Movement Disorders
Vol. 1, No. 1, pp. 3–15, 1986

Review Article

Striatal Inhomogeneities and Basal Ganglia Function

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It has always been something of a mystery as to why different diseases of the basal ganglia may produce completely opposite effects on movement. Thus, defective dopaminergic inhibitory input into the striatum in Parkinson's disease causes an akinetic-rigid syndrome, while destruction of the striatum in Huntington's disease usually causes chorea. This theoretic paradox may be resolved by more detailed examination of the exact sites of striatal damage in the two opposing conditions (1).

C. D. Marsden

The complexity of the internal organization of the basal ganglia and its connections with other brain regions makes it difficult to understand the basal ganglia's role in controlling normal motor movement and the pathophysiology of motor disorders. Nevertheless, it is useful to attempt to find underlying principles of organization in the basal ganglia that can be used to make testable hypotheses about basal ganglia function. In the past several years, considerable new information has been learned about the neurochemical anatomy of the internal organization of the striatum and its projections. It is necessary to incorporate this new information in any new hypothesis about basal ganglia function.

Any coherent hypothesis concerning basal ganglia function must provide tentative explanations for a variety of abnormal movements. In general, the symptoms of basal ganglia disorders can be described as either hypokinetic or hyperkinetic. Parkinson's disease is the prototype hypokinetic syndrome, characterized by bradykinesia, rigidity, tremor, loss of postural reflexes, and occasionally, dystonia (1,2). Huntington's disease is the classic hyperkinetic syndrome, characterized by chorea, abnormal eye movements, slowed and irregular fine motor coordination, and in advanced cases, dystonia and rigidity (3,4). Other less common disorders, such as Wilson's disease, Hallervorden-Spatz disease, and dystonia musculorum deformans, have combinations of the various hypo- and hyperkinetic syndromes. All of these disorders result in striatal dysfunction and yet can manifest quite disparate abnormalities in movement. In this article we

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will first describe the anatomy of the basal ganglia and then attempt to describe the pathophysiology of the movement disorders within the framework of our current knowledge of basal ganglia anatomy and physiology.

CLASSIC ANATOMY

Details of the connections of the basal ganglia have been reviewed elsewhere (5–8). Briefly, the major input to the basal ganglia comes from the cerebral cortex, and the neurotransmitter of this pathway is probably glutamic acid (9–11). All areas of cortex send somatotopically organized excitatory projections to the neostriatum (the olfactory tubercle, the nucleus accumbens, the caudate nucleus, and the putamen). The neostriatum also receives inputs from the intralaminar nuclei of the thalamus, the substantia nigra pars compacta, the ventral tegmental area, and the raphe nuclei. The dorsal part of the caudate nucleus and the putamen appear to be the most important in the pathophysiology of movement disorders.

Internally, the neostriatum consists largely of medium- to small-sized neurons with spiny dendrites (medium spiny neurons), which use gamma-aminobutyric acid (GABA) as their neurotransmitter (12,13). Many of these neurons appear to use one or more of a number of peptide neurotransmitters as well as GABA (8). The relationship of these peptides to different classes of medium spiny neurons will be discussed below. The medium spiny neurons are projection neurons and have a large number of recurrent axon collaterals that are distributed primarily within the cell's dendritic field (14–16). In addition to the medium spiny neurons, there are also small numbers of large cholinergic interneurons (large aspiny neurons) (17) and small somatostatin/neuropeptide Y interneurons (small aspiny neurons) (18–20).

The neostriatal projection areas include the lateral globus pallidus (LGP), the medial globus pallidus (MGP), the substantia nigra pars reticulata (SNr), and the ventral pallidum (5,6,21). Abnormal functions of the LGP, MGP, and SNr appear to be important in the pathogenesis of the movement disorders (22). These areas receive most of the output from caudate and putamen. Most of the neurons in LGP, MGP, and SNr are large projection neurons, and interneurons are infrequent. All pallidal cells appear to use GABA as an inhibitory neurotransmitter and do not appear to contain other neurotransmitter peptides (22–24).

