perspectives on disease

The functional anatomy of basal ganglia disorders

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Basal ganglia disorders are a heterogeneous group of clinical syndromes with a common anatomic locus within the basal ganglia. To account for the variety of clinical manifestations associated with insults to various parts of the basal ganglia we propose a model in which specific types of basal ganglia disorders are associated with changes in the function of subpopulations of striatal projection neurons. This model is based on a synthesis of experimental animal and post-mortem human anatomic and neurochemical data. Hyperkinetic disorders, which are characterized by an excess of abnormal movements, are postulated to result from the selective impairment of striatal neurons projecting to the lateral globus pallidus. Hypokinetic disorders, such as Parkinson's disease, are hypothesized to result from a complex series of changes in the activity of striatal projection neuron subpopulations resulting in an increase in basal ganglia output. This model suggests that the activity of subpopulations of striatal projection neurons is differentially regulated by striatal afferents and that different striatal projection neuron subpopulations may mediate different aspects of motor control.

Speculation about the function(s) of the basal ganglia have been strongly influenced by descriptions of the clinical phenomenology of human basal ganglia disorders. The study of Parkinson's disease (PD), in particular, has had a strong influence on speculation about basal ganglia function. The observation that parkinsonian patients have considerable difficulty in initiating movements led to the hypothesis that the basal ganglia are involved in the 'automatic execution of learned motor movements'[1]. In this scheme, the basal ganglia function as an entity devoted to sequencing individual motor programs into a smooth series of actions. This close linkage of conceptual schemes about function and the clinical details of human disease is virtually unique in contemporary neuroscience.

While there are obvious advantages to drawing on the phenomenology of human basal ganglia disease, there are also disadvantages. Disorders of the basal ganglia are associated with a broad spectrum of clinical phenomena ranging from uncontrollable excess of movement to the restriction of movement seen in parkinsonism. The anatomic basis of some of the clinical manifestations associated with basal ganglia disease, especially those characterized by an excess of movement, have not been well understood. For the purposes of conceptualization and hypothesis generation, this situation has led to dependence on the phenomenology of PD, whose pathologic anatomy and neurochemistry are relatively well understood. Concentration on PD, however, ignores the richness of symptoms produced by basal ganglia diseases and probably gives

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a distorted picture of the role of the basal ganglia in motor function.

In the past decade, substantial advances have been made in our understanding of basal ganglia anatomy, in experimental models of basal ganglia disease, and in post-mortem studies of the anatomic changes associated with human diseases of the basal ganglia. Correlation of these findings allows the construction of a model that specifies the anatomic and biochemical correlates of the clinical phenomenology seen in a wide variety of basal ganglia disorders. Although provisional, this model has substantial implications for our understanding of how the basal ganglia are involved in the organization of motor behavior and indicates potentially fruitful lines of future investigation.

Classical basal ganglia anatomy

The basal ganglia are a group of interconnected subcortical nuclei spanning the telencephalon, diencephalon, and midbrain. The following description of basal ganglia connections deals only with the major pathways of the basal ganglia. The known connectional anatomy of these structures is quite complex and the use of increasingly sensitive tract tracing methods will undoubtedly reveal new connections and facts about known connections.

The primary afferent structure of the basal ganglia is the striatum. In some mammals, the striatum is a single structure, but in most it consists of two portions, the medial caudate and lateral putamen, divided by the fibers of the internal capsule. The primary output structure(s) of the primate basal ganglia are the medial globus pallidus (MGP) and the substantia nigra pars reticulata (SNr). These nuclei are separated by the fibers of the cerebral peduncles in most mammals but contain cytologically similar neurons[2,3]. Like the caudate and putamen, the MGP and SNr can be considered parts of a single neuronal system separated by a white matter tract. In most mammals, the homologue of the MGP is the entopeduncular nucleus (EP), which is embedded in the fibers of the corticofugal tracts. The MGP and SNr receive direct projections from the striatum. In addition, an indirect projection from the striatum to the MGP and SNr begins with a projection from the striatum to the lateral globus pallidus (LGP). The latter gives rise to a large projection to the subthalamic nucleus (STN). The STN in turn projects upon the MGP and SNr. The STN also projects back upon the LGP in what could be a negative feedback loop[4]. The striatum projects also upon the substantia nigra pars compacta (SNc), and in turn, receives a substantial projection from the SNc. The classical neurotransmitter of striatal, pallidal, and SNr projection neurons is GABA[5]. The neurotransmitter of STN neurons has so far escaped

definition but recent studies indicate that it is excitatory and possibly glutamatergic[6,7]. The neurotransmitter of SNc neurons is dopamine (DA).

The striatum is primarily composed of projection neurons[8,9]. Studies in rats suggested that striatal projection neurons give rise to extensive collateral projections with axons from a single neuron going to both segments of the pallidum and the SNr[10] (Fig. 1). The striatum also contains a small number of interneurons. Striatal interneurons can be subdivided by histochemical or immunohistochemical identification of which neurotransmitter or neuropeptide is contained within them. The best characterized subpopulations of striatal interneurons are cholinergic interneurons[11] and another group that contain both the peptides somatostatin and neuropeptide Y[12,13].

The striatum receives afferents from all of the isocortex[14]. The neurotransmitter of the corticostriatal afferents is probably glutamate[15]. The only other basal ganglia structure to receive significant direct cortical input is the STN, which receives excitatory afferents from the motor and premotor cortex[16-19]. The striatum may receive an indirect cortical input through the intralaminar thalamic nuclei, especially the centromedian-parafascicular (CM-pf) nuclei[20-22], which give rise to striatal afferents. Since the CM-pf nuclei also receive input from the MGP and SNr (see below), Francois et al. have proposed inclusion of the CM-pf complex in the basal ganglia[23]. Other striatum afferents include the DA-containing fibers from the SNc[24], and serotonergic afferents from the dorsal raphe nuclei[20]. Output from the basal ganglia is directed to several regions of which the most important are the ventral tier (ventral-anterior and ventral-lateral; VA/VL) and mediodorsal (MD) thalamic nuclei[25]. These thalamic nuclei project to the prefrontal cortex, and areas receiving MGP and SNr afferents have particularly robust projections to the supplementary motor area[26,27]. These thalamocortical projections appear to be excitatory[28]. Collaterals of the neurons projecting to VA/VL and MD nuclei project also to the CM-pf nuclei of the thalamus[5]. Descending projections are less prominent but both MGP and SNr project upon the midbrain tegmentum[5]. The MGP also projects upon the lateral habenula while SNr projects to the superior colliculus[5].

Movement disorders

The spectrum of abnormal movements caused by disorders of the basal ganglia falls under the rubric of what neurologists term movement disorders. Traditionally, these abnormal movements were classified simply on the basis of their clinical appearance and without regard to any common features or common pathophysiological mechanism(s). A more systematic scheme can be based on modern clinical and pharmacological data. Three categories appear to exist.

