific portions of the putamen, the external (GPe) and internal (GPi) segments of the globus pallidus, the substantia nigra pars reticulata (SNr), the subthalamic nucleus (STN) and portions of the motor thalamus [ventralis lateralis pars oralis (VLo) and ventralis anterior], and returns to the same precentral motor fields from which it took origin.[22] The striatum, the major input structure of the basal ganglia, influences GPi and SNr, the major output structures, via two routes arising from separate subpopulations of inhibitory neurons: a 'direct' pathway with striatal neurons projecting directly to GPi/SNr, and an 'indirect' pathway with projections from the striatum influencing GPi/SNr neurons via the GPe and STN (Fig 1). All the intrinsic connections of the basal ganglia are inhibitory, except for the STN→GPi/SNr pathway, which is excitatory. The dopaminergic nigrostriatal pathway (from the substantia nigra compacta) appears to modulate the activity of the two striato-pallidal pathways differentially by activation of different dopamine receptors. Thus, dopamine appears to facilitate transmission in the 'direct' pathway via D1 receptors, and to inhibit transmission in the 'indirect' pathway via D2 receptors.[4,24] Output from GPi/SNr exerts a tonic inhibition on thalamocortical neurons.[25]

Based on this model, several hypotheses concerning the role of the basal ganglia in motor control have been proposed. One is that the basal ganglia thalamocortical 'motor' circuit acts to scale movement. Scaling of movement is proposed to occur by a combination of inhibition of GPi/SNr neurons via the direct pathway and excitation of these same neurons via the indirect pathway. Inhibition of these output neurons would facilitate movement by disinhibition of thalamocortical projections excitatory to the cortex. Activation of the same GPi/SNr neurons would lead to inhibition of movement by inhibiting these same thalamocortical projections.[22–24] The balance between excitatory and inhibitory inputs to GPi/SNr output neurons would modulate the amount of disinhibition of thalamocortical neurons, thus providing a mechanism by which movement could be scaled. A second hypothesis proposes that this circuit focuses motor activity. Focusing of motor activity is proposed to occur via activation of the 'direct' pathway, reducing GPi/SNr output, thereby disinhibiting movement-facilitating thalamic neurons, ultimately resulting in activation of prime mover muscles and execution of the desired movement. At the same time, activation of different GPi/SNr neurons by the 'indirect' pathway would increase GPi/SNr output, thus increasing inhibition in a population of thalamocortical neurons, which suppress antagonistic movements (similar to the mechanism of surround inhibition).[22,26] Based on this hypothesis of basal ganglia function, phasic reductions of GPi/SNr output via the direct pathway gate facilitate cortically initiated movements by disinhibition of the thalamus, while phasic increases in GPi/SNr output via the indirect pathway act to inhibit antagonistic or unwanted movements.

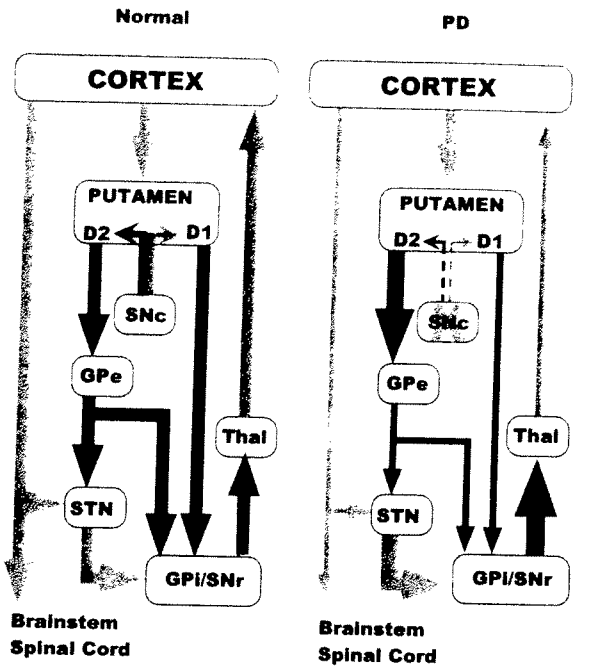

Fig 1. Schematic illustration of the basal ganglia thalamocortical 'motor' circuit and its neurotransmitters under normal conditions (Normal) and the previously proposed 'rate' model for hypokinetic disorders, e.g. Parkinson's disease (PD). 'Indirect' and 'direct' pathways from the striatum are labeled. The width of the lines represent the relative changes in mean discharge rate compared with normal. Wider lines represent an increase and thinner lines represent a decrease in mean discharge rate; black lines represent inhibitory projections and lighter colored lines represent excitatory projections. GPe, GPi, External and internal segments, respectively, of the globus pallidus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; D1, D2, dopamine 1 and 2 receptor subtypes; STN, subthalamic nucleus; thal, thalamus.

Hypokinetic Disorders

Changes in Neuronal Activity

Based on the presented model of intrinsic basal ganglia circuitry, depletion of dopamine in the striatum in PD will lead to increased mean discharge rates of neurons in GPi, excessive inhibition of the pallidal-receiving areas in the thalamus, and a corresponding reduction in thalamocortical activity (Fig 1).

Consistent with predictions of the model, single neuron recording studies in parkinsonian animals have demonstrated that the tonic discharge rate of neurons is increased in GPi and reduced in the pallidal receiving area, VLo.[7,27–29] The observed increases in tonic activity in GPi neurons are indicative of increased activity in the 'indirect' pathway and decreased activity in the 'direct' pathway under parkinsonian conditions. Activity in GPe is decreased as a result of increased striatal inhibition, which in turn leads to an increase in activity in the STN.[8,29,30] It is proposed that the increased activity in the STN results in increased excitation of GPi and suppression of thalamocortical activity. The suppression of thalamocortical activity is, in turn, considered the principle factor underlying the development of parkinsonian motor signs.[23] Consistent with these predictions, inactivation of the GPi or STN, either reversibly (with injections of muscimol or deep brain stimulation) or irreversibly (by injections of ibotenic acid or radiofrequency lesioning), both in animal models of PD (muscimol, ibotenic acid and radiofrequency lesions) and in patients with idiopathic PD (deep brain stimulation and radiofrequency lesions), is associated with significant improvement in parkinsonian motor signs.[8,19,31–41] Furthermore, the improvement in parkinsonian motor signs associated with inactivation of the GPi or STN occurs coincident with an increase in cortical metabolic activity, as determined by positron emission tomography studies using $H_2{}^{15}O$ [increases in the supplementary motor area (SMA) and dorsolateral prefrontal cortex (DLPFC)][42–45] and 2-[^{18}F]fluoro-2-deoxy-D-glucose (increases in the SMA, motor cortex and DLPFC).[46]

