The Basal Ganglia and Involuntary Movements

Impaired Inhibition of Competing Motor Patterns

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The basal ganglia are organized to facilitate voluntary movements and to inhibit competing movements that might interfere with the desired movement. Dysfunction of these circuits can lead to movement disorders that are characterized by impaired voluntary movement, the presence of involuntary movements, or both. Current models of basal ganglia function and dysfunction have played an important role in advancing knowledge about the pathophysiology of movement disorders, but they have not contained elements sufficiently specific to allow for understanding the fundamental differences among different involuntary movements, including chorea, dystonia, and tics. A new model is presented here, building on existing models and data to encompass hypotheses of the fundamental pathophysiologic mechanisms underlying chorea, dystonia, and tics.

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During the past 15 years, there has been substantial progress in understanding the pathophysiology of movement disorders related to basal ganglia dysfunction. Much of this progress can be attributed to the influential hypotheses of Albin et al[1] and DeLong.[2] If the success of a model is measured by the amount of research it stimulates, these schemes have been extraordinarily successful. In simple terms, these models propose that hypokinetic movement disorders (eg, parkinsonism) can be distinguished from hyperkinetic movement disorders (eg, chorea and dystonia) based on the magnitude and pattern of the basal ganglia output neurons in the globus pallidus pars interna (GPi) and substantia nigra pars reticulata (SNpr).[3] Basal ganglia output neurons inhibit the motor thalamus and the midbrain extrapyramidal area; their role has been proposed to be analogous to a braking mechanism such that increased activity inhibits and decreased activity facilitates motor pattern generators in the cerebral cortex and brainstem.[4] The inputs to the GPi and SNpr from the striatum and subthalamic nucleus

(STN) are organized anatomically and physiologically such that the striatum provides a specific, focused, context-dependent inhibition, while the STN provides a less specific, divergent excitation. Because the output from the GPi and SNpr is inhibitory, this organization translates to a focused facilitation and surround inhibition of motor mechanisms in thalamocortical and brainstem circuits (**Figure 1**). The function of this organization is to selectively facilitate desired movements and to inhibit potentially competing movements.

A shortcoming of the models of basal ganglia dysfunction in movement disorders[1,2] has been a lack of specificity as to the physiologic mechanisms responsible for the hyperkinetic movement disorders. In particular, chorea, hemiballismus, dystonia, and tics can all be viewed as hyperkinetic movement disorders due to a presumed reduction of the normal inhibitory basal ganglia output. For the purpose of this discussion, chorea and hemiballismus will be considered as mechanistically similar, differing only in the amplitude of the movements and body parts involved.[4] Dystonia, chorea, and tics manifest as recognizably distinct movement disorders. It should thus follow that

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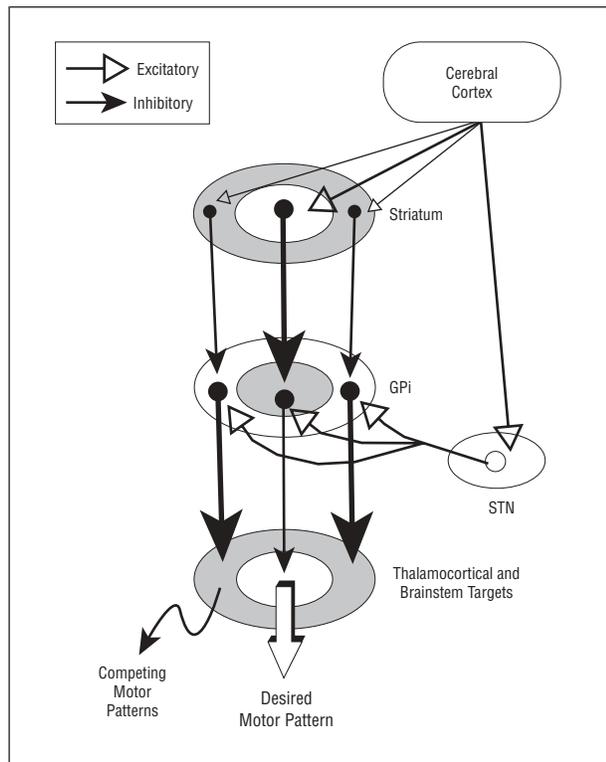
Figure 1. Functional organization of basal ganglia output for selective facilitation and surround inhibition of competing motor patterns. Open arrows indicate excitatory projections; filled arrows, inhibitory projections. Relative magnitude of activity is represented by line thickness. GPi indicates globus pallidus pars interna; STN, subthalamic nucleus.

they have distinct pathophysiologic mechanisms. A successful model must be able to account specifically for physiologic differences among these movement disorders. Available physiologic data are limited, but existing data are sufficient to develop specific anatomically and physiologically based hypotheses. Based on these data, a new model is presented here that encompasses specific hypotheses of the fundamental pathophysiologic mechanisms underlying chorea, dystonia, and tics.