The first of these may be called hyperkinetic movement disorders. All of these disorders are

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Abbreviations Used in the Text
CM-pf nuclei, centromedian-parafascicular nuclei
DA, dopamine
EP, entopeduncular nucleus
GP, globus pallidus
HD, Huntington's disease
LGP, lateral globus pallidus
MD, mediodorsal thalamic nuclei
MGP, medial globus pallidus
PD, Parkinson's disease
SNc, substantia nigra pars compacta
SNr, substantia nigra pars reticulata
STN, subthalamic nucleus
VA/VL, ventral-anterior and ventral-lateral thalamic nuclei

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characterized by an excess of movement with uncontrollable and relatively rapid motor acts intruding into the normal flow of motor activity. In addition, all these abnormal movements share a common pharmacology in that the abnormal movements are suppressed by the administration of dopamine D_2 receptor antagonists and exacerbated by dopamine agonists. Chorea is probably the most common of these hyperkinetic movement disorders. Derived from the Greek word for dance, chorea connotes rapid movements of the trunk, head, face, and limbs that interrupt normal movement. It has been suggested that chorea represents the intrusion of fragments of undesirable motor programs into the normal flow of motor acts[29,30]. Chorea is often accompanied by athetosis, which has a slower, writhing character. Huntington's disease (HD), an autosomal dominant hereditary neurodegenerative condition in which the most pronounced pathologic changes occur in the striatum, is the prototypic choreoathetoid disorder[31]. Choreoathetosis, however, is seen in an impressive array of human diseases[30,32]. Largely because of HD, neurologists tend to think of choreoathetosis as a consequence of striatal pathology, despite the fact that traumatic, ischemic, or ablative lesions of the striatum in man or animals rarely produce choreoathetosis[33,34]. Choreoathetoid movements similar to those seen in HD are commonly observed in patients with Parkinson's disease overdosed with dopamine replacement therapy.

Ballism is a rare syndrome produced usually by infarction of the subthalamic nucleus[35]. It is characterized by violent, flinging motions of the extremities. While traditionally classified as a separate disorder, ballism appears to be part of the spectrum of choreoathetosis. HD patients with particularly violent chorea have movements indistinguishable from classic vascular ballism (Albin, R. L., Young, A. B. and Penney, J. B., unpublished observations). Similarly, in patients with classic ballism the violent movements will often subside into choreoathetosis and some patients with infarcts of the STN present with choreoathetosis[36]. Again, this hyperkinetic movement disorder can be suppressed with D_2 receptor antagonists.

Tics comprise a third hyperkinetic movement

disorder[37]. Like chorea, tics are rapid movements that interrupt normal motor acts. Unlike chorea, which occurs in random order over a number of muscle groups, tics are stereotyped and repetitive in character, usually involve several muscle groups simultaneously, and may assume the form of complex motor acts. The best examples of the potential complexity of tics are the forced vocalizations of Gilles de la Tourette's syndrome, in which affected persons may utter whole words and obscene phrases uncontrollably. Tics are also reliably suppressed by D_2 receptor antagonists.

Another pharmacologic feature of hyperkinetic disorders is their response to cholinergic and anti-cholinergic medications. In Huntington's disease, cholinergic agonists will alleviate choreoathetosis while anti-cholinergic drugs will exacerbate it[38].

The next general category of movement disorders are the hypokinetic disorders, in which akinesia, bradykinesia and rigidity are the most prominent features. Parkinsonism, the prototypic hypokinetic disorder, is characterized by slowness of movement, increased muscular tone, a paucity of spontaneous movements, and tremor. This clinical picture results from impaired nigrostriatal dopaminergic neurotransmission, and may arise from blockade of DA receptors with D_2 receptor antagonists, depletion of catecholamines by reserpine, or degeneration of

Fig. 1. *Simplified diagram of basal ganglia circuitry based on the initial concepts of basal ganglia functional anatomy. The primary inputs to striatum were considered to be the cerebral cortex (excitatory and glutamatergic, glu), the parafascicular complex (PF) (excitatory but transmitter unknown), and the substantia nigra pars compacta [SNc, dopaminergic (DA) and presumably inhibitory]. Filled symbols are inhibitory neurons and open symbols are excitatory neurons. Notice the presence of dopaminergic synapses on acetylcholine striatal interneurons (ACh) which provide excitatory input to striatal projection neurons. In this scheme, striatal GABAergic projection neurons were thought to give rise to branched axons with collaterals projecting to both segments of the pallidum and the substantia nigra pars reticulata (SNR). The neurotransmitter of the pallidal (GP/LGP, globus pallidus and its primate homologue, the lateral globus pallidus; EPN/MGP, entopeduncular nucleus and its primate homologue, the medial globus pallidus) and SNr neurons is GABA, and these pallidal neurons send projections to both thalamic and non-thalamic nuclei. See text for amplification of this model and the results of experiments testing it.*

SNc neurons [39]. The latter is the basis for idiopathic Parkinson's disease and can be induced in man and non-human primates by the neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)[40]. Pharmacologically, parkinsonism is the inverse of hyperkinetic disorders with exacerbation by D_2 receptor antagonists and cholinergic agonists, and amelioration with DA agonists and anti-cholinergics[39].

Dystonia is the final category of movement disorders we will discuss. This disorder consists of the spontaneous assumption of unusual fixed postures lasting seconds to minutes[41]. It can affect branchial, axial, or extremity muscles. Generalized dystonia occurs frequently as an idiopathic hereditary disorder. Sporadic focal or segmental [affecting specific muscle groups or those innervated by a given motor root(s)] dystonias are commonly seen in clinical practice. Little is known about the pathologic anatomy or pathophysiology of dystonia. Necropsies of patients with idiopathic generalized or focal dystonias have been unrevealing. Radiologic studies of patients with so-called symptomatic hemidystonia, in whom symptoms are confined to one side of the body and an intracranial lesion can be identified, have implicated the putamen, pallidum, or the thalamic target regions of the pallidum[42]. Dystonia also occurs in some cases of cerebral palsy[43,44], in a neurodegenerative disorder called progressive supranuclear palsy[45], and in advanced HD, where the choreoathetosis may be replaced by prominent dystonia[46].

In addition to causing the abnormal movements described above, all these movement disorders are characterized by impairment of normal movements. This is particularly true for rapid or finely coordinated movements, which become clumsy and slow.

A prior model of basal ganglia disease

Based on the connectional anatomy described above and supplemented by physiological studies of the effects of neurotransmitters on striatal neurons, two of us (JBP, ABY) developed a model of basal ganglia function that attempted to explain the pharmacology of parkinsonism and HD. In this model, the basal ganglia were conceived as participating in a corticocortical feedback loop to control the sequencing of motor programs[47] (Fig. 1).