There are, however, some problems with this scheme of basal ganglia function. Based on this model, thalamotomy should worsen parkinsonian motor signs since thalamotomy would further reduce thalamocortical activity. Contrary to these predictions, however, thalamotomy does not worsen parkinsonian motor signs. Indeed, most studies report little or no change in bradykinesia following thalamotomy, although it is very effective in alleviating parkinsonian tremor and reducing rigidity.[47,48] It could also be predicted from this model that pallidotomy should induce excessive involuntary movement (dyskinesias), since pallidotomy would disinhibit the thalamus, leading to excessive thalamocortical activity. However, in addition to improving rigidity, bradykinesia and tremor, pallidotomy is also very effective in alleviating drug-induced dyskinesias. These observations are difficult to reconcile with the current hypothesis for hypokinetic disorders and have led to the development of an alternative model.[7,20,49–51]

Alternative Model

In addition to changes in the mean discharge rate, neuronal responses to proprioceptive inputs are more frequent, greater in magnitude, and less specific in both GPi and VLo in the parkinsonian state.[31,52] Furthermore, studies in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-monkey model of PD have reported that the pattern and degree of synchronization of neuronal activity in the pallido-thalamocortical circuit is altered, i.e. the incidence of bursting activity in pallidal and thalamic neurons, and the degree of synchronization of neurons in GPi is increased in the parkinsonian state.[6,7,30,52–55] Widened receptive fields and similar changes in the pattern of neuronal activity in GPi have also been described in patients with idiopathic PD.[15,17,19,50,56,57]

We propose that changes in receptive field characteristics, together with changes in the pattern and degree of synchronization of neuronal activity in the pallidum and thalamus, contribute to the development of parkinsonian motor signs. We further suggest that they do so by interfering with thalamocortical signal transmission, disrupting the normal spatio-temporal pattern of cortical neuronal activity, which leads, in turn, to errors in cortical output and disordered motor control. Support for this concept is derived, in part, from the observation in the MPTP-monkey model of PD that, coincident with improvement in parkinsonian motor signs following lesions of the STN, the pattern and rate of neuronal activity in the pallidum and thalamus normalized[58] (Kaneoke and Vitek, unpublished observations). Further support is derived from the observations in humans with idiopathic PD that improvement in parkinsonian motor signs following pallidotomy or during deep brain stimulation in the GPi or STN was associated with normalization of the pattern of cortical metabolic activity.[42–45,59] Although Limousin and colleagues[44] reported a difference in the pattern of change in cortical metabolic activity depending on which site (GPi or STN) was stimulated, another difference between the two groups in the Limousin study was that the motor symptoms in those patients with GPi stimulation did not improve as much as those with STN stimulation. Davis and colleagues[45] reported changes in cortical metabolic activity coincident with marked improvement in bradykinesia, rigidity and tremor during GPi stimulation that were similar to those reported in the study of Limousin and colleagues[44] during STN stimulation. Thus, an alternative explanation for Limousin and colleagues' observations, which is consistent with the present hypothesis of cortical

dysfunction in PD, is that those patients with relatively greater improvement in parkinsonian motor signs demonstrated significantly greater normalization of cortical metabolic activity.[44] Based on this model, thalamotomy and pallidotomy are effective in alleviating parkinsonian motor signs because each removes abnormal neuronal activity that disrupts function in the motor circuit. Removal of this abnormal neuronal activity leads to improvement in motor function by allowing normalization of thalamo→cortical and cortical→cortical signal transmission.

Additional Pathways

Changes in mean discharge rate and somatosensory responsiveness have been demonstrated to occur not only in pallidal (VLo), but also in the cerebellar receiving area, ventralis posterior lateralis pars oralis (VPLo) of the motor thalamus.[60] Since GPi does not project directly to VPLo, other pathways must contribute to the changes in neuronal activity that occur in VPLo in the parkinsonian state. One pathway that may contribute to these changes is that from GPe to the reticularis nucleus of the thalamus (Rt).[7,49,61] The projections from GPe and Rt are both inhibitory. Thus, since Rt has extensive projections across thalamic subnuclei,[62–64] it is likely to project to thalamic relay neurons in both pallidal and cerebellar receiving areas of the motor thalamus. Since mean discharge rates in GPe are reduced in the parkinsonian state, mean discharge rates in Rt would be increased and lead to excessive inhibition of thalamic relay neurons in both VLo and VPLo. Support for this hypothesis is derived from studies in the parkinsonian monkey, where electrical stimulation in the STN, a procedure which improves parkinsonian motor signs, produced an increase in the mean firing rate in GPe and thalamic neurons coincident with a decrease in mean discharge rate of Rt neurons.[65,66]

A second pathway that could also contribute to the changes in neuronal activity in both pallidal and cerebellar receiving areas of the motor thalamus is that from the pedunculopontine nucleus (PPN). The PPN receives projections from the GPi and SNr, and has extensive projections to the thalamus.[67–69] These projections are cholinergic and have a differential effect on the Rt (hyperpolarizing inhibitory) and thalamic relay neurons (depolarizing excitatory).[70–72] Thus, in the parkinsonian state, excessive inhibitory output from the GPi to the PPN would decrease excitatory input to thalamic relay neurons and reduce inhibitory input to the Rt (leading to increased activity in the Rt), both of which would lead to decreased excitation of thalamic relay neurons and a reduction in mean discharge rate. Since the Rt has widespread projections across the motor thalamus, projects to inhibitory interneurons as well as relay neurons, and plays an important role in the development of synchronous activity in thalamocortical projections during the sleep state,[73] changes in neuronal activity in the Rt may also contribute to changes in the receptive field characteristics, as well as the pattern and degree of synchronization of thalamic neuronal activity (see later).