CHOREA

Chorea is a disorder of involuntary movement that is commonly described as frequent, brief, sudden, twitchlike movements that flow from body part to body part in a chaotic manner. Although usually described as chaotic or random, chorea often resembles fragments of normal movement, and many individuals with chorea incorporate the involuntary movements into motor patterns that appear voluntary. Chorea exists as a spectrum of movements that can be proximal or distal, large or small in amplitude, and intermittent or nearly continuous. Chorea is seen in many disease states. In diseases with well-defined neuropathologic characteristics, chorea has been associated with abnormalities in the striatum or STN. Experimentally, chorea can be produced with inactivation (or lesion) of the STN, disinhibition of the GP pars externa, or by administering dopaminergic agents to parkinsonian primates. In primate models of chorea and in the human conditions of hemiballism and dopa-

induced choreatic dyskinesia, it has been shown that the overall activity of GPi neurons is decreased.[4,5] This would appear to be consistent with the prevailing models of hyperkinetic movement disorders.[1,2] However, tonic reduction of GPi activity alone cannot explain chorea because (1) experimental lesions of the GPi do not cause chorea; (2) monkeys with STN lesions have decreased GPi discharge rates after the dyskinesia has resolved; and (3) ablation of the GPi eliminates choreatic dyskinesia in Parkinson disease[6] and hemiballismus.[5]

If chorea is not due to tonically reduced GPi output, what is the underlying pathophysiologic mechanism? It seems obvious that there is abnormal phasic neuronal activity originating somewhere in the motor system. At present, it is not known whether the activity driving the choreatic movements originates in the basal ganglia or in thalamocortical (or brainstem) motor pattern generators. Abnormal phasic bursting of GPi neurons has been described in people with chorea or hemiballism.[3,7] Abnormal phasic bursting of GPi neurons would intermittently and alternately disinhibit and then inhibit thalamocortical motor circuits. However, a temporal correlation between the GPi bursts and electromyographic bursts has not been demonstrated. Alternatively, it is possible that partial reduction of tonic GPi activity causes target neurons in the thalamus to depolarize to near threshold so that random small fluctuations in other, non–basal ganglia inputs can cause them to fire in random bursts. In either case, cortical motor pattern generators would be "gated in" or "gated out" in a random temporal pattern, causing the involuntary movement of chorea (**Figure 2**). If motor pattern generators rather than random individual groups of neurons are gated in or out, it would be expected that the spatial pattern of chorea is nonrandom, as has been shown recently.[8]

DYSTONIA

Dystonia is a movement disorder characterized by involuntary muscle spasms that produce twisting postures of different parts of the body. Many different human neurologic conditions are associated with dystonia, including focal lesions in the putamen, globus pallidus, or thalamus. There is mounting evidence that some dystonias are associated with relative dopamine deficiency or dopamine type 2 receptor dysfunction.[9] Studies of motor physiology in dystonia show abnormal cocontraction of agonist and antagonist muscles that is usually exacerbated by movement.[10] During voluntary movement, involuntary contractions are also seen in muscles that would not normally be active in the task. Despite the excessive activity of nearby muscles, activity in the prime movers is usually normal.

Relatively little is known about basal ganglia neuronal activity in dystonia, but knowledge is increasing with the growing use of neurosurgical treatment for dystonia. There appears to be reduced tonic firing of GPi neurons, accompanied by abnormal temporal discharge patterns in some individuals with dystonia.[7] The size of somatosensory receptive fields in GPi neurons is increased in patients with dystonia. These data have been used to support the idea that dystonia is associated with increased activity in the "direct" pathway from the stria-

tum to the GPi, leading to excessive inhibition of the GPi and excessive disinhibition of motor cortical areas. This would be reflected as enhanced facilitation and possibly expansion of the "center" of the present center-surround model (Figure 1). An alternative scheme, based on reduced dopamine D_2 receptor binding in the striatum in dystonic monkeys and in people with dystonia, is that abnormal activity in the "indirect" pathway influencing activity in the STN-GPi projection is the basis for decreased GPi discharge in dystonia.[9] In the present model, this would be seen as reduced activity in the inhibitory "surround" (Figure 2).