In this scheme, cortical afferents excited striatal neurons, which in turn inhibited the neurons of the pallidum and nigra. The inhibition of the GABAergic and inhibitory output neurons of the basal ganglia resulted in increased activity by the thalamocortical neurons of the VA/VL/MD/CM-pf nuclei. DA was proposed to modify this circuit by inhibiting cholinergic striatal interneurons which normally excite striatal projection neurons. In PD, the absence of dopamine would leave the cholinergic interneurons driving the striatal projection neurons. This would eventually result in supranormal thalamocortical neuron activity. The latter would excite the premotor cortex and facilitate the execution of any ongoing motor program.

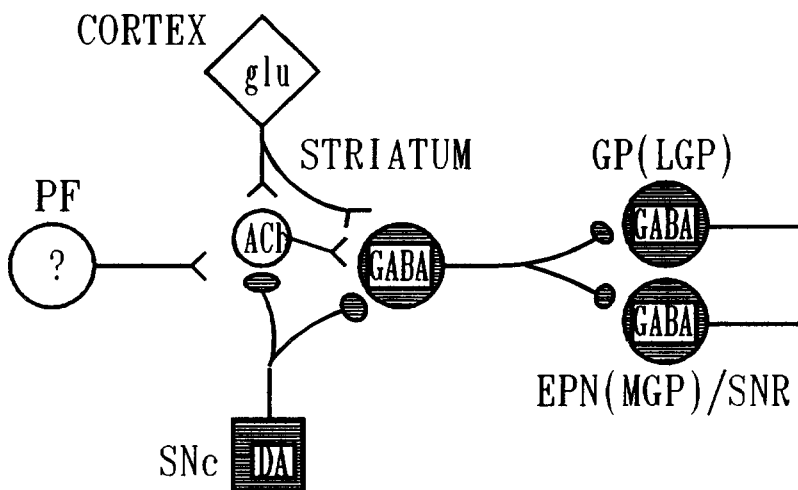Huntington's disease, by contrast, is marked by striatal projection neuron degeneration. The loss of

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striatal output was hypothesized to result in disinhibition of the MGP and SNr and inhibition of the VA/VL/MD/CM-pf nuclei. The loss of activity of these thalamocortical projections would result in decreased drive to execute the ongoing motor program. Competing programs or fragments of motor programs would then corrupt the ongoing motor act and appear as adventitious movements inserted into a normal motor act.

Not surprisingly, this simple but heuristically useful model was soon challenged by confounding data. This model suffered from the defect that it predicted that adventitious movements should result from striatal destruction, when in fact ablative striatal lesions in both man and other mammals do not produce a hyperkinetic movement disorder. This model also failed to take into account the fact that a hyperkinetic movement disorder is reliably produced in man by lesions of the STN.

Additional testable predictions could also be derived from this model. Striatal lesions in animals would be expected to produce GABA receptor up-regulation in the pallidum and SNr because of the loss of GABAergic afferents to these nuclei. This prediction proved to be correct[48]. On the other hand, this model predicted that destruction of the nigrostriatal dopaminergic projection would result in down-regulation of pallidal and SNr GABA receptors because of excessive activity by the GABAergic striatal output neurons. When this experiment was performed in rats with unilateral 6-hydroxydopamine lesions of the median forebrain bundle, decreased receptor density was found in the globus pallidus (GP; the rodent homologue of the LGP), but in contrast to the prediction, GABA receptor densities in the EP and SNr were increased[49]. The implications of these studies were that dopamine functionally inhibited striatal projections to GP and excited striatal projections to EP/SNr. This result appeared paradoxical as afferent striatal axons to the GP and SNr in rodents were thought to be collaterals[10]. In addition, electrophysiological studies gave conflicting results about the effects of DA on striatal neurons[50]. In some studies, DA did appear to be inhibitory, but in other studies it appeared to excite striatal neurons.

The failure of this simple model suggested shortcomings in the anatomic and physiological knowledge on which it was based.

More recent basal ganglia anatomy

In the model described above, it was assumed that the striatum was essentially a uniform structure and that striatal afferents had a uniform effect on striatal projection neurons. This notion was based on the traditional anatomic concept of the striatum as a histologically uniform structure. In the past 15 years, however, it has been discovered that the striatum is richly heterogeneous. In 1972, Olson et al.[51] showed that dopamine terminals were heterogeneously distributed in neonatal and adult rats. Subsequently, Mensah[52] demonstrated that the rat neostriatum was cytoarchitectonically inhomogeneous. Beginning with the work of Graybiel and her

colleagues, it has been demonstrated that the striatum can be divided into two broad compartments, the striosomes and the matrix[53]. These compartments are defined by the intensity of histochemical staining for acetylcholinesterase in cats and primates[53], and by the heterogeneous distribution of μ-opioid receptors in rodents[54]. Subsequent work revealed that striosomes and matrix also have different connections. The striosomes receive cortical afferents from prefrontal and limbic cortices while the matrix receives cortical afferents from primary motor and somatosensory cortex as well as frontal, parietal, and occipital cortex[55–58]. Striatal afferents from the SNc also appear to be differentially distributed to the striatum with different groups of midbrain dopaminergic neurons projecting to striosomes and matrix[59–61]. Projections from the striosomes go mainly back to the SNc while matrix projections go mainly to the pallidum and SNr[9,60]. These two striatal compartments may be linked functionally by interneurons that contain both somatostatin and neuropeptide Y[57,62]. Some striatal neurons also seem to possess dendrites that cross the borders between the striosomes and the matrix[63].

In addition to this compartmental segregation, striatal projection neurons can also be differentiated by which neuropeptides they contain and the target zone they project upon. Matrix neurons containing substance P mainly project upon the MGP or SNr, while those containing enkephalins project mainly upon the LGP[64]. Those striosome neurons projecting to the SNc contain mainly substance P[64,65]. A high percentage of these peptidergic neurons also contain GABA[66]. Recent tract-tracing studies in cats and primates have demonstrated that striatal neurons projecting to a given striatal target zone have few collaterals to other target nuclei[67–69]. In contrast to the classical view, the striatum appears to consist of discrete populations of projection neurons, each with relatively restricted inputs and outputs (Fig. 2A).

Ultrastructural studies discredited the notion that the effect of DA on striatal projections is mediated through striatal cholinergic interneurons. These studies reveal that striatal dopaminergic terminals synapsed primarily upon striatal projection neurons[70–72], and suggest that DA exerts its effects directly upon striatal projection neurons.