The LGP sends projections to the subthalamic nucleus (5,6), which also receives a direct excitatory (presumably glutamatergic) projection from the motor cortex (25). The subthalamic nucleus sends a reciprocal projection back to LGP and additional projections to the MGP and SNr (5,6). The MGP and SNr, in turn, send their major inhibitory GABAergic projections to the ventral tier nuclei of the thalamus (5,6). Both MGP and SNr send minor projections to the intralaminar thalamic nuclei and to the nucleus tegmenti pedunculopontis of the brainstem (5,6). The SNr's major projection goes to the "ventromedial" nucleus of thalamus, which in turn projects to the entire frontal lobe in rat (26). In primates, the projection goes to magnocellular portions of the ventral anterior and dorsal medial thalamic nuclei, which then project onto prefrontal cortex, with some projections going to premotor and supplementary motor cortex (27). The MPG sends its major projection to the pars oralis of the ventral lateral thalamic nucleus. Pars oralis in turn sends its projection to the supplementary motor cortex (28).

This thalamic projection is excitatory on cortical cells (29), and its neurotransmitter may be glutamate (30).

Additional projections of the SNr are to the superior colliculus, the reticular formation, the nucleus tegmenti pedunculopontis, and the substantia nigra pars compacta (5, 6). The projection to the superior colliculus is important to the generation of normal eye movements (31). Finally, the substantia nigra pars compacta (SNc) consists of the dopamine cells that degenerate in Parkinson's disease. These neurons send a dense dopaminergic projection to the entire neostriatum (32,33).

THE ORIGINAL HYPOTHESIS

Based on these anatomical data, we have previously proposed a model for the functional anatomy of the movement disorders (21). This hypothesis was based on the idea that normal motor behaviors or motor programs are reinforced via the basal ganglia by a cortico–striato–pallido–thalamo–cortical feedback loop. In conjunction with this reinforcing loop, there is a rich series of interconnections between striatal GABAergic neurons, which reciprocally inhibit each other and thereby inhibit inappropriate motor movements. Within this scheme, the reinforcing feedback loop depends on excitatory cortical input to striatum, and then two sequential GABAergic inhibitory connections from striatum to pallidum and from pallidum to thalamus, and then a final excitatory pathway from thalamus to cortex. Thus, when cortex is activated, there is disinhibition (34–36) of the thalamocortical pathway, which reinforces the ongoing motor behavior. We hypothesized that in Parkinson's disease, there was a loss of inhibitory dopaminergic input to striatum that resulted in excessive activation of the reinforcing feedback for any particular motor behavior and consequent inability to initiate new motor behaviors. In contrast, in Huntington's disease, the neuronal loss in the striatum itself would impair the reinforcing feedback loop and make it difficult to maintain a given motor behavior, while also impairing the inhibition of unwanted activities. This scheme was also consistent with the neuropharmacology of basal ganglia disorders (21).

This model, however, had a number of shortcomings. It led to the prediction that after striatal lesions, such as those seen in Huntington's disease, there should be an up-regulation of GABA receptors in all the striatal projection areas (LGP, MGP, and SNr), whereas in contrast, in Parkinson's disease, there should be down-regulation of GABA receptors in these same regions. Recent behavioral and neurochemical experiments have shown that this latter situation is not the case. In particular, after lesions of the nigrostriatal pathway, GABA receptors do appear to down-regulate locally in striatum and in LGP, but they up-regulate in MGP and SNr (37). Behavioral and metabolic experiments on the effects of nigrostriatal lesions also dissociate the effects of the lesions on the LGP from those on the MGP and SNr (38–40). Overall, dopamine appears to be inhibitory on striatal outputs to LGP, but excitatory onto output to MGP and SNr (37). This differentiation between striatal outputs must be incorporated into any consistent model of basal ganglia function.

A second difficulty with the model is that it leads to the prediction that Parkinsonian patients should move faster, rather than slower, than normal. Such a prediction would be inconsistent with our current knowledge of the disorder (1). Third, in experimental

animals, extensive striatal lesions do not elicit chorea in primates, cats, or rodents (41). Only lesions of the subthalamic nucleus can reliably cause choreiform movements in primates and humans (41). Recent anatomical evidence concerning the basal ganglia will allow the incorporation of these features into a modified model of basal ganglia function.