A model incorporating these pathways and the changes in the pattern of neuronal activity is presented in Fig 2.

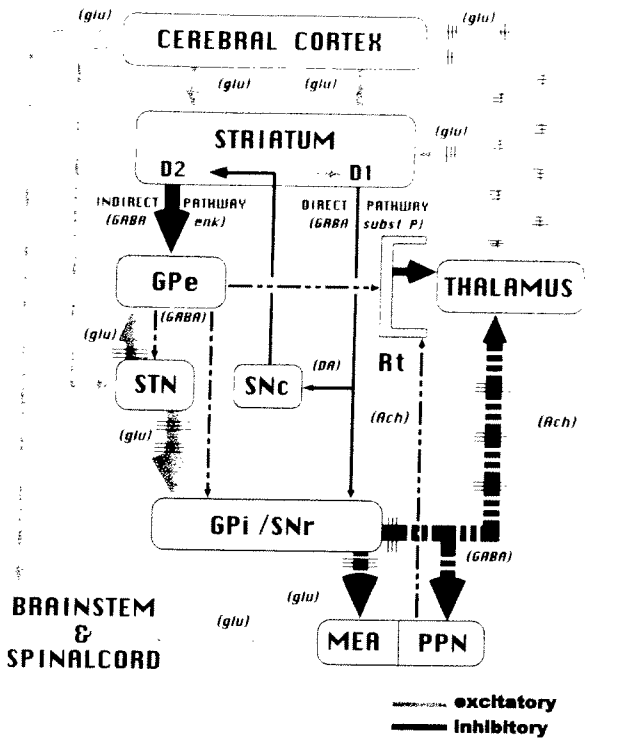

Fig 2. Schematic illustration of the basal ganglia thalamocortical 'motor' circuit incorporating changes in pattern of neuronal activity and alternative pathways from the external segment of the globus pallidus (GPe) and pedunculopontine nucleus (PPN). Interrupted lines represent an alteration in the pattern of neuronal activity. The grouped lines which cross the projections from the subthalamic nucleus (STN), the internal segment of the globus pallidus (GPi) and thalamus represent the presence of bursting activity. SNc, Substantia nigra pars compacta; SNr, substantia nigra pars reticulata; D1, D2, dopamine 1 and 2 receptor subtypes; Rt, reticularis nucleus of the thalamus; GABA, γ-aminobutyric acid; MEA, midbrain extrapyramidal area; glu, glutamate; enk, enkephalin; subst P, substance P; DA, dopamine; Ach, acetylcholine.

Hyperkinetic Disorders

In contrast to the increased GPi output in parkinsonism, studies in animal models and humans with hyperkinetic disorders (e.g. hemiballismus, dystonia and drug-induced dyskinesias) suggest that these disorders result from abnormally lowered GPi output.[16,20,21,74–80] It is postulated that the resulting lowered level of inhibition in the

thalamus leads to excessive movement by 'release' or disinhibition of thalamocortical activity. In drug-induced dyskinesias, this appears to be associated with a reduction of tonic and phasic excitatory STN drive on GPi and may be viewed as an extreme of the postulated normal operation of the 'motor' circuit; i.e., facilitation of cortically-initiated movement.

Support for this proposal is derived from studies in parkinsonian patients receiving apomorphine intraoperatively, in which the development of dyskinesia was associated with a reduction in mean discharge rate of GPi neurons.[16,80] In these reports, coincident with the development of dyskinesia, mean discharge rates of GPi neurons were significantly reduced, while mean discharge rates of GPe neurons were increased. We also observed a relative decrease in the mean discharge rate of GPi neurons during the development of dyskinesia in a patient who experienced motor fluctuations during intraoperative mapping (Vitek and Hashimoto, unpublished observations). Furthermore, we observed that the reduction in mean discharge rate of GPi neurons was progressively lower as the patient evolved from being parkinsonian (e.g. akinetic and rigid with tremor) to 'on' (e.g. improvement in bradykinesia and rigidity, with a reduction or amelioration of tremor) without dyskinesia, and then to 'on' with dyskinesia. Thus, a further reduction in the mean discharge rate of GPi neurons, below that which was associated with improvement in parkinsonian motor signs without the development of dyskinesia, occurred with the development of dyskinesia. Pappa and colleagues[74] reported similar observations in the development of dyskinesia associated with a reduction in mean discharge rate in GPi neurons in parkinsonian monkeys, which was lower when the monkey had dyskinesia than when parkinsonian signs were ameliorated and the monkey did not have dyskinesia. Similarly, Hayase and colleagues[81] observed that the reduction in mean discharge rate of GPi neurons which occurred in parkinsonian monkeys receiving dopamine agonists or during deep brain stimulation was greater in the animals that developed dyskinesias than in those which did not. Thus, there appears to be a normal level of neuronal activity in GPi below which dyskinesias develop and above which parkinsonian motor signs emerge.

One mechanism by which excessive reductions in the GPi mean discharge rate could contribute to the development of dyskinesias is by inducing a change in the pattern and degree of synchronization of thalamic neuronal activity. Since the pattern of thalamic neuronal activity is dependent on the degree of membrane polarization of thalamic neurons,[82–84] changes in net inhibitory input to the thalamus from the pallidum may lead to changes in the pattern of thalamic neuronal activity. Based on this hypothesis, excessive reductions in mean discharge rates of GPi neurons would lead to excessive increases in mean discharge rate, and changes in the pattern and degree of synchronization of thalamic neuronal activity, which underlie the development of dyskinesias. It is not difficult to understand how removal of such activity by thalamotomy may abolish drug-induced dyskinesias.[85] It is, however, much more difficult to understand how lesions in the GPi, which would lead to a further reduction in inhibitory control over the thalamocortical pathway, improve dyskinesia.[33–35,86] Thus, a decreased mean discharge rate in GPi cannot, by itself, account for the development of drug-induced dyskinesia. However, since changes in the level of membrane polarization of thalamic neurons may induce changes in the pattern of thalamic neuronal activity via a mechanism that is voltage dependent,[82–84] some level of inhibitory (hyperpolarizing) input may be necessary to sustain these changes. Removal of such input via pallidotomy could, therefore, result in a normalization of the pattern of neuronal activity. Thus, pallidotomy may be effective in alleviating drug-induced dyskinesias because it removes the source of inhibitory input to the thalamus, which induced the changes in the pattern of thalamic neurons that underlie their development. However, another possible explanation for the ameliorating effect of pallidotomy on dyskinesias is that changes in the pattern and degree of synchronization of pallidal neurons themselves are transmitted directly to thalamic neurons (see later). In this case, pallidotomy would be effective in ameliorating drug-induced dyskinesias because it directly removes the abnormal pattern of neuronal activity. A close examination of the changes in pallidal neuronal activity in patients with, and animal models of, hyperkinetic disorders (e.g. hemiballismus, dystonia and drug-induced dyskinesia) is therefore critically important to examine this hypothesis and to further our understanding of the physiological basis which underlies the development of dyskinesias.