A revised model of basal ganglia disorders

Based on new anatomical, pharmacological, and physiological data we constructed a new model of basal ganglia function that accounts for the clinical phenomenology of movement disorders. This revised model differs from our prior model in several important respects. Two fundamental attributes of the revised model are the existence of subpopulations of striatal projection neurons with different projection targets and the idea that DA has different effects on these subpopulations of striatal projection neurons. We have also incorporated the LGP–STN–MGP/nigra pathway into the revised model. In the revised model the effects of disease

states on thalamocortical projections are quite different from those predicted by the prior model. We continue to believe the basal ganglia are regulators of cortical function via their influence on thalamocortical projections. The nature of the revised model is best appreciated by showing how it can explain the functional anatomy underlying movement disorders.

Hyperkinetic movement disorders

Ballism has historically been the only hyperkinetic movement disorder with a well established anatomical localization. Both in humans and in non-human primates, destruction of the STN produces ballism[73,74]. In recent years, Crossman and his associates have exploited this non-human primate model to study the pathophysiology of hyperkinetic movement disorders[75]. They have demonstrated that either blocking the activity of the STN or its output to the MGP produces a movement disorder similar to that seen in human hyperkinetic movement disorders[75,76]. These facts and our previous studies of pallidal and nigral GABA receptors in rats with 6-hydroxydopamine lesions led us to predict that facilitation of the major inhibitory input to the STN should produce a hyperkinetic movement disorder from the resulting decrease in STN neuron activity[77]. Crossman's group subsequently produced hyperkinetic movements by infusing bicuculline, a GABA receptor antagonist, into the LGP[78]. In effect, they blocked the GABAergic input from the striatum and potentiated the activity of the GABAergic LGP neurons projecting to the STN. The logical corollary of this result is that the choreoathetosis of HD should be the result of a loss of neurons projecting to the LGP. Recent work of ours, performed in collaboration with Anton Reiner and Keith D. Anderson, has shown that in the early stages of HD, when chorea is most prominent, there is a selective loss of striatal neurons projecting to the LGP[79]. We were able to demonstrate a selective loss of enkephalin-immunoreactive striatal terminals in the LGP of early-stage HD specimens. Substance P-immunoreactive striatal terminals in the MGP were well preserved until the later stages of HD, when they too became depleted. We inferred a temporal gradient of cell loss in HD, in which enkephalinergic neurons projecting to the LGP are lost early in the course of the disease, and substance P-containing neurons projecting to the MGP are lost late in the course of the disease.

This selective involvement of a specific subpopulation of striatal projection neurons also explains the effectiveness of D_2 receptor antagonists in ameliorating hyperkinetic movements. It is now known that DA antagonists do not have uniform effects on the various subpopulations of striatal projection neurons. Studies of striatal neuropeptides have shown that administration of D_2 antagonists increases the synthesis of enkephalins and pre-proenkephalin mRNA in the striatum. LGP enkephalin levels also rise, indicating that this increased synthesis of enkephalins is taking place in striatal neurons projecting to LGP[80-82]. Similar results have

been obtained by 6-hydroxydopamine ablation of the nigrostriatal projection in rats and MPTP destruction of the SNc in non-human primates[83,84]. The effects of D_2 receptor antagonists can be blocked by the co-administration of the anti-muscarinic cholinergic agent scopolamine[80]. These increases in enkephalin levels and mRNA presumably reflect increases in neuronal activity, and indicate that D_2 receptor antagonists potentiate the activity of striatal neurons projecting to the LGP. DA agonists produce the opposite effect. Relevant changes in the activity of this subpopulation of striatal projection neurons have been demonstrated in 2-deoxyglucose studies of MPTP-treated primates. Without dopamine replacement, there is an increase in the activity of the striatal–LGP projection in these parkinsonian monkeys. In monkeys given doses of dopamine agonists sufficient to induce hyperkinetic movements, there is a decrease in the activity of the striatal–LGP projection[85-88]. In HD, the administration of D_2 antagonists would result in the stimulation of the remaining striatal–LGP neurons and partially overcome the deficit created by degeneration of this subpopulation of projection neurons. In ballism, administration of D_2 antagonists would result in inhibition of LGP neurons projecting to the STN and a potentiation of residual STN function. Anticholinergics antagonize this effect of DA blockade, and this would explain why chorea worsens with administration of anticholinergic drugs.

Because of a lack of post-mortem data, it is harder to bring tic disorders into this scheme. The distribution of neuropeptides in one case of Tourette's syndrome has been studied[89]. In this specimen, it was noted that there was a decrease in dynorphin-like immunoreactivity in the LGP. This result probably reflected impaired function of enkephalinergic striatal neurons projecting to the LGP because it has subsequently been found that the antibody used in this study cross-reacts with enkephalins (Reiner, A., pers. commun.) and because relatively few striatal neurons projecting to the GP in rats and other species contain dynorphin[64,90,91].

In summary, the hyperkinetic movement disorders of choreoathetosis, ballism and tics appear to result from decreased activity of the STN, either because of STN destruction or because of selective dysfunction of a subpopulation of striatal neurons projecting to the LGP. The ultimate effect would be loss of STN-derived excitatory drive to the MGP and SNr and disinhibition of the VA/VL/MD/CM-pf thalamocortical projections (Fig. 2B, C).