STRIATAL INHOMOGENEITIES

Our original hypothesis was based on the concept that the striatum was a homogeneous structure and that striatal output neurons sent axon collaterals to the LGP, MGP, and SNr. Thus, differences in the function of different striatal regions were explained by the differences in their afferent projections from the cortex. In the past 10 years, it has become increasingly obvious that the internal organization of the striatum is far from homogeneous (7).

In 1977, Mensah described islands of increased cell density within the caudate putamen (42). Apparently separate from the cell islands are inhomogeneities of acetylcholinesterase (AChE) staining, which have been demonstrated in fetal and adult striatum and are called "striosomes" or "patches" (43). During fetal mammalian development, there are regions of intense AChE staining, termed striosomes, and lighter surrounding areas, termed matrix. This pattern is reversed in the adult, where the striosome is less intensely stained for AChE than the matrix. Subsequently, dense areas of dopamine terminals were observed in developing striatum that were called "dopamine islands" (44,45). The dopamine islands become less distinct near birth as dopamine terminals innervate the matrix. Studies have also demonstrated that in the fetus, the densely AChE-staining striosomes coincide with the dopamine islands (7,45). Interestingly, the cells destined to be part of the striosomes are born simultaneously during development, as evidenced by ^{3}H-thymidine studies; the cells of the matrix are born later (46).

The connections of cells in the striosomes differ from those in the matrix. The cells in the striosomes receive inputs from the dopamine cells in the medial part of the SNc (47, 48). They project back primarily to the SNc, but not to the SNr (49,50). Other inputs to the striosomal neurons may come from medial frontal cortex, but not from lateral prefrontal, motor, or sensory cortex or from thalamus (51–55). The medial frontal cortical projection to the striosomes is from an area that also receives direct dopaminergic input from the ventral tegmental area (51). Striosomal neurons are primarily GABAergic, as are the matrix neurons, but the striosomes also have many neurons that stain intensively for substance P, dynorphin, and possibly, neurotensin (45,56,57). In adulthood, the striosomes contain high concentrations of mu-opiate receptors in rodents and high concentrations of enkephalin and low levels of AChE staining in carnivores (55, 58). The dendrites of the striosomal neurons appear to obey the boundaries of the striosomes and do not cross into the matrix (59).

The matrix neurons receive inputs from motor, sensory, supplementary motor, and association cortices, as well as from intralaminar nuclei of thalamus (7,52–55). The cells of the matrix also receive dopaminergic input from the dopamine cells in the SNc and ventral tegmental area (VTA) (47,48). The level of dopaminergic input is probably lower in the matrix than in the striosomes (60). The neurons of the matrix are for the most part GABAergic and have projections to SNr, MGP, and LGP (12,13,61). Cells

that project to one area are unlikely to project to the other areas, and so the matrix itself has substantial inhomogeneities (6,15,62).

An important feature of matrix inhomogeneity is the effect of dopamine on the neurons of the matrix. For many years, there has been controversy as to whether dopamine is excitatory or inhibitory onto striatal projections to LGP, MGP, and SNr (63). Some studies have suggested an excitatory effect and others an inhibitory effect, but few studies have measured the effects of dopamine on striatal projections to all these areas simultaneously. Those studies that have made these measurements actually suggest that the ultimate effect of dopamine on striatal output to MGP and SNr is excitatory, whereas dopamine's effects on striatal projections to LGP are inhibitory (37–40).

These differential effects of dopamine on striatal projections have important implications for basal ganglia disorders, as they suggest that the loss of dopamine cells in Parkinson's disease removes excitatory influences on cells projecting to MGP and SNr, thereby reducing the GABAergic striatal inhibition of MGP and SNr cells. In addition, the inhibitory effects of dopamine on striatal neurons projecting to LGP are lost, thereby increasing striatal GABAergic inhibition of LGP. In Huntington's disease, the loss of striatal neurons will result in some similarities to and some differences from Parkinson's disease. The similarity would be the reduced GABAergic inhibition of MGP and SNr neurons and the difference would be a loss of GABAergic striatal inhibition of LGP neurons. Clinically, Parkinson's disease patients differ from Huntington's disease patients in that the former manifest rigidity and tremor, whereas the latter have chorea. The two diseases are similar in that in both, the patients have bradykinesia and bradyphrenia.