Neuronal Activity in GPi in Hyperkinetic Movement Disorders: A Model for Dyskinesia

Drug-Induced Dyskinesia

Merello and colleagues[80] reported a change in the pattern of GPi neuronal activity in patients developing dyskinesias following administration of apomorphine. Coincident with the reduction in discharge rate, GPi neuronal activity changed from a high-frequency tonic discharge pattern to a noncontinuous burst-like discharge,[80] similar to that reported in patients with dystonia and hemiballismus (see later).[20] Although Hutchison and colleagues[16] stated they had not observed any obvious change in the firing pattern of GPi neurons in a similar group of patients receiving apomorphine, they did report a prolongation of pauses in GPi neurons that decreased their activity, a pattern not dissimilar to that reported by Merello and colleagues.[80]

Changes in the pattern of neuronal activity in GPi during the development of dyskinesia have also been reported in animal models of PD. Decreased rates and intermittent pauses in GPi neurons following apomorphine injections were associated with the development of dyskinesia in parkinsonian monkeys.[87] Similarly, Hamada recently reported changes in the pattern of discharge of GPi neurons associated with reduced mean discharge rates, following inactivation of the STN and the development of dyskinetic movements.[88] Thus, coincident with the reduction in mean discharge rate, changes in the pattern of neuronal activity in GPi may be related to, and may even be necessary for, the development of dyskinesias. Based on this hypothesis, a simple reduction in discharge rate in GPi without an associated change in the pattern of neuronal activity would not be associated with the development of dyskinesias. Consistent with this prediction, Hayase and colleagues[81] reported improvement in parkinsonian motor signs during STN stimulation without the development of dyskinesias. This improvement in parkinsonian motor signs occurred coincident with a reduction in the mean discharge rate and normalization of the pattern of discharge of GPi neurons.

Dystonia and Hemiballismus

Mean discharge rates in GPi are also reduced in patients with other hyperkinetic disorders, such as dystonia and hemiballismus, in a similar manner to that observed during drug-induced dyskinesia in patients with PD. Examination of spontaneous neuronal activity in patients with hemiballismus and dystonia also reveals changes in the pattern, degree of synchronization and somatosensory responsiveness of neurons in the pallidum. Contrary to the tonic pattern of discharge present in normal animals, spontaneous discharge patterns of neurons in GPi are highly abnormal in patients with dystonia and hemiballismus, occurring in irregularly grouped discharges with intermittent pauses. Unlike PD, where the mean discharge rate of neurons is increased in GPi and decreased in GPe, and the patterns of discharge are clearly different, in dystonia and hemiballismus, the mean rates and patterns of discharge of GPe and GPi neurons appear very similar (Fig 3).

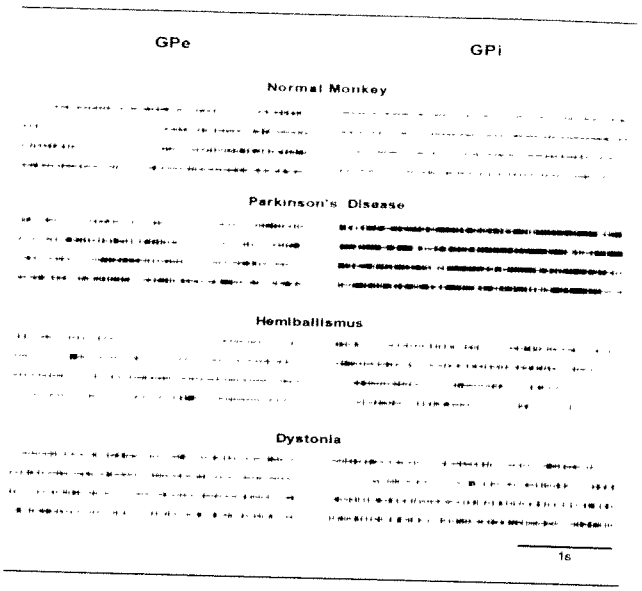

Fig 3. Rasters displaying the pattern of spontaneous neuronal activity from the external (GPe) and internal (GPi) segments of the globus pallidus in a normal monkey, and the irregular altered pattern of spontaneous neuronal activity in the pallidum in humans with Parkinson's disease, hemiballismus and dystonia.

Changes in Synchronization

In addition to the change in pattern of neuronal activity, changes in the degree of synchronization of pallidal neurons are also likely to contribute to the development of dyskinesia. In hemiballismus, we have previously observed a strong correlation of neuronal to electromyographic (EMG) activity in the ballistic limb, which was present for both flexor and extensor muscles.[20] The strong correlation of neuronal to EMG activity suggests there may have been an increased degree of synchronization of neurons in the GPi in the patient with hemiballismus. Although we did not record from multiple GPi neurons simultaneously to determine the degree of synchronicity, hypothetically it would seem unlikely to observe such a strong correlation between neuronal and EMG activity unless a large enough population of pallidal neurons were discharging in concert. Indeed, a strong correlation of unit to EMG activity was found for 23% of the cells in GPi that were sampled, suggesting that a high degree of synchronization of neuronal activity in GPi was present.[20] While increases in synchronization of neuronal activity may occur normally,[89,90] and are even likely to be necessary for the production of voluntary movement, uncontrolled increases in synchronization are likely to be disruptive, interfering with voluntary modulation and producing involuntary movement. Certain forms of dystonia, such as that occurring during rest, or the occurrence of involuntary movement as in hemiballismus and drug-induced dyskinesia, could develop as a consequence of a progressive increase in the amount and degree of uncontrolled synchrony of spontaneous neuronal activity in the pallidum.