The fact that pallidotomy is an effective treatment for dystonia creates some problems for the hypothesis that decreased GPi discharge alone is the fundamental basis for dystonia. To account for this, it has been proposed that an abnormal temporal pattern of the GPi output could be the basis for dystonia.[7] However, abnormal temporal (bursting) patterns have been described in Parkinson disease, chorea/hemiballism, and dystonia,[3,7] and it is not clear whether there are critical differences in those patterns that explain the unique characteristics of the different movement disorders. The current hypothesis is that dystonia results from incomplete suppression of competing motor patterns due to insufficient surround inhibition of competing motor pattern generators[9] (Figure 2). This deficient surround inhibition may also lead to expansion of the facilitatory center, which would lead to "overflow" contraction of adjacent muscles. Decreased efficacy of the surround with or without expansion of the center causes inappropriate disinhibition of unwanted muscle activity.

TICS

Tics are stereotyped, repetitive movements that tend to change in type and anatomical location over long periods of time. The primary difference between tics and chorea is that tics are stereotyped, whereas choreatic movements tend to vary in location from movement to movement. Similarly, the difference between dystonic tics and the muscle contractions of dystonia is that dystonia tics tend to be highly stereotyped. A comprehensive scheme for understanding the pathophysiologic characteristics of involuntary movements must be able to account for the stereotyped, repetitive qualities of tics. Based on the known physiologic properties of basal ganglia neurons, it is most likely that specific movement patterns would result from activation of striatal neurons. Microstimulation of the putamen can evoke stereotyped movements, but microstimulation of the STN, GPi, or SNpr does not evoke movement. Thus, a stereotyped motor output can result from a focal population of striatal neurons becoming active. If they become abnormally active and cause unwanted inhibition of a group of GPi or SNpr output neurons, an unwanted motor pattern can be triggered. If a specific set of striatal neurons becomes overactive in discrete repeated episodes, the result would be a repeated, stereotyped, unwanted movement, ie, a tic. This scheme has been developed in detail elsewhere.[11] Unwanted activation of discrete sets of striatal neurons could
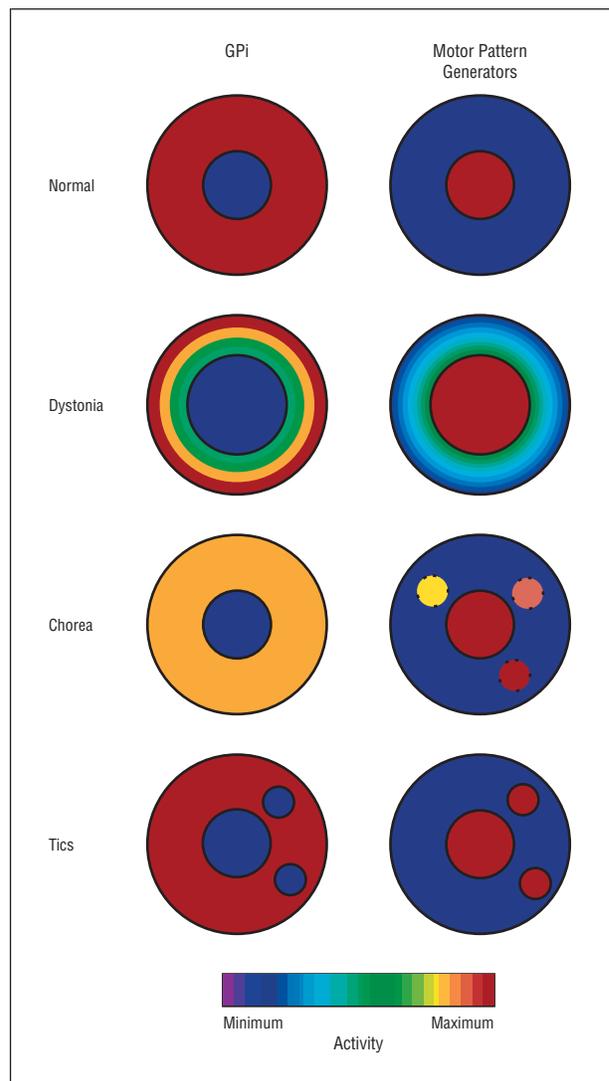