Parkinsonism

In parkinsonism, the challenge has been to explain the action of DA on striatal neurons. As mentioned above, electrophysiological studies gave conflicting results. It is now known that impairment of DA action increases the activity of striatal neurons projecting to the LGP. DA appears also to produce significant but different changes in other striatal projection neuron subpopulations. The
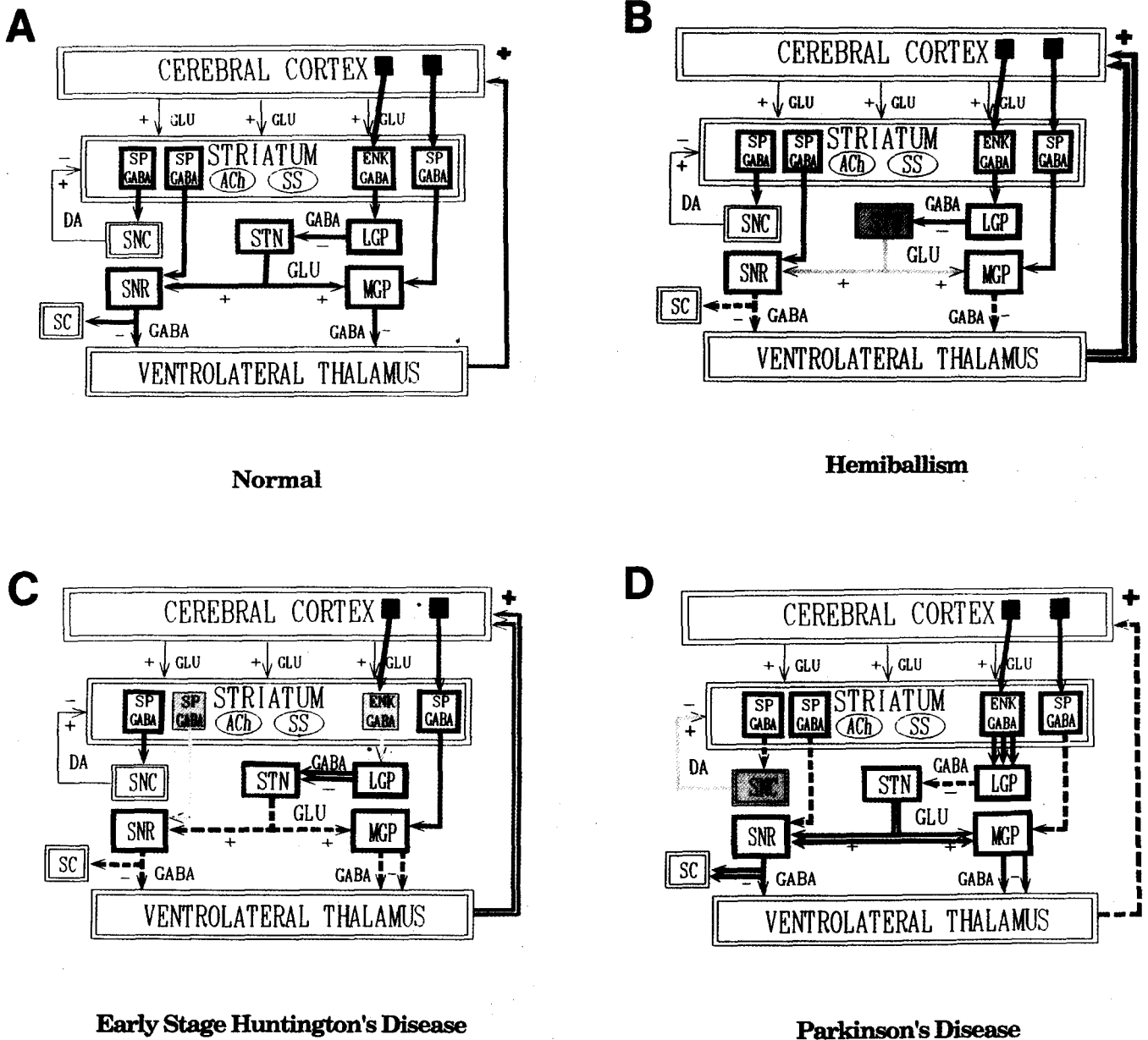
A

Normal

B

Hemiballism

C

Early Stage Huntington's Disease

D

Parkinson's Disease

Fig. 2. *This set of diagrams depicts a revised model of basal ganglia dysfunction in movement disorders based on recent anatomical, neurochemical and neuropathological knowledge. In these figures, ovals represent interneurons, and boxes, projection neurons. Red boxes and arrows represent excitatory neurons and projections. Blue boxes and arrows represent inhibitory neurons and projections. Yellow boxes and arrows represent degenerating neurons and projections. Yellow shading indicates partial or complete loss of neurons. Doubling of arrows represents a functional increase in a projection's activity while interruption of arrows represents a functional decrease in activity without loss of anatomic integrity.* **(A)** *Normal. In contrast to Fig. 1, this diagram displays the segregation of striatal projection neurons into subpopulations with specific projection targets and different types of neuropeptides.* **(B)** *Hemiballism. This diagram shows the effects of destruction of the STN. The loss of excitatory STN input to the MGP and SNR results in disinhibition of thalamocortical projections.* **(C)** *Early Huntington's disease. This diagram shows the probable changes in striatal projection neuron subpopulations at an early stage of Huntington's disease (HD). At this stage, choreoathetosis is usually prominent and this stage of HD probably exemplifies choreoathetotic disorders. Degeneration is especially marked in striatal neuron subpopulations projecting to the LGP and SNR. The disinhibition of the LGP causes diminished activity in the STN. As in hemiballism, the end result is disinhibition of thalamocortical projections. In addition, the loss of striatal and STN input to the SNR probably results in abnormalities of saccadic eye movements.* **(D)** *Parkinson's disease. This diagram shows the degeneration of the SNC and the ensuing changes in the activity of striatal projection neuron subpopulations. Striatal projections to the LGP become more active, while striatal projections to the MGP and SNR become less active. The loss of GABAergic striatal input and increased STN excitatory input result in increased activity of MGP and SNR neurons and inhibition of thalamocortical projection neurons. Simultaneously, there is excessive inhibition of the SC.* **Abbreviations:** ACh, acetylcholine; DA, dopamine; ENK, enkephalins; GABA, γ-aminobutyric acid; GLU, glutamate; LGP, lateral globus pallidus (globus pallidus in most mammals); MGP, medial globus pallidus (entopeduncular nucleus in most mammals); SC, superior colliculus; SNC, substantia nigra pars compacta; SNR, substantia nigra pars reticulata; STN, subthalamic nucleus; SP, substance P; SS, somatostatin.

administration of DA antagonists in rats decreases the concentration of substance P in the striatum, entopeduncular nucleus (EP) and the SNr, and striatal preprotachykinin mRNA levels also decrease[82,92,93]. Electrophysiological studies of MPTP-treated monkeys have also shown increased single unit activity in the MGP and decreased single unit activity in the LGP, consistent with increased activity in striatal neurons projecting to the LGP and decreased activity in striatal neurons projecting to the MGP[94,95]. Similar results have been observed in 6-hydroxydopamine-lesioned rats[96]. These electrophysiological and neuropeptide synthesis results parallel the changes in pallidal and nigral GABA receptor density we have described in 6-hydroxydopamine-lesioned rats[49].

One would expect, consequently, to find decreased concentrations of substance P in the SNr and MGP of victims of Parkinson's disease, and indeed, this has been described[97,98]. On the other hand, one would predict that the levels of enkephalins in the LGP should increase, but this has not been observed[98].

In addition to these effects on the direct striatal–MGP and striatal–SNr projections, DA blockade will increase also the activity of MGP and SNr neurons via the striatal–LGP–STN circuit. The increased activity of the striatal–LGP projection neurons will result in disinhibition of the STN and increased excitatory drive to the MGP and SNr from the STN.

In summary, it appears likely that parkinsonism is associated with a complex series of changes in the activity of striatal projection neuron subpopulations. Striatal projections to the MGP and SNr are less active while the projection to the LGP is more active. The end result is disinhibition of the major output centers of the basal ganglia and increased inhibition of VA/VL/MD/CM-pf thalamocortical neurons (Fig. 2D).