Basis for Differences Between Hyperkinetic Disorders

Although hyperkinetic disorders are similar in many aspects, they are different in terms of the type of involuntary movement which occurs. Differences in some aspects of the changes in neuronal activity in the direct and indirect pathways, however, may account for at least some of the differences in phenotypic appearance in the

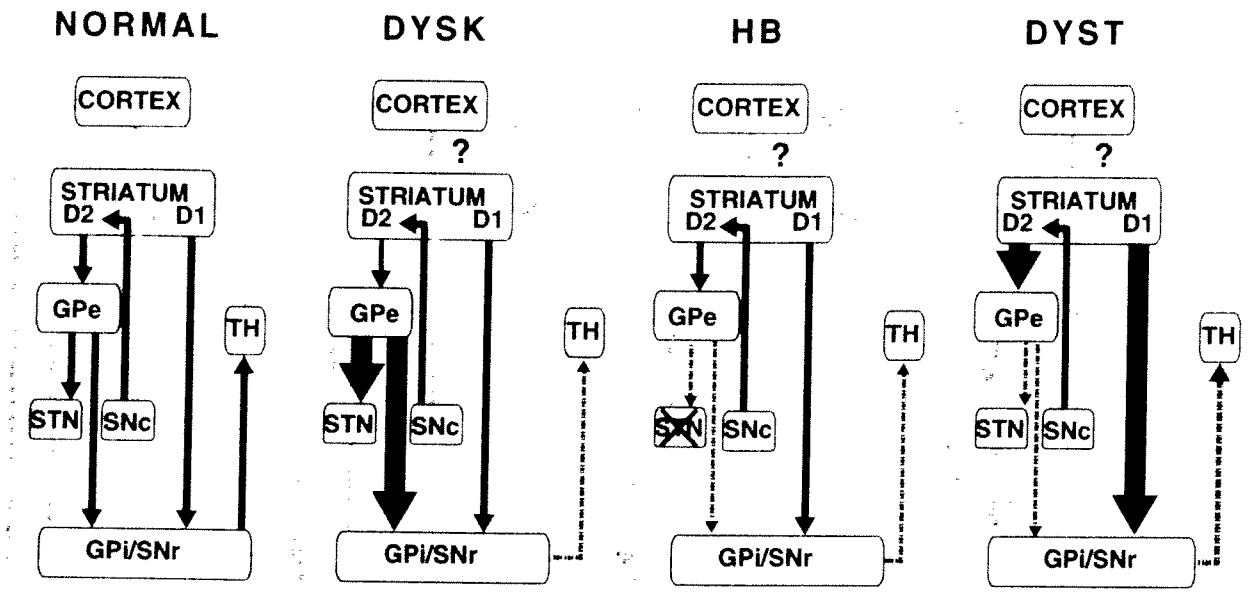

Fig 4. Models of hyperkinetic disorders incorporating changes in pattern and increased synchronization of neuronal activity in the basal ganglia and thalamus (TH), leading to disruption of thalamocortical and cortical-cortical signal transmission. Disrupted lines represent the altered patterns and suggested increase in synchronization of neuronal activity in the basal ganglia thalamocortical circuit, leading to unregulated cortical output. Striatal underactivity in the indirect pathway is postulated to play a significant role in the development of drug-induced dyskinesias (DYSK). Loss of excitatory input from the subthalamic nucleus (STN) to the internal segment of the globus pallidus (GPi) is postulated to underlie the development of hemiballismus (HB), while striatal overactivity in both the direct and indirect pathways is postulated to account for the observed changes in neuronal activity in dystonia (DYST). The connections to and from the pedunculopontine nucleus and midbrain extrapyramidal area, and those from the external segment of the globus pallidus (GPe) to the reticularis nucleus of the thalamus, which are not shown because of space constraints, are likely to contribute to the changes in neuronal activity that occur in hyperkinetic disorders as well as in Parkinson's disease (PD). SNc, Substantia nigra pars compacta; SNr, substantia nigra pars reticulata; D1, D2, dopamine 1 and 2 receptor subtypes.

different hyperkinetic disorders. For example, GPi neurons in patients with dystonia and PD have widened receptive fields, while in hemiballismus, somatosensory responsiveness of neurons in GPi is reduced. In dystonia and hemiballismus, GPe output is decreased,[20,21,50,91–93] while mean discharge rates in GPe are increased during drug-induced dyskinesias.[16,80,87] Thus, while excessive inhibitory output in the direct pathway appears to play a predominant role in the reduced mean discharge rate and altered patterns of neuronal activity in GPi in dystonia, the indirect pathway appears to play a more predominant role in the development of drug-induced dyskinesias. Changes in the indirect pathway alone, however, cannot account for the development of drug-induced dyskinesias, since lesions in GPe do not alleviate them.[9,4] Thus, contributions from both the direct and indirect, as well as alternative, pathways are likely necessary for the development of drug-induced dyskinesias. We propose that the different types of dyskinesias (e.g. drug-induced dyskinesias, dystonia and hemiballismus) result from differences in the balance between the direct, indirect and alternative pathways from GPe and PPN,[20,50,95] together with the relative change in mean rate, pattern, degree of synchronization and altered somatosensory responsiveness of neuronal activity in each of these pathways. Interruption of this activity, whether at the level of the pallidum or the thalamus, would allow neuronal activity throughout the remaining portion of the motor circuit to normalize, resulting in alleviation of the involuntary movement and accounting for the beneficial effect of ablative lesions in these areas on dyskinesia. A model for hyperkinetic movement disorders based on these observations is presented in Fig 4.