Interestingly, recent studies have indicated that groups of neurons are selectively spared in the striatum of Hungtington's disease patients (64,65). It is possible that the selective sparing is due to the preferential vulnerability of one or the other group of striatal output neurons. In future studies, it will be important to define which output neurons die earliest in the disease.

Communication between striosomal neurons and matrix neurons has not been demonstrated directly, although the large cholinergic aspiny neurons of striatum do not appear to obey the borders of the striosome or matrix (C. J. Wilson, personal communication). Biochemically and behaviorally, however, dopamine appears to have inhibitory inputs on cholinergic neurons, which in turn appear to be excitatory on GABAergic striatal projection neurons (8,66,67). Because dopamine appears to inhibit cholinergic neurons, it is most likely that, functionally, cholinergic effects on striatal projections to LGP predominate. The existence of this possible interconnection could be determined experimentally, using studies combining immunohistochemical stains for acetylcholine neurons and retrograde tracing of striato-lateral pallidal cells.

An additional level of complexity to the striatal organization is provided by the presence of peptides within GABAergic striatal neurons. It now appears that a great many of the GABAergic medium spiny neurons also contain a peptide (either substance P, enkephalin, neurotensin, or dynorphin) (68–70). The somatostatin neurons (which also contain neuropeptide Y) appear to be interneurons that are largely confined to the matrix (50). The dynorphin and, possibly, neurotensin neurons appear to be largely located in the striosomes (56,57). The enkephalin neurons appear to be largely located in the matrix (6,56). The localization of substance P neurons is less certain, with some

studies suggesting they are largely in striosomes and others suggesting they are largely in matrix (56,58,69). There is less confusion about the distribution of the peptides in striatal efferent projections (6). The enkephalin neurons project largely to the LGP (71–73). The substance P neurons project largely to the MGP and SNr (73,74), whereas the dynorphin neurons project largely to the SNr (75,76). The neurotensin neurons may project to SNc (77). The significance of the neuropeptides in the various striatal projection neurons is currently unknown, but presumably they could function either as modifiers of GABA's effects, as trophic factors, or as neuromodulators in their own right.

In our initial hypothesis, we predicted that the cells of the subthalamic nucleus would be inhibitory on cells of the medial globus pallidus. Recent evidence suggests that the cells of the subthalamic nucleus are excitatory and that they may drive the cells of the medial globus pallidus and substantia nigra pars reticulata (78). They may even use glutamic acid as a neurotransmitter (A. J. Beitz, personal communication).

REVISED HYPOTHESIS

The recent biochemical, anatomical, and electrophysiological studies concerning the inhomogeneities of the striatal system provide a new framework in which to interpret the pathophysiology of movement disorders. In the new scheme (Fig. 1), motor behaviors would still be maintained under normal conditions by a reinforcing feedback loop from cortex through basal ganglia to thalamus and back to cortex, as previously hypothesized (21). The input from motor cortex would synapse on matrix neurons which project to MGP and/or to SNr, and these striatal cells in turn would be inhibitory on the MGP and SNr cells projecting to the thalamus. These latter projections would be inhibitory onto thalamocortical neurons. Additional cortical inputs would excite the striatal matrix neurons which project to and inhibit LGP. The cortical inputs to these matrix neurons would be those important in regulating the suppression of unwanted motor behaviors, whereas the cortical inputs to neurons projecting to MGP and SNr would be involved in promoting a particular motor behavior (Fig. 2). The inhibition of LGP would result in disinhibition of subthalamic nucleus, which would in turn drive or excite those MGP and SNr neurons that would suppress unwanted movements. In addition to these rather simple feedback loops, rich axonal collaterals between striatal neurons would provide communication between striatal neurons for more sophisticated refinement of acquired motor programs.

