Primate models of movement disorders of basal ganglia origin

Mahlon R. DeLong

Movement disorders associated with basal ganglia dysfunction comprise a spectrum of abnormalities that range from the hypokinetic disorders (of which Parkinson’s disease is the best-known example) at one extreme to the hyperkinetic disorders (exemplified by Huntington’s disease and hemiballismus) at the other. Both extremes of this movement disorder spectrum can be accounted for by postulating specific disturbances within the basal ganglia-thalamocortical ‘motor’ circuit. In this paper, Mahlon DeLong describes the changes in neuronal activity in the motor circuit in animal models of hypo- and hyperkinetic disorders.

Hypokinetic disorders are characterized by significant impairments in movement initiation (akinesia) and reductions in the amplitude and velocity of voluntary movements (bradykinesia). Hypokinetic disorders are usually accompanied by muscular rigidity and tremor at rest. By contrast, hyperkinetic disorders are characterized by excessive motor activity in the form of involuntary movements (dyskinesias) and varying degrees of hypotonia. In recent years, the development of primate models of these disorders (induced by systemic or local administration of selective neurotransmitters) has made it possible to clarify some of the pathophysiological mechanisms underlying such diverse symptoms as akinesia in hypokinetic parkinsonism and the involuntary, hyperkinetic movements of hemiballismus and other dyskinesias. This range of movement disorders can be explained using a functional model of the basal ganglia–thalamocortical ‘motor’ circuit that incorporates current data from a variety of experimental fields.1-3

Functional model of the ‘motor’ circuit

The main organizational features and postulated mode of operation of the motor circuit are presented elsewhere in this issue (see article by G. E. Alexander and M. D. Crutcher). In brief, this circuit, like other basal ganglia–thalamocortical circuits, represents a re-entrant pathway through which influences emanating from specific areas of cortex are returned to certain of those same areas after intermediated processing within the basal ganglia and thalamus. The ‘closed’ portion of the motor circuit comprises (1) several precentral motor areas including the supplementary motor area (SMA) and parts of the motor and premotor cortex, (2) the putamen, which is part of the striatum or ‘input’ stage of the basal ganglia and receives projections from the precentral motor areas, (3) the ‘motor’ portion of the internal segment of the globus pallidus (GPI) and substantia nigra pars reticulata (SNr), both of which receive projections from the putamen and are considered output nuclei of the basal ganglia, (4) portions of the external segment of the globus pallidus (GPi) and the subthalamic nucleus (STN), and (5) parts of the ventral intermediate thalamus that receives projections from the motor portions of GIF and SNr and in turn project back to specific portions of the precentral motor fields.4

Within the circuit are two projection systems that arise from separate subpopulations of putamen neurons and terminate within GIF and SNr (for reviews, see Refs 1,2,5). The ‘direct’ pathway arises from putamen neurons that contain both GABA and substance P and projects directly to the motor portions of GIF and SNr. The ‘indirect’ pathway, on the other hand, arises from putamen neurons that contain both GABA and enkephalin and whose influences are conveyed to the basal ganglia output nuclei only indirectly, through a sequence of connections involving GIF and the STN.

From the polarity of the sequential connections, it would appear that under normal conditions the direct pathway effectively provides positive feedback to the precentral motor fields, from which much of the movement-related activity within the circuit is thought to arise (see Fig. 3 of G. E. Alexander and M. D. Crutcher, this issue). In contrast, activity conducted along the indirect pathway appears to provide negative feedback to the precentral motor fields.

There is now considerable evidence indicating that shifts in the balance between activity in the direct and indirect pathways and the resulting alterations in GABA/SNR output may account for the hypo- and hyperkinetic features of basal ganglia disorders. Thus, in general, it appears that enhanced conduction through the indirect pathway leads to hypokinesia (by increasing pallidodisincoupling inhibition), whereas reduced conduction through the direct pathway results in hyperkinesia (by reduction of pallidothalamocortical inhibition).1-3

Hypokinetic disorders: experimental parkinsonism

There have been numerous approaches to the production of a suitable primate model of Parkinson’s disease, but parkinsonism induced by MPTP represents the first model with features that closely resemble the clinical, pathological and biochemical characteristics of the human disorder.4-6 MPTP is converted in the brain to the toxin MPP+ by the enzyme monoamine oxidase. MPP+ is then selectively taken up into nigrostriatal neurones, where MPP+ destroys nigral neurones in still uncertain, but evidence suggests that interference with mitochondrial oxidation and redox reactions. Animals treated with MPTP develop signs virtually identical to those in humans with Parkinson’s disease, including akinesia, bradykinesia, flexed posture, muscular rigidity, and postural tremor. Not all primate species develop the tremor characteristic of idiopathic Parkinson’s disease, but one species, the African green monkey, does exhibit typical resting tremor in a high percentage of cases. MPTP-treated animals exhibit the pathological hallmark of Parkinson’s disease, i.e. loss of melanin-containing neurones of the pars compacta of the substantia nigra (SNc) and resulting loss of dopamine in the striatum and the substantia nigra itself. Some degree of neural cell loss has also been reported in the locus coeruleus and the raphe, as is
the case is idiopathic Parkinson’s disease. Studies of neuronal activity in MPTP-treated animals have been directed primarily at the globus pallidus since the major output from the basal ganglia portions of the motor circuit arises from GP. In MPTP-treated monkeys, altered tonic neuronal activity has been observed in both pallidal segments and in the STN. A major finding of these studies was a significant increase in tonic neuronal discharge in GP and STN neurons after MPTP treatment. In GP, by contrast, the mean tonic discharge rate is significantly decreased. These changes in tonic discharge are consistent with the reported changes in metabolic activity studied shortly following MPTP treatment. However, they differ somewhat from those reported in animals studied several weeks following treatment. Such differences may reflect various influences, including possible acute effects of MPTP itself, damage to terminals and cell bodies and changes in receptors. It should be emphasized that the regional metabolic activity reflects summed synaptic activity of both afferents and local axon collaterals, and therefore, may not be well correlated with local neuronal activity. Such discrepancies underscore the need for direct physiological measures of cellular activity.