Summary

Dyskinesias develop as a result of a combination of changes in pattern, synchronization, mean discharge rates and somatosensory responsiveness of neurons in the direct, indirect and alternative pathways in the pallidothalamocortical 'motor' circuit. Altered patterns and increased synchronization of pallidal output neurons may be transmitted directly to thalamic relay neurons, while

excessively reduced mean discharge rates in GPi may contribute to changes in the pattern and induce synchronization of thalamic relay neurons via changes in local membrane or network properties. The particular phenotypic appearance of the involuntary movement probably depends on the relative change in neuronal activity, which occurs in the direct, indirect and alternative pathways, together with the relative degree and particular combination of changes in mean discharge rate, pattern, degree of synchronization and somatosensory responsiveness of neurons in each of these pathways. The beneficial effect of ablation or deep brain stimulation in the GPi, STN or thalamus for involuntary movements associated with hyperkinetic disorders likely occurs as a result of the interruption of this abnormal activity, allowing the remaining portion of the motor circuit to function more normally.

References

1. Weiner W, Lang A. Movement disorders: a comprehensive survey. Mount Kisco, NY: Futura Publishing, 1989
2. Meyers R. Surgical interruption of the pallidofugal fibres: its effect on the syndrome paralysis agitans and technical considerations in its application. NY State J Med 1942;42:317–325
3. Meyers R. The modification of alternating tremors, rigidity and festination by surgery of the basal ganglia. Assoc Nerv Ment Disord 1942;20:602–665
4. Gerfen CR, Engber TM, Mahan LC, et al. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 1990;250:1429–1432
5. Filion M, Tremblay L, Bédard PJ. Abnormal influences of passive limb movement on the activity of globus pallidus neurons in parkinsonian monkeys. Brain Res 1988;444:165–176
6. Miller WC, DeLong MR. Altered tonic activity of neurons in the globus pallidus and subthalamic nucleus in the primate MPTP model of parkinsonism. In: Carpenter MB, Jayaraman A, eds. The basal ganglia II. New York: Plenum Press, 1987:415–427
7. Vitek JL, Ashe J, Kaneoke Y. Spontaneous neuronal activity in the motor thalamus: alteration in pattern and rate in parkinsonism [abstract]. Neuroscience 1994;20(Part 1):561
8. Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 1990; 249:1436–1438
9. Pan HS, Frey KA, Young AB, Penney JBJ. Changes in [^{3}H]muscimol binding in substantia nigra, entopeduncular nucleus, globus pallidus and thalamus after striatal lesions as demonstrated by quantitative receptor autoradiography. J Neurosci 1983;3:1189–1198
10. Pan HS, Penney JB, Young AB. Gamma-aminobutyric acid and benzodiazepine receptor changes induced by unilateral 6-hydroxydopamine lesions of the medial forebrain bundle. J Neurochem 1985;45:1396–1404
11. Mitchell IJ. Neural mechanisms underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Neuroscience 1989;32:213–226
12. Porrino LJ, Burns RS, Crane AM, et al. Changes in local cerebral glucose utilization associated with Parkinson's syndrome induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the primate. Life Sci 1987;40:1657–1664
13. Schwartzman RJ, Alexander GM, Ferraro TN, et al. Cerebral metabolism of parkinsonian primates 21 days after MPTP. Exp Neurol 1988;102:307–313
14. Crossman AR, Mitchell IJ, Sambrook MA. Regional brain uptake of 2-deoxyglucose in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the macaque monkey. Neuropharmacology 1985;24:587–591
15. Hutchison WD, Lozano AM, Davis K, et al. Differential neuronal activity in segments of globus pallidus in Parkinson's disease patients. Neuroreport 1994;5:1533–1537
16. Hutchison WD, Levy R, Dostrovsky JO, et al. Effects of apomorphine on globus pallidus neurons in Parkinsonian patients. Ann Neurol 1997;42:767–775
17. Sterio D, Beric A, Dogali M, et al. Neurophysiological properties of pallidal neurons in Parkinson's disease. Ann Neurol 1994;35: 586–591
18. Vitek JL, Kaneoke Y, Turner R, et al. Neuronal activity in the internal (GPi) and external (GPe) segments of the globus pallidus (GP) of parkinsonian patients is similar to that in the MPTP-treated primate model of parkinsonism. Soc Neurosci Abstr 1993; 19:1584 (Abstract)
19. Vitek JL, Bakay RAE, Hashimoto T, et al. Microelectrode-guided pallidotomy: technical approach and application for treatment of medically intractable Parkinson's disease. J Neurosurg 1998;88:1027–1043
20. Vitek JL, Chockkan V, Zhang J, et al. Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. Ann Neurol 1999;46:22–35
21. Suarez J, Verhagen-Metman L, Reich S, et al. Pallidotomy for hemiballismus: efficacy and characteristics of neuronal activity. Ann Neurol 1997;42:807–811
22. Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, 'prefrontal' and 'limbic' functions. Prog Brain Res 1990;85: 119–146.
23. DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990;13:281–285
24. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989;12:366–375
25. Yoshida M, Rabin A, Anderson A. Monosynaptic inhibition of pallidal neurons by axon collaterals of caudatonigral fibers. Exp Brain Res 1972;15:333–347
26. Smith Y, Wichmann T, DeLong MR. The external pallidum and the subthalamic nucleus send convergent inputs onto single neurons in the internal pallidal segment in the monkey: anatomical organization and functional significance. In: Percheron G, McKenzie JS, Féger J, eds. The basal ganglia IV: new ideas and data on structure and function. New York: Plenum Press, 1994:51–61
27. Miller WC, DeLong MR. Parkinsonian symptomatology: an anatomical and physiological analysis. Ann NY Acad Sci 1988; 515:287–302
28. Filion M. Effects of interruption of the nigrostriatal pathway and of dopaminergic agents on the spontaneous activity of globus pallidus neurons in the awake monkey. Brain Res 1979; 178:425–441
29. Filion M, Tremblay L, Bédard P. Effects of dopamine agonists on the spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res 1991;547:152–161
30. Filion M, Tremblay L. Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res 1991;547:142–151
31. Wichmann T, Baron MS, DeLong MR. Local inactivation of the sensorimotor territories of the internal segment of the globus pallidus and the subthalamic nucleus alleviates parkinsonian motor signs in MPTP treated monkeys. In: Percheron G, McKenzie JS, Féger J, eds. The basal ganglia IV: new ideas and data on structure and function. New York: Plenum Press, 1994:357–364