Saccades

The study of eye movements has been particularly rewarding in both clinical and experimental studies of basal ganglia function. Saccades, the very rapid eye movements used to move the fovea from one target to another, have been intensively studied because they appear to be an example of pre-programmed movements and consequently serve as a window into the central mechanisms of motor control[99]. The basal ganglia appear to be intimately involved in the control of saccades.

The initiation of certain types of saccades appears to begin in the frontal eye fields of the cortex. While this area projects directly to the pontine areas containing the command neurons for saccade generation, it also projects indirectly to these pontine areas through a complex circuit with synapses in the caudate nucleus, SNr and tectum[100]. The tectum projects to the pontine neurons involved in generating saccades.

Clinical studies of patients with basal ganglia disorders have revealed characteristic abnormalities of saccadic eye movements. In both PD and HD,

there are increases in the latency of initiation of saccades, slowing of saccadic velocity, and interruption of saccades[101–104]. As we have seen, in PD there is probably decreased striatal inhibition of the SNr neurons. This probably results in increased inhibition of tectal neurons involved in the control of saccades. A similar decrease in striatal input to the SNr seems to occur in HD. We have recently shown that there is an early loss of substance P-containing striatal terminals in the SNr of HD victims[79]. The loss of these substance P-containing terminals probably indicates the loss of striatal neurons projecting to the SNr. This depletion of striatal neurons projecting to the SNr occurs at the same time as the loss of striatal neurons projecting to the LGP, and is a feature of the early stages of the disease. As many of these neurons are also GABAergic, the SNr is losing a substantial inhibitory input. Again, this probably results in over-inhibition of tectal neurons involved in the control of saccades. A similar impairment of saccadic eye movements has been produced in monkeys by infusion of the GABA agonist muscimol into the tectum, and by infusion of the GABA antagonist bicuculline into the SNr[105,106]. These experimental manipulations mimic the loss of inhibitory striatal input that seems to occur in PD and HD.

HD patients also exhibit an abnormality of saccadic control not seen in PD patients. When tested in a paradigm in which they are instructed to maintain fixation on a single point and other stimuli are briefly presented, HD patients have involuntary saccades to the new target[101,102]. Because of the loss of striatal–LGP projection, the SNr in HD patients has a decreased excitatory drive from the STN. The abnormal input from STN may further perturb SNr regulation of the tectum and result in this so-called saccadic distractability. The STN dysfunction produced by increased inhibition from the LGP could also affect the influence of cortical projections upon the STN. Kita and Kitai[107] have pointed out that neurotransmission from cortex to the MGP and SNr is faster through the STN circuit than through the striatal circuit. They have speculated that the cortex–STN circuit could activate pallidal and SNr neurons before inhibition arrives from the striatum. This proposed process of cortical activation of the pallidum and SNr via the STN would probably be perturbed by STN dysfunction. Analogous saccadic distractability has been observed in monkeys that receive muscimol injections into the SNr[105,106]. This paradigm of increased inhibition of SNr neurons might be equivalent to the loss of excitatory STN output that seems to occur in hyperkinetic movement disorders. If impairment of basal ganglia function is involved in the occurrence of saccadic distractability, either because of changes in the frontal eye field–striatum–LGP–STN–SNr circuit or frontal eye field–striatum–SNr circuit, one might predict that alterations in part of the circuit(s) would produce saccadic distractability. Indeed, saccadic distractability has been documented in monkeys that have undergone ablation of the frontal eye fields[108].

Tourette's syndrome offers an interesting contrast to HD and PD. There are no abnormalities of saccadic control in Tourette's syndrome[109]. In the one case that has been studied with immunohistochemistry, the density of substance P-immunoreactive terminals in the SNr appeared to be normal, indicating preservation of striatal neurons projecting to the SNr[89].

Dystonia

The lack of post-mortem data on dystonia victims makes it difficult to correlate anatomic changes with clinical phenomena. In four situations, however, it is possible to attempt some correlations. Symptomatic hemidystonia, as mentioned above, seems to be associated with lesions of the putamen, pallidum, or thalamus. In HD, dystonia is common and becomes especially prominent as the disease progresses[46]. Our studies of striatal projection neurons in HD have shown that the projections to LGP and SNr are impaired early in the disease with sparing of projections to the SNc and MGP. By late stages of the disease, all projections are severely depleted[79]. In addition, it appears that end-stage HD is marked by trans-synaptic degeneration of pallidal and SNr neurons[110]. Dystonic cerebral palsy, similarly, is associated with lesions of the pallidum, but not the striatum[43,44]. Finally, necropsies of patients stricken with progressive supranuclear palsy show marked degeneration of the MGP and SNr[45]. We suggest that some cases of dystonia result from gross loss of basal ganglia output rather than a specific alteration in any striatal neuron subpopulation. In these situations, the motor system continues to function, but without the modulating influence of the basal ganglia.

Summary

It appears that the complex clinical phenomenology of hyperkinetic and hypokinetic movement disorders results from the altered behavior or loss of subpopulations of striatal projection neurons. In the hyperkinetic disorders, the abnormal movements result from impairment of STN function, either as a result of destruction of the STN itself, or more commonly, as a consequence of the selective impairment of output from the striatum to the LGP. Parkinsonism seems to be correlated with an increase in basal ganglia output due to complex changes in the activity of striatal neuron subpopulations. This scheme is only a gross approximation of the physiological changes underlying movement disorders. It is likely that the activity of striatal and other basal ganglia neurons encodes information in a complex manner and that the interaction of the nuclei of the basal ganglia with each other is similarly complex. Our scheme also suffers from the defect that it does not completely assimilate the compartmentalization of the striatum. At present the relationship between the patch/matrix architecture and striatal connections has been well studied only in rat. It is not known how the striatal compartments communicate. As further information is accrued on the relationship between striatal compartments, and between compartments and striatal connections, it will be necessary to revise the model.

Nonetheless, these correlations between specific clinical syndromes and the activity of striatal neuron subpopulations have important implications for our understanding of basal ganglia function. The differential effect of DA on different subpopulations of striatal projection neurons suggests that differential regulation of striatal projection neuron subpopulations by striatal afferents may be an important feature of striatal function. This hypothesis is supported by a recent report by Uhl et al.[111] in which decortication selectively reduced the expression of enkephalin mRNA in striatal neurons. The existence of correlations between disease states and the activity of subpopulations of striatal neurons suggests also that subpopulations of striatal projection neurons are probably involved in different aspects of the control of motor behavior. Consequently, in future physiological studies it may be necessary to differentiate striatal neurons anatomically in order to classify their behavior properly.