In addition to increases in tonic discharge, there is evidence of enhanced phasic responses to proprioceptive stimuli and voluntary movement in GP neurons. The responses of GP neurons to passive manipulations of the extremities are increased in MPTP-treated animals. Responses to passive displacement of the limb are also detectable in a large percentage of pallidal neurons from normal and less specific, with loss of directional effects and responses from multiple joints. Although phasic activity during active movement or in more complex tasks has not yet been studied in detail, in preliminary studies an increase has been seen in GP neurons during these tasks (Miller, C. D., and DeLong, M. R.; unpublished observations). Together, these data suggest that there is increased tonic output from the basal ganglia (GP) to animals rendered parkinsonian with MPTP, and that phasic signals associated with proprioceptive feedback and active movement are increased in magnitude and decreased in selectivity. By enhancing transmission through the direct pathway and suppressing transmission through the indirect pathway, the dopaminergic nigrostriatal inputs to the motor circuit seem to have the net effect of augmenting positive feedback to the precentral motor fields, thereby facilitating cortically initiated movements.

The MPTP-induced changes in neuronal activity observed in GP, GPi, and the STN are consistent with the evidence indicating that a loss of striatal dopamine results in an increase in transmission through the indirect pathway and a reduction in transmission through the direct pathway. The overall effect of such inducements would be to increase the output from GPi/SNr, leading to excessive tonic and phasic inhibition of thalamocortical neurons as indicated in Fig. 1.

The changes in basal ganglia output observed in experimental parkinsonism could produce the observed behavioral disturbances by any of several mechanisms. For example, increased tonic output from GPi, by reducing the tonic activity of thalamocortical neurons, might lessen the responsiveness of those prefrontal motor fields that are engaged by the motor circuit. In addition, the increased gain and decreased selectivity within the basal ganglia circuits would be expected to disturb the normal processing of phasic signals associated with proprioceptive inputs and voluntary movement within the basal ganglia.

Bradykinesia

In normal individuals, rapid limb movements are performed with a triphasic pattern of muscle activity involving an initial agonist burst, an antagonist burst, and a second agonist burst. As movement amplitude is increased, movement velocity is also increased. The increase in movement velocity is produced by...
Akinnesia

The term 'akinnesia' is used in a variety of ways by different authors. It may be taken to encompass the multiple movement abnormalities seen in parkinsonism, including difficulty initiating movements, difficulty performing simultaneous and repeated motor acts and even slowing of movement (i.e. bradykinesia). In its

![Diagram of motor circuit](attachment:image.png)

Fig. 2. Schematic representation of the 'motor' circuit in hyperkinetic disorders. Reduced excitatory projections from the STN to GPi, due either to STN lesions (as in hemiballismus) or reduced striatothalamic inhibitory influences along the indirect pathway (as in Huntington's disease and L-DOPA-induced dyskinesia), lead to reduced inhibitory outflow from GPi/SNr and increased discharge of the thalamus. The overall effect is that of excessive positive feedback to the precentral motor fields engaged by the motor circuit (SMA, PMC, MC), which results in hyperkinetic movements. Abbreviations: CM, centromedian nucleus; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; MC, primary motor cortex; PMC, premotor cortex; SARA, supplementary motor area; SNV, substantia nigra pars reticulata; STN, subthalamic nucleus; VPe, nucleus ventralis anterior pars magnocellularis; VAp, nucleus ventralis anterior pars parvocellularis; VLo, nucleus ventralis lateralis pars oralis.


283
simplest form, however, 'akinseia' refers to a relative paucity of volitional movement, due to an impairment of movement initiation.