32. Baron MS, Wichmann T, DeLong MR. Inactivation of the sensorimotor territory in the internal pallidum reverses parkinsonian signs in MPTP-treated monkeys. Soc Neurosci Abstr 1992;18:69 (Abstract)
33. Baron MS, Vitek JL, Bakay RAE, et al. Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. Ann Neurol 1996;40:355–366
34. Lozano AM, Lang AE, Galvez-Jimenez N, et al. Effect of GPi pallidotomy on motor function in Parkinson's disease. Lancet 1995; 346:1383–1387
35. Lang A, Lozano A, Montgomery E, et al. Posteroventral medial pallidotomy in advanced Parkinson's disease. N Engl J Med 1997; 337:1036–1042
36. Dogali M, Sterio D, Fazzini E, et al. Effects of posteroventral pallidotomy on Parkinson's disease. Adv Neurol 1996;69:585–590
37. Limousin P, Krack P, Pollack P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 1998;339:1105–1111
38. Kumar R, Lozano AM, Montgomery E, Lang AE. Pallidotomy and deep brain stimulation of the pallidum and subthalamic nucleus in advanced Parkinson's disease. Mov Disord 1998;13(Suppl 1): 73–82
39. Volkman J, Sturn V, Weiss P, et al. Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. Ann Neurol 1998;44:953–961
40. Gross C, Rougier A, Guehl D, et al. High-frequency stimulation of the globus pallidus internalis in Parkinson's disease: a study of seven cases. J Neurosurg 1997;87:491–498
41. Limousin P, Pollack P, Benazzous A, et al. Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 1995;345:91–95
42. Grafton S, Waters C, Sutton J, et al. Pallidotomy increases activity of motor association cortex in Parkinson's disease: a positron emission tomographic study. Ann Neurol 1995;37:776–783
43. Samuel M, Ceballos-Baumann A, Turjanski N, et al. Pallidotomy in Parkinson's disease increases SMA and prefrontal activation during performance of volitional movements: an $H_2{}^{15}O$ PET study. Brain 1997;120:1301–1313
44. Limousin P, Greene J, Pollack P, et al. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. Ann Neurol 1997;42:283–291
45. Davis K, Taub E, Houle S, et al. Globus pallidus stimulation activates the cortical motor system during alleviation of parkinsonian symptoms. Nat Med 1997;3:671–674
46. Eidelberg D, Moeller J, Ishikawa T, et al. Regional metabolic correlates of surgical outcome following unilateral pallidotomy for Parkinson's disease. Ann Neurol 1996;39:450–459
47. Marsden CD, Obeso JA. The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. Brain 1994;117:877–897
48. Narabayashi H. Tremor: its generation mechanism and treatment. In: Vinken PJ, Bruyn GW, Klawans HL, eds. Handbook of clinical neurology, Vol 5. Amsterdam: Elsevier Science, 1986:597–607
49. Vitek J. Stereotaxic surgery and deep brain stimulation for movement disorders. In: Watts RL, Koller WC, eds. Movement disorders: neurologic principles and practice. New York: McGraw-Hill, 1997:237–255
50. Vitek JL, Zhang J, Evatt ML, et al. GPi pallidotomy for dystonia: clinical outcome and neuronal activity. Adv Neurol 1998;78: 211–219
51. Wichmann T, DeLong M. Functional and pathophysiological models of the basal ganglia. Curr Opin Neurobiol 1996;6: 751–758
52. Vitek JL, Ashe J, DeLong MR, Alexander GE. Altered somatosensory response properties of neurons in the 'motor' thalamus of MPTP treated parkinsonian monkeys. Soc Neurosci Abstr 1990; 16:425 (Abstract)
53. Raz A, Feingold A, Vaadia E, et al. In phase neuronal oscillations in the basal ganglia of tremulous MPTP-treated vervet monkeys. Soc Neurosci Abstr 1997;23:466 (Abstract)
54. Nini A, Feingold A, Slovin H, Bergman H. Neurons in the globus pallidus do not show correlated activity in the normal monkey but phase-locked oscillations appear in the MPTP model of parkinsonism. J Neurophysiol 1995;74:1800–1805
55. Feingold A, Nini A, Raz A, et al. Neuronal oscillations and correlations in the basal ganglia of normal and MPTP-treated monkeys. Soc Neurosci Abstr 1996;22:414 (Abstract)
56. Taha J, Favre J, Baumann T, Burchiel K. Tremor control after pallidotomy in patients with Parkinson's disease: correlation with microrecording findings. J Neurosurg 1997;86:642–647
57. Taha JM, Favre J, Baumann TK, Burchiel KJ. Characteristics and somatotopic organization of kinesthetic cells in the globus pallidus in patients with Parkinson's disease. J Neurosurg 1996;85:1005–1012
58. Ryan LJ, Sanders DJ. Subthalamic nucleus lesion regularizes firing patterns in globus pallidus and substantia nigra pars reticulata neurons in rats. Brain Res 1993;626:327–331
59. Eidelberg D, Moeller JR, Ishikawa T, et al. Regional metabolic correlates of surgical outcome following unilateral pallidotomy for Parkinson's disease. Ann Neurol 1996;39:450–459
60. Kaneoke Y, Vitek JL, Ashe MR, et al. Altered somatosensory response properties of neurons in the cerebellar receiving area of the motor thalamus in MPTP treated parkinsonian monkeys. Soc Neurosci Abstr 1993;19:1585 (Abstract)
61. Hazrati L-N, Parent A. Projection from the external pallidum to the reticular thalamic nucleus in the squirrel monkey. Brain 1991;550:142–146
62. Ilinsky IA, Kultas-Ilinsky K. Reticular thalamic nucleus input to the nuclei of the monkey thalamus: light and electron-microscope study [abstract]. Neuroscience 1993;19(Part 2):14363
63. Yen CT, Jones EG. Intracellular staining of physiologically identified neurons and axons in the somatosensory thalamus of the cat. Brain Res 1983;280:148–154
64. Scheibel ME, Scheibel AB. The organization of the nucleus reticularios thalami: a golgi study. Brain Res 1966;1:43–62
65. Benazzouz A, Piallat B, Pollak P, Benabid A-L. Responses of substantia nigra pars reticulata and globus pallidus complex to high frequency stimulation of the subthalamic nucleus in rats: electrophysiological data. Neurosci Lett 1995;189:77–80
66. Benabid AL, Pollak P, Limousin P, et al. Mechanism of action of STN stimulation in alleviation of Parkinson's disease symptoms. Soc Neurosci Abstr 1994;20(Part 1):2 (Abstract)
67. Hallanger AE, Levey AI, Lee HJ, et al. The origins of cholinergic and other subcortical afferents to the thalamus in the rat. J Comp Neurol 1987;262:105–124
68. Levey AI, Hallanger AE, Wainer BH. Cholinergic nucleus basalis neurons may influence the cortex via the thalamus. Neurosci Lett 1987;74:7–13
69. Steriade M, Pare D, Parent A, Smith Y. Projections of cholinergic and non-cholinergic neurons of the brainstem core to relay and associational thalamic nuclei in the cat and macaque monkey. Neuroscience 1988;25:47–67
70. McCormick DA, Prince DA. Acetylcholine induces burst firing in thalamic reticular neurones by activating a potassium conductance. Nature 1986;319:402–405
71. McCormick DA, Pape H-C. Acetylcholine inhibits identified interneurons in the cat lateral geniculate nucleus. Nature 1988;334:246–248
72. McCormick DA. Cholinergic and noradrenergic modulation of thalamocortical processing. Trends Neurosci 1989;12:215–221
73. Jones EG. The thalamus. New York: Plenum Press, 1985
74. Pappa SM, Desimone R, Fiorani M, Oldfield EH. Internal globus pallidus discharge is nearly suppressed during levodopa-induced dyskinesias. Ann Neurol 1999;46:732–738