The association of STN dysfunction with hyperkinetic movement disorders emphasizes the key role this small nucleus plays in the regulation of motor function. Receiving output from the LGP and the motor cortex, and projecting to the output nuclei of the basal ganglia, it seems to be a nexus of motor control activity.

The correlation of changes in the activity of subpopulations of striatal projection neurons and the saccadic abnormalities seen in HD and PD supports physiological data implicating the basal ganglia in the control of eye movements. This correlation suggests also that the study of eye movements, especially saccades, in animal models of movement disorders would be a fruitful line of investigation into basal ganglia function. It would be particularly interesting to study eye movements in models of hyperkinetic movements. If the saccadic distractability of HD is reproduced in these models, then saccadic distractability might be the oculomotor equivalent of chorea.

Chorea itself may result from an inability to suppress unwanted responses to sensory stimuli. Electrophysiological studies have shown that striatal neurons are responsive to sensory stimuli[112-115], and Lidsky et al. have suggested that one of the motor functions of the basal ganglia is to gate sensory influences onto motor areas[116]. The idea that the basal ganglia subserve a sensorimotor integration function is also supported by the clinical observation that some dystonic patients can ameliorate their dystonic movements by cutaneous stimulation of the affected body part. We would extend this line of speculation about possible basal ganglia sensorimotor integration by hypothesizing that one of the functions of the basal ganglia is to regulate sensorimotor interactions in a way that determines which sensory stimuli are used to initiate motor action and which are disregarded. Hikosaka et al., after an extensive electrophysiological study of caudate neurons involved in the execution of

saccades, have reached analogous conclusions. They suggest that caudate neurons involved in the initiation of saccades are part of a mechanism in which sensory data are evaluated in the context of learned behaviors and anticipated actions, and then used to initiate behavior[117-119]. We would further speculate that this function is executed not by the striatum as a whole but by a circuit involving the subpopulation of striatal neurons projecting to the LGP and probably involving the STN as an integrator of information from the striatum,motor cortex, and premotor cortex.

Finally, while we have concentrated on the motor aspects of basal ganglia function, it is clear that the basal ganglia are also involved in a variety of so-called cognitive functions. Alexander, DeLong and Strick[120] have proposed that the basal ganglia are integral parts of a series of parallel corticothal-amic–cortical loops that are involved in the regulation of motor, oculomotor, and cognitive behavior. Heimer and his colleagues have extended the boundaries of the basal ganglia to include basal forebrain structures with important connections to the amygdala and hippocampus[121]. Motor and oculomotor behavior can be studied most easily experimentally, and knowledge of how the basal ganglia are involved in motor and oculomotor functions may cast light on how the basal ganglia participate in cognitive functions. A crucial aspect of basal ganglia motor and oculomotor function is the differential activity of striatal neuron subpopulations and it will be necessary to study these in detail to gain a proper understanding of basal ganglia function.

Selected references

1 Marsden, C. D. (1982) Neurology 32, 514–539
2 Yelnik, J., Percheron, G. and Francois, C. (1984) J. Comp. Neurol. 227, 200–213
3 Yelnik, J., Francois, C., Percheron, G. and Heyner, S. (1987) J. Comp. Neurol. 265, 455–472
4 Nauta, H. J. W. and Cuenod, M. (1982) Neuroscience 7, 2725–2734
5 Parent, A. (1986) Comparative Neurobiology of the Basal Ganglia Wiley-Interscience
6 Nakanishi, H., Kita, H. and Kitai, S. T. (1987) Brain Res. 427, 45–55
7 Smith, Y. and Parent, A. (1988) Brain Res. 442, 353–356
8 Grofova, I. (1979) in The Neostriatum (Divac, I. and Oberg, R. G. E., eds), pp. 37–51, Pergamon
9 Graybiel, A. M., Ragsdale, C. W. and Moon-Edley, S. (1979) Exp. Brain Res. 34, 189–195
10 Loopjuit, L. D. and Van der Kooy, D. (1985) Brain Res. 348, 86–99
11 DiFiglia, M. (1987) J. Comp. Neurol. 255, 245–258
12 Vincent, S. R. et al. (1983) J. Comp. Neurol. 217, 252–263
13 Vincent, S. R. and Johansson, O. (1983) J. Comp. Neurol. 217, 264–270
14 Kemp, J. M. and Powell, T. P. S. (1970) Brain 93, 525–546
15 Young, A. B., Bromberg, M. B. and Penney, J. B. (1981) J. Neurosci. 1, 241–249
16 Hartmann-Von Monakow, K., Akert, K. and Kunzle, H. (1978) Exp. Brain Res. 33, 395–403
17 Afsharpour, S. (1985) J. Comp. Neurol. 236, 14–28
18 Stanton, G. B., Goldberg, M. E. and Bruce, C. J. (1988) J. Comp. Neurol. 271, 473–492
19 Rouzaire-Dubois, B. and Scarnati, E. (1987) Neuroscience 21, 429–440
20 Parent, A., Mackey, A. and De Bellefeuille, L. (1983) Neuroscience 10, 1137–1150
21 Beckstead, R. M. (1984) J. Comp. Neurol. 223, 313–346
22 Royce, G. J. and Mourey, R. J. (1985) J. Comp. Neurol. 235, 277–300
23 Francois, C., Percheron, G., Yelnik, J. and Tande, D. (1989) Brain Res. 473, 181–186
24 Moore, R. Y., Bhatnagar, R. K. and Heller, A. (1971) Brain Res. 30, 119–135
25 Carpenter, M. B. (1981) in Handbook of Physiology (Vol. 2: The Nervous System) (Brooks, V. B., ed.), pp. 947–995, American Physiological Society
26 Jones, E. G. (1985) The Thalamus Plenum
27 Schell, G. R. and Strick, P.L. (1984) J. Neurosci. 4, 539–560
28 Araki, T. and Endo, K. (1976) Brain Res. 113, 405–410
29 Kinnier-Wilson, S. A. (1929) Modern Problems in Neurology W. Wood
30 Shoulson, I. (1986) Clin. Neuropharmacol. 9, 585–599
31 Martin, J. B. and Gusella, J. F. (1986) New Engl. J. Med. 315, 1267–1276
32 Padberg, G. W. and Bruyn, G. W. (1986) in Handbook of Clinical Neurology, Vol. 5(49), Extrapyramidal Disorders (Vinken, P. J., Bruyn, G. W. and Klawans, H. L., eds), pp. 549–564, Elsevier
33 Villablanca, J. R., Marcus, R. J. and Olmstead, C. E. (1976) Exp. Neurol. 52, 389–420
34 Kinnier-Wilson, S. A. (1914) Brain 36, 425–492
35 Buruma, O. J. S. and Lakke, J. P. W. F. (1986) in Handbook of Clinical Neurology, Vol. 5(49), Extrapyramidal Disorders (Vinken, P. J., Bruyn, G. W. and Klawans, H. L., eds), pp. 369–380, Elsevier
36 Klawans, H. L., Moses, H., Nauseida, P. A., Bergen, D. and Weiner, W. J. (1976) New Engl. J. Med. 295, 1348–1350
37 Jankovic, J. (1987) in Movement Disorders 2 (Marsden, C. D. and Fahn, S., eds), pp. 383–405, Butterworth
38 Klawans, H. L. and Rubovits, R. (1972) Neurology 22, 107–116
39 Barbeau, A. (1986) in Handbook of Clinical Neurology, Vol. 5(49), Extrapyramidal Disorders (Vinken, P. J., Bruyn, G. W. and Klawans, H. L., eds), pp. 87–152, Elsevier
40 Langston, J. W. (1987) in Movement Disorders 2 (Marsden, C. D. and Fahn, S., eds), pp. 73–90, Butterworth
41 Fahn, S., Marsden, C. D. and Calne, D. B. (1987) in Movement Disorders 2 (Marsden, C. D. and Fahn, S., eds), pp. 332–358, Butterworth
42 Marsden, C. D., Obeso, J. A., Zarranz, J. J. and Lang, A. E. (1985) Brain 108, 461–483
43 Malamud, B. N. (1950) J. Pediatr. 37, 610–616
44 Brun, A. and Kyllerman, M. (1979) Eur. J. Neurol. 131, 93–111
45 Steele, J. C., Richardson, J. C. and Olszewski, J. (1964) Arch. Neurol. 10, 333–358
46 Young, A. B. et al. (1986) Neurology 36, 224–249
47 Penney, J. B. and Young, A. B. (1983) Annu. Rev. Neurosci. 6, 73–94
48 Pan, H. S., Frey, K. A., Young, A. B. and Penney, J. B. (1983) J. Neurosci. 3, 1189–1198
49 Pan, H. S., Penney, J. B. and Young, A. B. (1985) J. Neurochem. 45, 1396–1404
50 Kitai, S. L. (1981) in Handbook of Physiology (Vol. 2, The Nervous System) (Brooks, V. B., ed.), pp. 997–1015, American Physiological Society
51 Olson, L., Sieger, A. and Fuxe, K. (1972) Brain Res. 44, 283–288
52 Mensah, P. L. (1977) Brain Res. 137, 53–66
53 Graybiel, A. M. and Ragsdale, C. W. (1978) Proc. Natl Acad. Sci. USA 75, 5723–5726
54 Herkenham, M. and Pert, C. (1981) Nature 291, 415–418
55 Ragsdale, C. W. and Graybiel, A. M. (1981) Brain Res. 208, 259–266
56 Donohue, J. P. and Herkenham, M. (1986) Brain Res. 365, 397–403
57 Gerfen, C. R. (1984) Nature 311, 461–464
58 Gerfen, C. R. (1984) J. Comp. Neurol. 236, 454–476
59 Gerfen, C. R., Herkenham, M. and Thibault, J. (1987) J. Neurosci. 7, 3915–3934
60 Gerfen, C. R., Baimbridge, K. G. and Thibault, J. (1987) J. Neurosci. 7, 3935–3944
61 Jimenez-Castellanos, J. and Graybiel, A. M. (1987) Neuroscience 23, 223–242

