Primate models of movement disorders of basal ganglia origin

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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.*

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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 neurotoxins) has made it possible to clarify some of the pathophysiological mechanisms underlying such diverse symptomatology as the hypokinesia of 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 intermediate processing within the basal ganglia and thalamus[4]. 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' portions 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 (GPe) and the subthalamic nucleus (STN), and (5) parts of the ventrolateral thalamus that receive projections from the motor portions of GPi and SNr and in turn project back to specific portions of the precentral motor fields[2].

Within the circuit are two projection systems that arise from separate subpopulations of putamen neurons and terminate within GPi and SNr (for reviews, see Refs 1,2,5). The 'direct' pathway arises from putamen neurons that contain both GABA and substance P and project directly to the motor portions of GPi 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 GPe 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 GPi/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 pallidothalamic inhibition), whereas reduced conduction through the direct pathway results in hyperkinesia (by reduction of pallidothalamic 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[6–8]. MPTP is converted in the brain to the toxin MPP+ by the enzyme monoamine oxidase. MPP+ is then selectively taken up into nigrostriatal neurons. How MPP+ destroys nigral neurons is still uncertain, but evidence exists for interference with mitochondrial oxidation and redox reactions[9]. 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 neurons 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 neuronal cell loss has also been reported in the locus coeruleus and the raphe, as is

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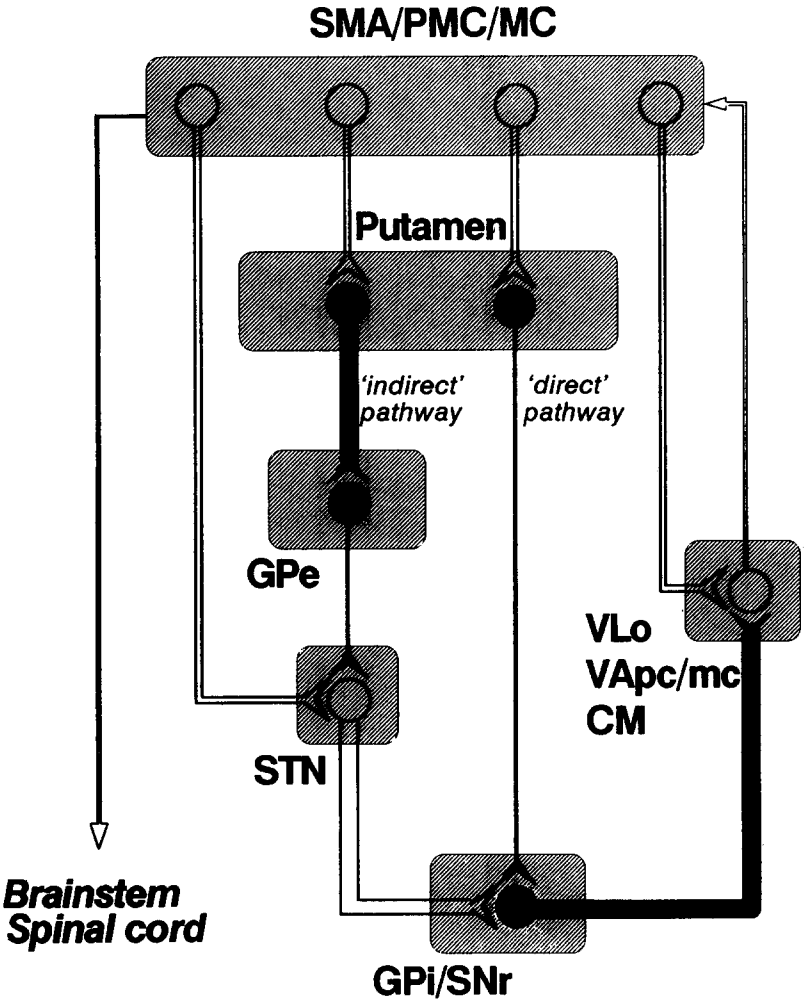

Fig. 1. *Schematic representation of neuronal activity in the 'motor' circuit in hypokinetic disorders. Excessive inhibition of GPe within the indirect pathway leads to disinhibition of the STN, which in turn provides excessive excitatory drive to the basal ganglia output nuclei (GPi/SNr), thus leading to excessive thalamic inhibition. This is reinforced by reduced inhibitory input to GPi/SNr through the direct pathway. Overall, these effects are postulated to result in a reduction in the usual reinforcing influence of the motor circuit upon cortically initiated movements. In this figure and in Fig. 2, inhibitory neurons are represented by filled symbols and excitatory neurons by open symbols. Both figures should be compared with Fig. 3 in the article by G. E. Alexander and M. D. Crutcher, this issue, which represents the operation of the motor circuit under normal conditions. 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; SMA, supplementary motor area; SNr, substantia nigra pars reticulata: STN, subthalamic nucleus; VAmc, nucleus ventralis anterior pars magnocellularis; VApc, nucleus ventralis anterior pars parvocellularis; VLo, nucleus ventralis lateralis pars oralis.*

the case in idiopathic Parkinson's disease[10,11].