According to this scheme, the primary feedback loop reinforcing a particular motor behavior would be impaired in both Parkinson's and Huntington's diseases. In Parkinson's disease, there would be a loss of excitatory dopaminergic input to striatal cells projecting to MGP and SNr. In Huntington's disease, the striatal neurons themselves would be damaged, thus interrupting the circuit. The result of this damage in both cases would be a slowness and poverty of movement. The distinguishing feature between Parkinson's disease and Huntington's disease would rest in alteration of the striatal projections to LGP. In Parkinson's disease, inhibitory dopaminergic input to striatal neurons projecting to LGP would be lost. Thus, there would be decreased activity (i.e., increased inhibition) of LGP neurons, which would result in disinhibition of subthalamic nucleus input to MGP and SNr, reinforcing inhibition of unwanted movements. If this suppression is excessive, then it would be difficult to switch to new behaviors in

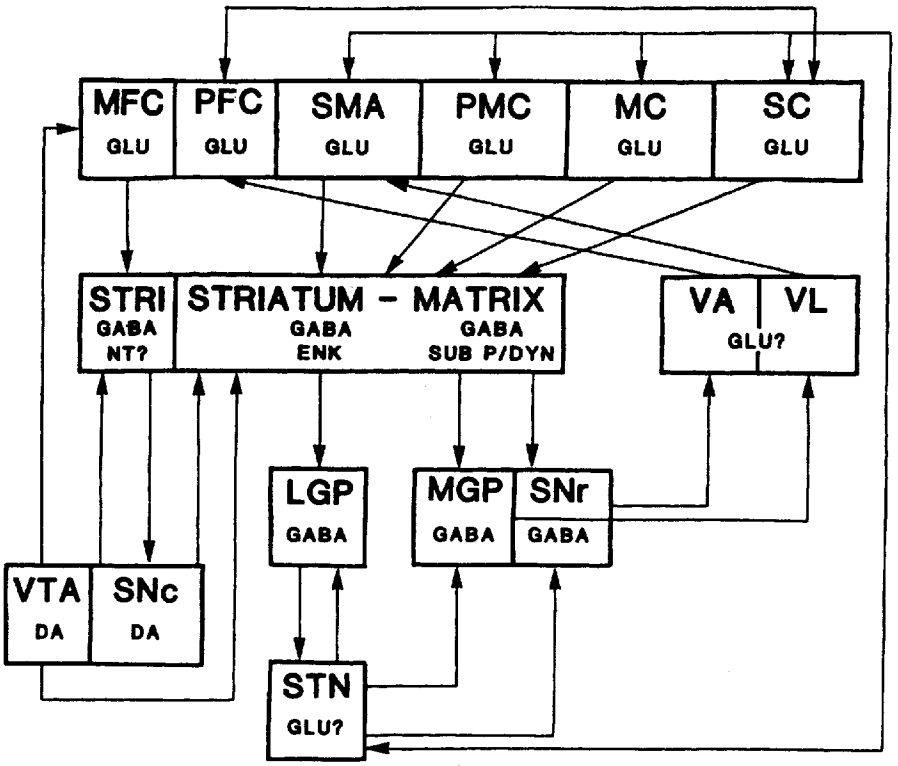

FIG. 1. Schematic diagram of the connections of the basal ganglia. Connections are indicated by the arrows. In large letters are the brain regions areas and in smaller letters are the putative neurotransmitters of the pathways. Abbreviations: MFC, medial prefrontal cortex; PFC, prefrontal cortex; SMA, supplementary motor area; PMC, premotor cortex; MC, motor cortex; SC, sensory and parietal cortex; STRI, striosomes in striatum; VL, ventral lateral thalamus; VA, ventral anterior thalamus; LGP, lateral globus pallidus; MGP, medial globus pallidus; SNr, substantia nigra pars reticulata; VTA, ventral tegmental area; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; GLU, glutamic acid or glutamate-like substance; GABA, gamma-aminobutyric acid; NT, neurotensin; ENK, leucine-enkephalin; SUB P, substance P; DYN, dynorphin; DA, dopamine.

the context of additional difficulty in maintaining the ongoing behavior. Thus, the parkinsonian patient would have slowness and poverty of movement and difficulty switching to new motor programs. The gradual decrescendo pattern seen in parkinsonians' attempts to maintain motor behaviors (1,79) may be the result of excess negative input to the striatal cells that project to MGP and SNr from collaterals of the overactive striatal cells that project to LGP.