The pathophysiological basis of akinseia remains uncertain. Although classically attributed to loss of nigrostriatal dopamine neurons with resultant dys- function in striatogigantid mechanisms, it has also been proposed that akinseia might be related to damage that occurs outside the dopaminergic neurons of the SNc, perhaps in the dopaminergic neurons of the ventral tegmental area, which project to the nucleus accumbens and frontal cortex (see Ref. 30 for review). However, the MPTP model of parkinsonism suggests that akinseia may be produced by damage limited to the SNc and the nigrostriatal dopamine system.27,28 In these animals, akinseia appears to be a relatively dramatic and early feature following admin- istration of the neurotoxin. Although large doses of MPTP have been shown to produce damage outside the SNc,18,30 smaller doses with damage apparently limited to the SNc appear sufficient for the production of akinseia. Thus, it must be considered that akinseia may be produced by dopamine depletion limited to the neostriatum. In human Parkinson's disease and in the primate MPTP model of parkinsonism, a large per- centage of the nigrostriatal dopaminergic projection, especially that innervating the putamen, is lost.25 It is thus possible that akinseia results from selective depletion of dopamine in the motor circuit at the striatal (putamen) level. Akinseia might result simply from increased tonic inhibition of thalamocortical neurons that renders the cortical projection areas less responsive to other inputs normally involved in initiating movements. A secondary factor may be the lowered gain in the direct pathway of dopaminergic- depleted animals, which would lead to decreased phasic disinhibition of thalamocortical neurons during attempted movements. It is conceivable, therefore, that akinseia may represent an extreme form of tardy akinsetesia. Another possibility is that some aspects of akinseia might result from a disturbance of 'set' functions, which appear to be highly dependent upon the integrity of basal ganglia pathways (see G. E. Alexander and M. D. Crutcher, this issue).

Hyperkinetic disorders: experimental hemibalismus

Apart from parkinsonism, the basal ganglia disorder for which the neuropathological substratum has seemed least doubt, is hemibalismus. In humans, vascular lesions restricted to the STN frequently result in involuntary, often violent movements of the contralateral limbs (termed 'hemibalismus' because of the superficial resemblance of the movements to throwing motions). This disorder provides one of the clearest correlations in clinical neurology between localized pathological change and movement abnor- mality. In addition to the proximal ballistic move- ments, these involuntary movements may take the form of more distal, irregular (chorea), or more continuous writhing (athetoid) movements. Hemibalismus has been produced in monkeys by experi- mental lesions of the STN.26 This primate model has provided new insights into the pathophysiology of the hyperkinetic disorders.

Recently, hemibalismus was generally thought to result from a 'release' of GPs from an inhibitory control from the STN. However, recent evidence indicates that the projections from STN to GP$ are actually excitatory, and probably glutamatergic.27 Moreover, monkeys with hemibalismus secondary to inactivation of the STN show decreased metabolic activity both in GPs and in the ventrolateral thalamus, suggesting that GP$ output may be reduced in this disorder.14 The effect of STN lesions (produced by the axon-sparing neurotoxin ibotenate) on GP$ activity was recently studied directly in the monkey19 and indeed, a significant reduction of GPs tonic discharge was found. A decrease in the phasic responses of GPs to limb displacement was also found. Together, these findings suggest that hemibalismus results from a disinhibition of the thalamus due to a reduction of tonic (and perhaps phasic) inhibitory output from GPs. Conceivably, thalamocortical neurons under such conditions might become increas- ingly responsive to cortical inputs or exhibit an increased tendency to discharge spontaneously, thus leading to involuntary movements.

It should be mentioned that there is now evidence of a common mechanism underlying both the chore- form movements of Huntington's disease and the dyskinetic movements that are seen in hemibalismus. It has been shown that early in the course of Huntington's disease there is a selective loss of the striatal GABA$ergic neurons that give rise to the indirect pathway.14 The consequent loss of inhibition of GPs neurons would be expected to lead to excessive inhibition of STN neurons, and this func- tional inactivation of the STN could thus explain the choreiform motor disturbances in Huntington's disease that resemble those seen in hemibalismus (Fig. 2). Most recently, these workers have found that the rigid akinetic signs in advanced Huntington's disease are associated with evidence of additional loss of GABA$ substance P-containing striatal neurons projecting to GP$21. This would lead to increased discharge of the partially deafferented GP$SN neurons, by removal of inhibition. The phenomenon of 6-OHDA-induced dyskinesia (which occur during periods of dopamine excess associated with the pharmacological treatment of Parkinson's disease) can be explained on a similar basis. That is, excessive dopaminergic inhibition of the striatal GABAergic neurons would lead to reduced excitatory input to GP$SN via the indirect pathway, and this effect could be compounded by excessive dopaminergic stimulation of the striatal GABA substance P neurons that send inhibitory projections to GP$SN via the direct pathway.

Effects of STN lesions in parkinsonian animals

According to the proposed functional model of the motor circuit, the motor disturbances of Parkinson's disease are postulated to result in large part from increased thalamic inhibition due to excessive excit- atory drive from the STN to the output nuclei of the basal ganglia (GP$SN). It is predicted, therefore, that a lesion or inactivation of the STN in parkinsonian subjects would ameliorate some of the motor impair- ments. This has been tested recently by selective lesioning of the STN with the fiber-sparing neurotoxin ibotenate in MPTP-treated monkeys (Bergman, R. Wichmann, T. and DeLong, M. R., unpublished observations). Such lesions produced an immediate...