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 GPi. In MPTP-treated monkeys, altered tonic neuronal activity has been observed in both pallidal segments and in the STN[12,13]. A major finding of these studies was a significant increase in tonic neuronal discharge in GPi and STN neurons after MPTP treatment. In GPe, 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 (days) following MPTP treatment[14–16]. However, they differ somewhat from those reported in animals studied several weeks following treatment[17,18]. 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 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 GPi neurons[19,20]. 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 larger percentage of pallidal neurons than normal and are 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, W. C. and DeLong, M. R., unpublished observations). Together, these data suggest that there is increased tonic output from the basal ganglia (GPi) in 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 GPe, 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 imbalances 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, the increased tonic output from GPi, by reducing the tonic activity of thalamocortical neurons, might lessen the responsiveness of those precentral 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[21]. As movement amplitude is increased, movement velocity is also increased. The increase in movement velocity is produced by

generating a greater initial agonist burst. In parkinsonian subjects, the normal amplitude–velocity relation is disturbed and the large-amplitude movements are performed at abnormally low velocities[22]. The abnormal velocities are due to a failure to generate adequate initial agonist bursts[23]. The resultant overall movement is therefore discontinuous, with several segmented, small-amplitude movements apparent in the velocity tracing.

Recent studies[24] have shown that while the magnitude of the first agonist burst shows scaling in parkinsonian subjects, the range over which the scaling occurs is diminished. It should be noted as well that bradykinesia may also result from additional difficulties resulting from attempts to perform more complex simultaneous and sequential motor acts[25–29]. In normal individuals, the simultaneous or sequential performance of two simple motor acts does not significantly affect the movement time of each act. In parkinsonian subjects, however, movement times are prolonged to a greater extent when simple movements are performed sequentially or simultaneously than when performed alone. In sequential movements, the deficit arises from both a prolongation of the individual movement times and an abnormal delay between the movements.

Altered activity in the basal ganglia motor circuit in parkinsonian subjects could result in bradykinesia by several mechanisms. First, there may be relatively less grading of phasic neuronal responses during attempted movements of different amplitudes, which would diminish the range of velocities permitted by the basal ganglia output. Increased tonic inhibition of thalamic neurons by excessive output from GPi could simply reduce the overall responsiveness of cortical mechanisms through a reduction of thalamocortical activation. Also, with an excessively high level of tonic discharge in GPi neurons, it is possible that the superimposed phasic reductions in GPi activity that occur during movement execution would not be transmitted faithfully to the cortex, thereby resulting in a reduced range of neuronal amplitude changes and scaling of movement.

It is also conceivable that the linearly graded neuronal responses observed in normal animals during limb movement are not directly related to the scaling of movement amplitude and velocity. If, instead, the basal ganglia were involved in a monitoring or comparator function (whereby motor commands are compared with proprioceptive feedback), such neuronal responses could reflect the feed-forward of motor commands from the motor cortex and SMA. Abnormally large phasic output from the motor circuit during movement in the parkinsonian condition might lead to misinterpretation of the command by the cortex and thus to reduced output to the agonist musculature[30]. This type of feed-forward system would be particularly important in movements performed without visual feedback, the types of movements most impaired in parkinsonian subjects. Another possibility is that increased gain in the feedback from proprioceptors might signal apparent excessive movement or velocity, leading to a slowing or premature arrest of ongoing movements.

In general, the available data from studies in normal and MPTP-treated animals are consistent with the view that voluntary movements are normally associated with a graded phasic reduction of thalamic inhibition mediated by the direct pathway. Bradykinesia may be due to increased levels of inhibition in the thalamic targets of basal ganglia output, resulting from excessive tonic and phasic activity in the indirect pathway and consequent increased negative feedback conveyed to the precentral motor areas. In addition, reduced activity in the direct pathway would result in decreased positive feedback and thereby contribute to the bradykinesia.