In Huntington's disease, we would hypothesize that there is first a loss of matrix neurons projecting to LGP. This loss would result in disinhibition of the LGP and subsequent excessive inhibition of subthalamic nucleus. As the subthalamic nucleus would normally drive the MGP and SNr cells that suppress abnormal movements, this suppression would now be impaired and unwanted movements would be expressed randomly. Excess inhibition of subthalamic nucleus in Hungtington's disease would provide a tentative explanation for the failure of investigators to produce involuntary

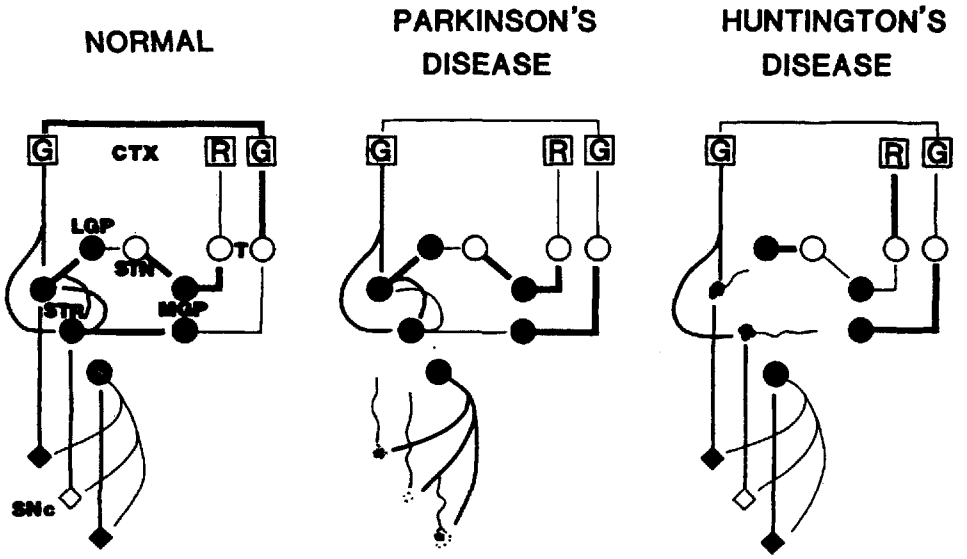

FIG. 2. Schematic diagram of reinforcing and suppressing feedback loops for motor programs in normal individuals, Parkinson's disease patients and Huntington's disease patients. The loops are drawn for a hypothetical "motor program" for grasp (G). While maintaining a grasp, release (R) programs would normally be suppressed (or not reinforced). The open neurons are excitatory, and the closed ones are inhibitory. Under normal circumstances, when the grasp movement is initiated and sustained, the pathway from cortex through striatum (STR), medial globus pallidus (MGP), and thalamus (T) is reinforced for grasp. (The thickness of the lines indicates relative activity in the various pathways.) The pathway for suppression of unwanted movements goes through STR, lateral globus pallidus (LGP), subthalamic nucleus (STN), MGP, and T back to cortex. In Parkinson's disease both excitatory dopamine input from substantia nigra pars compacta (SNc) to the reinforcing loop is lost (resulting in impaired reinforcement of grasp) as well as inhibitory input to the suppressing loop (enhancing the suppression of unwanted movements). In Huntington's disease, striatal neurons degenerate (with relative sparing of striosomal neurons—closed circle with white S), and the reinforcing loop is impaired, as is the suppressing loop. This latter situation leads to poor maintenance of the ongoing grasp and relative excitation or disinhibition of unwanted movements (release).

movements with striatal lesions in animals (41), as it would require a selective lesion of those cells projecting to LGP. The loss of subthalamic activity in Huntington's disease would result in a decreased ability to suppress unwanted movements in the face of difficulty in maintaining ongoing movements. Thus, patients would have slowness of voluntary movement and chorea. Later in the disease, striosomal neurons would also become damaged, and at this point, symptoms of rigidity and dystonia may appear. This scheme could be tested by examination of early Huntington's cases in which a subset of matrix neurons projecting to lateral globus pallidus would predictably be affected first. There is some evidence for this hypothesis from the prominent enkephalin loss in Huntington's disease while neurotensin is preserved (80,81). Furthermore, younger patients with Hungtinton's disease have more prominent parkinsonian symptoms (I. Shoulson, personal communication), and pathologically, these early patients have more severe neuronal loss (82).