Figure 2. Schematic representation of globus pallidus pars interna (GPi) and motor pattern generator activity underlying involuntary movement disorders. The center of each annulus represents the desired motor pattern during voluntary movement. The surround represents potentially competing motor patterns. Foci within the surround represent areas of abnormal activity. The broken lines around the foci in the choreic condition indicate that the specific foci vary from movement to movement, while the solid lines in the tic condition indicate that these are repetitive, stereotyped patterns of activity. The color scale represents relative magnitude of activity.

result from many mechanisms, including excessive cortical or thalamic input to the striatum, deficiency of intrastriatal inhibition, abnormal dopamine transmission, or abnormal membrane excitability.

In the current model, tics would be caused by abnormal activity of striatal neurons, leading to multiple foci of inhibition in the GPi occurring at different times. Voluntary movement would be facilitated in a normal fashion but might be accompanied by unwanted facilitation of other motor patterns, resulting in tics accompanying the desired motor pattern. The foci of facilitation would be the same for relatively long periods (weeks to years), leading to a stable, stereotyped pattern of involuntary movements. By contrast, the foci of facilitation in chorea would change on a time scale of hundreds of milliseconds. The predictable nature of tics is due to the sta-

bility of the populations of striatal neurons that are abnormally active.

In summary, lesions or diseases that affect the basal ganglia cause movement disorders that can be understood as a failure to facilitate desired movements (eg, Parkinson disease), failure to inhibit unwanted movements (eg, chorea, dystonia, and tics), or both.[1,2,4] The involuntary movements of chorea, dystonia, and tics differ in important spatial and temporal characteristics that reflect important pathophysiologic differences. The hypotheses presented here provide a framework for understanding the fundamental anatomic and physiologic bases for these different movement disorders. These hypotheses are directly testable. With the development of better animal models of involuntary movements and with the increased knowledge obtained from neurophysiologic studies performed during neurosurgery for movement disorders, it is expected that data will be available in the near future to further advance our understanding of these disorders. The increasing use of pallidotomy and deep brain stimulation for the treatment of Parkinson disease and dystonia owes to the models of Albin et al[1] and DeLong.[2] It is hoped that improved models of involuntary movement disorders will similarly lead to improved therapeutics for these conditions.

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REFERENCES

1. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci.* 1989;12:366-375.
2. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* 1990;13:281-285.
3. Wichmann T, DeLong MR. Functional and pathophysiological models of the basal ganglia. *Curr Opin Neurobiol.* 1996;6:751-758.
4. Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. *Prog Neurobiol.* 1996;50:381-425.
5. Suarez JI, Metman LV, Reich SG, Dougherty PM, Hallett M, Lenz FA. Pallidotomy for hemiballismus: efficacy and characteristics of neuronal activity. *Ann Neurol.* 1997;42:807-811.
6. Lang AE, Lozano AM, Montgomery E, Duff J, Tasker R, Hutchinson W. Posteroventral medial pallidotomy in advanced Parkinson's disease. *N Engl J Med.* 1997; 337:1036-1042.
7. Vitek JL. Pathophysiology of dystonia: a neuronal model. *Mov Disord.* 2002;17: S49-S62.
8. Mink JW. Quantitative kinematic analysis of chorea. *Mov Disord.* 2002;17: S323.
9. Perlmutter JS, Tempel LW, Black KJ, Parkinson D, Todd RD. MPTP induces dystonia and parkinsonism: clues to the pathophysiology of dystonia. *Neurology.* 1997;49:1432-1438.
10. Berardelli A, Rothwell JC, Hallett M, Thompson PD, Manfredi M, Marsden CD. The pathophysiology of primary dystonia. *Brain.* 1998;121:1195-1212.
11. Mink JW. Basal ganglia dysfunction in Tourette's syndrome: a new hypothesis. *Pediatr Neurol.* 2001;25:190-198.