Akinesia

The term 'akinesia' 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

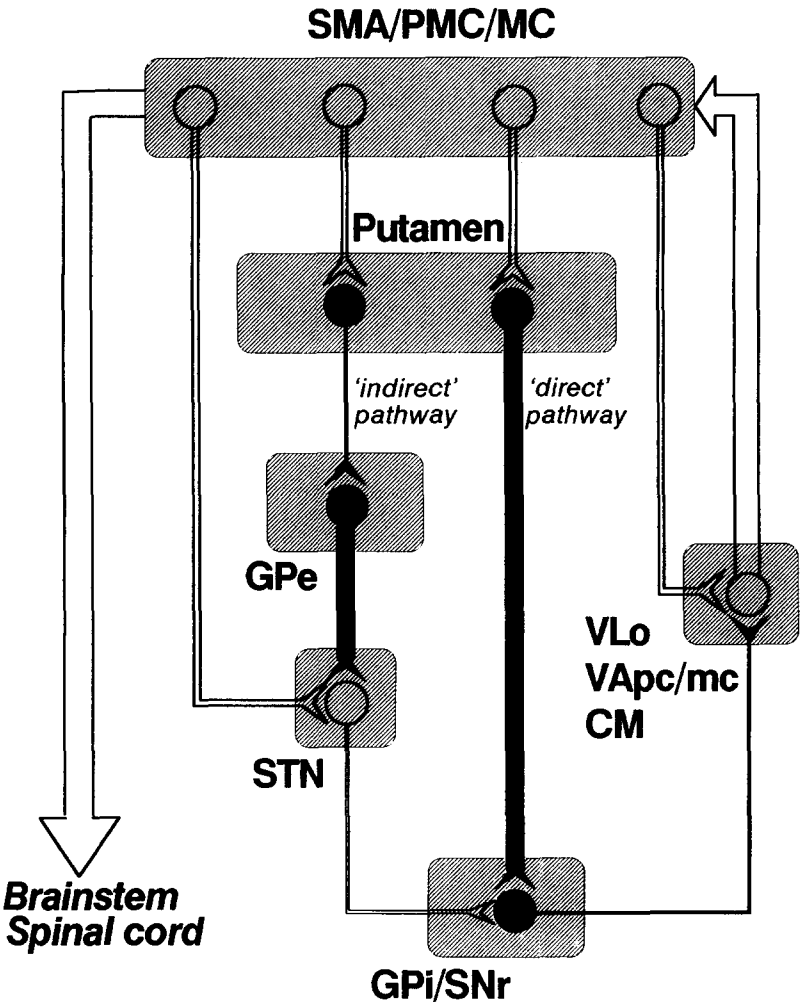

Fig. 2. *Schematic representation of the 'motor' circuit in hyperkinetic disorders. Reduced excitatory projections from the STN to GPi, due either to STN lesions (as in hemiballismus) or reduced striatopallidal inhibitory influences along the indirect pathway (as in Huntington's disease and L-DOPA-induced dyskinesias), lead to reduced inhibitory outflow from GPi/SNr and excessive disinhibition 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; SMA, supplementary motor area; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VAmc, nucleus ventralis anterior pars magnocellularis; VApc, nucleus ventralis anterior pars parvocellularis; VLo, nucleus ventralis lateralis pars oralis.*

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

The pathophysiological basis of akinesia remains uncertain. Although classically attributed to loss of nigrostriatal dopamine neurons with resultant dysfunction in striopallidal mechanisms, it has also been proposed that akinesia 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. 31 for review). However, the MPTP model of parkinsonism suggests that akinesia may be produced by damage limited to the SNc and the nigrostriatal dopamine system[7,32]. In these animals, akinesia appears to be a relatively dramatic and early feature following administration of the neurotoxin. Although large doses of MPTP have been shown to produce damage outside the SNc[11,33], smaller doses with damage apparently limited to the SNc appear sufficient for the production of akinesia. Thus, it must be considered that akinesia 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 percentage of the nigrostriatal dopaminergic projection, especially that innervating the putamen, is lost[34]. It is thus possible that akinesia results from selective depletion of dopamine in the motor circuit at the striatal (putamen) level. Akinesia 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 dopamine-depleted animals, which would lead to decreased phasic disinhibition of thalamocortical neurons during attempted movements. It is conceivable, therefore, that akinesia may represent an extreme form of bradykinesia. Another possibility is that some aspects of akinesia 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 hemiballismus

Apart from parkinsonism, the basal ganglia disorder for which the neuropathological substratum has seemed least in doubt, is hemiballismus. In humans, vascular lesions restricted to the STN frequently result in involuntary, often violent movements of the contralateral limbs (termed 'hemiballismus' 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 abnormality. In addition to the proximal ballistic movements, these involuntary movements may take the form of more distal, irregular (choreiform), or more continuous writhing (athetoid) movements. Hemiballismus has been produced in monkeys by experimental lesions of the STN[35–37]. This primate model has provided new insights into the pathophysiology of the hyperkinetic disorders.