This interpretation of basal ganglia circuitry would provide a tentative explanation for the physiologic chorea seen in newborn infants (83). At approximately 2–6 months postnatally, human infants display choreic movements. Striosomal neurons make their connections before matrix neurons (84). We have observed intense patches of AChE staining in a 6-week-old human brain (unpublished observations), which were similar to those seen in prenatal cats before the matrix develops (45). Between 2 and 6 months postnatally, therefore, there may be a paucity of neurons that would mediate both the maintenance of motor behavior and suppression of unwanted movements. The late development of these matrix neuron connections may be part of the reason why the movement disorders seen often after perinatal asphyxia are delayed in onset. The movement disorders associated with perinatal asphyxia may be characterized by a mix of abnormalities, such as chorea, dystonia, rigidity, or spasticity. Perhaps each particular movement disorder depends on the developmental stage of the striatal neuronal subtypes at the time of injury. Such a possibility can be tested experimentally by analyzing whether or not specific populations of matrix neurons have degenerated in cases of neonatal asphyxia.

IMPLICATIONS FOR NEUROPHARMACOLOGY

The neuropharmacology of movement disorders still fits very consistently into the new scheme. In Parkinson's disease, dopaminergic input is lost and must be replaced with either precursers for dopamine or dopamine agonists. As dopamine has inhibitory effects on excitatory cholinergic interneurons within striatum (85,86), anticholinergic medications would also be expected to be helpful (87). Within the model, the cholinergic interneurons would be predicted to influence primarily those striatal neurons that project to LGP and not those projecting to MGP and SNr. At the current time, information concerning the cholinergic connections is still rudimentary, and the connections between the striosomal and matrix neurons are still unknown.

Although it is still under investigation, dopamine receptors on striosomes and certain subsets of matrix neurons may differ from those on other matrix neurons. D_1 receptors may be localized to specific sets of striatal neurons, and excitation of these receptors may result in different pharmacologic effects than activation of D_2 receptors. Preliminary evidence in rat striatum would suggest that D_1 receptors are localized preferentially on striosomal neurons (88). Future studies of the differential effects of D_1 and D_2 agonists and antagonists on movement disorders will help to refute or substantiate these possibilities.

GABAergic manipulations in both Huntington's and Parkinson's diseases have been disappointing (89,90). The lack of effectiveness of these drugs may be due to the importance of spatial and temporal sequencing of signals between the GABAergic neurons during the regulation of normal motor movements. It is unlikely that replacement therapy would be helpful in alleviating abnormalities in such complex circuitry. The interesting clinical observation that opiate agonists suppress akathesia (91) would predict that this neuroleptic-induced side effect is mediated by striatal projections to LGP, as these neurons contain GABA and enkephalins.

CONCLUSIONS

Although this revised model of the functional anatomy of basal ganglia disorders is likely to be refuted with time, it provides a framework in which to test specific predictions of basal ganglia function. With new techniques for looking at human brain function and pharmacology *in vivo* it may be possible to test some predictions directly. Also, more intense and sophisticated analyses of postmortem material from various basal ganglia disorders would be helpful in defining the selective vulnerability of specific striatal subsets of neurons. The future will undoubtedly provide interesting new twists and complexities to incorporate into our understanding of the pathophysiology of movement disorders.

Acknowledgment: This hypothesis was developed after useful discussions with Ann Graybiel, Charles Wilson, Patricia Goldman-Rakic, and Ira Shoulson. We thank Jan Pappas for secretarial assistance. This work was supported by the Hereditary Disease Foundation, the Huntington's Disease Foundation of America, and USPHS Grants NS 15655 and NS 19613.

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