75. Mitchell IJ, Boyce S, Sambrook MA, Crossman AR. A 2-deoxyglucose study of the effects of dopamine agonists on the parkinsonian primate brain. Implications for the neural mechanisms that mediate dopamine agonist-induced dyskinesia. Brain 1992;115: 809–824
76. Mitchell IJ, Luquin R, Boyce S, et al. Neural mechanisms of dystonia: evidence from a 2-deoxyglucose uptake study in a primate model of dopamine agonist-induced dystonia. Mov Disord 1990;5:49–54
77. Boyce S, Clarke CE, Luquin R. Induction of chorea and dystonia in parkinsonian primates. Mov Disord 1990;5:3–7
78. Clarke CE, Sambrook MA, Mitchell IJ, Cross AR. Levodopa-induced dyskinesia and response fluctuations in primates rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). J Neurol Sci 1987;78:273–280
79. Hamada I, DeLong MR. Excitotoxic acid lesions of the primate subthalamic nucleus result in reduced pallidal neuronal activity during active holding. J Neurophysiol 1992;68:1859–1866
80. Merello M, Balej J, Delfino M, et al. Apomorphine induces changes in GPi spontaneous outflow in patients with Parkinson's disease. Mov Disord 1999;14:45–49
81. Hayase N, Filion M, Richard H, Boraud T. Electrical stimulation of the subthalamic nucleus in fully Parkinsonian (MPTP) monkeys: effects on clinical signs and pallidal activity. In: Ohye O, Kimura M, McKenzie J, eds. The basal ganglia V. New York: Plenum Press, 1996:241–248
82. Llinas RR. Rebound excitation as the physiological basis for tremor: a biophysical study of the oscillatory properties of mammalian central neurones in vitro. In: Findley LJ, Capildeo R, eds. Movement disorders: tremor. London: Macmillan, 1984:165–182
83. Llinas RR. The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. Science 1988;242:1654–1664
84. Jahnsen H, Llinas R. Electrophysiological properties of guinea-pig thalamic neurones: an in vitro study. J Physiol 1984;349:205–226
85. Narabayashi H, Yokochi F, Nakajima Y. Levodopa-induced dyskinesia and thalamotomy. J Neurol Neurosurg Psychiatry 1984;47: 831–839
86. Dogali M, Fazzine E, Kolodny E, et al. Stereotactic ventral pallidotomy for Parkinson's disease. Neurology 1995;45:753–761
87. Yoshida M. The neuronal mechanism underlying parkinsonism and dyskinesia: differential roles of the putamen and caudate nucleus. Neurosci Res 1991;12:31–40
88. Hamada I. Direct and indirect pathways: why do pallidotomy and subthalamic stimulation work? In: Proceedings International Basal Ganglia Society, 6th Triennial Meeting, Brewster, MA, 1998
89. Singer W. A new job for the thalamus. Nature 1994;369:444–445
90. Riehle A, Grun S, Diesmann M, Aertsen A. Spike synchronization and rate modulation differentially involved in motor cortical function. Science 1997;278:1950–1953
91. Vitek JL, Zhang J, DeLong MR, et al. Neuronal activity in the pallidum in patients with medically intractable dystonia [abstract]. Mov Disord 1996;12(3):9
92. Vitek JL, Kaneoke Y, Hashimoto T, et al. Neuronal activity in the pallidum of a patient with hemiballismus. In: 120th Annual Meeting, American Neurological Association, Washington, DC, 1995, Abstracts 38–39
93. Hutchison W, Gross R, Lang A, Lozano A. Altered activity of globus pallidus (GP) neurons in dystonia. In: Society for Neuroscience 27th Annual Meeting, New Orleans, LA, 1997. Proceedings 23(1):471 (Abstract)
94. Blanchet PJ, Boucher R, Bédard PJ. Excitotoxic lateral pallidotomy does not relieve L-dopa-induced dyskinesia in MPTP parkinsonian monkeys. Brain Res 1994;650:32–39
95. Boyce S, Clarke CE, Luquin R, et al. Induction of chorea and dystonia in parkinsonian primates. Mov Disord 1990;5:3–7