Until recently, hemiballismus was generally thought to result from a 'release' of GPi from an inhibitory control from the STN. However, recent evidence indicates that the projections from STN to GPi are actually excitatory, and probably glutamatergic[38,39]. Moreover, monkeys with hemiballismus secondary to inactivation of the STN show decreased metabolic activity both in GPi and in the ventrolateral thalamus, suggesting that GPi output may be reduced in this disorder[14]. The effect of STN lesions (produced by the axon-sparing neurotoxin ibotenate) on GPi activity was recently studied directly in the monkey[40] and, indeed, a significant reduction of GPi tonic discharge was found. A decrease in the phasic responses of GPi neurons to limb displacement was also found. Together, these findings suggest that hemiballismus results from a disinhibition of the thalamus due to a reduction of tonic (and perhaps phasic) inhibitory output from GPi. Conceivably, thalamocortical neurons under such conditions might become increasingly 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 choreiform movements of Huntington's disease and the dyskinetic movements that are seen in hemiballismus. It has been shown that early in the course of Huntington's disease there is a selective loss of the striatal GABA/enkephalin neurons that give rise to the indirect pathway[41]. The consequent loss of inhibition of GPe neurons would be expected to lead to excessive inhibition of STN neurons, and this functional inactivation of the STN could thus explain the choreiform motor disturbances in Huntington's disease that resemble those seen in hemiballismus (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 GPi[42]. This would lead to increased discharge of the partially deafferented GPi/SNr neurons, by removal of inhibition.

The phenomenon of L-DOPA-induced dyskinesias (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 GABA/enkephalin neurons would lead to reduced excitatory input to GPi/SNr 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 GPi/SNr 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 excitatory drive from the STN to the output nuclei of the basal ganglia (GPi/SNr). It is predicted, therefore, that a lesion or inactivation of the STN in parkinsonian subjects would ameliorate some of the motor impairments. This has been tested recently by selective lesioning of the STN with the fiber-sparing neurotoxin ibotenate in MPTP-treated monkeys (Bergman, H., Wichmann, T. and DeLong, M. R., unpublished observations). Such lesions produced an immediate

and dramatic reduction of akinesia and bradykinesia (as well as tremor and rigidity) in the contralateral limbs. These results provide the first direct support for the postulated 'positive' role of the STN (and the indirect pathway) in the pathogenesis of hypokinetic disorders. The fact that STN-lesioned animals also showed a marked reduction in contralateral tremor and rigidity suggests that the STN and the indirect pathway may play a critical role in the pathogenesis of these abnormalities as well. It is noteworthy that, as expected, the animals exhibited dyskinesias of the contralateral limbs, but that these were transient, whereas the amelioration of the parkinsonian signs persisted until the time of death.

Concluding remarks

There is now considerable evidence that the respective pathophysiological mechanisms underlying hypo- and hyperkinetic movement disorders (representing both ends of the clinical spectrum of basal ganglia-associated motor disturbances) involve changes in the operational features of the basal ganglia–thalamocortical motor circuit that are essentially polar opposites. Thus, hypokinetic disorders (e.g. Parkinson's disease) are thought to be associated with excessive tonic and phasic inhibitory output from the basal ganglia to the thalamus, and the hyperkinetic disorders (e.g. hemiballismus) with an abnormally low level of basal ganglia outflow. Future studies are expected to reveal that the spectrum of basal ganglia-associated movement disorders can be accounted for by varying combinations of these two pathophysiological extremes.

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Next Month

The August issue of *TINS* will include the following articles:

Patch-clamping in slices of mammalian CNS, *by A. Konnerth*

Brief seizure episodes induce long-term potentiation and mossy fibre sprouting in the hippocampus, *by Y. Ben-Ari and A. Represa*

Molecular approaches to the segmentation of the hindbrain, *by D. Wilkinson and R. Krumlauf*

The cellular basis for segmentation in the developing hindbrain, *by A. Lumsden*

Target regulation of neurotransmitter phenotype, *by S. C. Landis*

The Korsakoff syndrome: a neurochemical perspective, *by W. J. McEntee and R. G. Mair*

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