62 Chesselet, M-F. and Graybiel, A. M. (1986) *Neuroscience* 17, 547–571

63 Bolam, J. P., Izzo, P. N. and Graybiel, A. M. (1988) *Neuroscience* 24, 853–875

64 Graybiel, A. M. (1986) in *Neuropeptides in Neurologic and Psychiatric Disease* (Martin, J. B. and Barchas, J. D., eds), pp. 135–161, Raven Press

65 Chesselet, M-F. and Robbins, E. (1989) *Neurosci. Lett.* 96, 47–53

66 Penny, G. R., Afsharpour, S. and Kitai, S. T. (1986) *Neuroscience* 17, 1011–1045

67 Feger, J. and Crossman, A. R. (1986) *Neurosci. Lett.* 49, 7–12

68 Beckstead, R. M. and Cruz, C. J. (1986) *Neuroscience.* 19, 147–158

69 Parent, A., Bouchard, C. and Smith, Y. (1984) *Brain Res.* 303, 385–390

70 Lehmann, J. and Langer, S. Z. (1983) *Neuroscience.* 10, 1105–1120

71 Pickel, V. M., Beckley, S. C., Joh, T. H. and Reis, D. J. (1981) *Brain Res.* 225, 373–385

72 Groves, P. M. (1980) *Proc. Natl Acad. Sci. USA* 77, 6926–6929

73 Whittier, J. R. and Mettler, F. A. (1949) *J. Comp. Neurol.* 90, 319–372

74 Carpenter, M. B., Whittier, J. R. and Mettler, F. A. (1950) *J. Comp. Neurol.* 92, 293–332

75 Crossman, A. R. (1987) *Neuroscience* 21, 1–40

76 Robertson, R. G., Farmery, S. M., Sambrook, M. A. and Crossman, A. R. (1989) *Brain Res.* 476, 317–322

77 Penney, J. B. and Young, A. B. (1986) *Movement Disorders* 1, 3–15

78 Crossman, A. R., Mitchell, I. J., Sambrook, M. A and Jackson, A. (1988) *Brain* 111, 1211–1233

79 Reiner, A. *et al.* (1988) *Proc. Natl Acad. Sci. USA* 64, 5733–5737

80 Hong, J. S., Yang, H-Y. T., Gillin, J. C. and Costa, E. (1980) *Adv. Biochem. Psychopharmacol.* 24, 223–232

81 Mocchetti, I., Naranjo, J. R. and Costa, E. (1987) *J. Pharm. Exp. Ther.* 241, 1120–1124

82 Bouras, C., Schultz, P., Constantinidis, J. and Tissot, R. (1986) *Neuropsychobiology* 16, 169–174

83 Young, W. S., Bonner, T. I. and Brann, M. R. (1986) *Proc. Natl Acad. Sci. USA* 83, 9827–9831

84 Augood, S. J., Emson, P. C. and Crossman, A. R. (1988) *Soc. Neurosci. Abstr.* 13, 390

85 Mitchell, I. J., Cross, A. J., Sambrook, M. A. and Crossman, A. R. (1986) *Neurosci. Lett.* 63, 61–65

86 Crossman, A. R., Mitchell, I. J. and Sambrook, M. A. (1985) *Neuropharmacology* 24, 587–591

87 Porrino, L. J. *et al.* (1987) *Life Sci.* 40, 1647–1664

88 Porrino, L. J., Palombo, E., Bankiewicz, K. S. and Kopin, I. J. (1987) *Soc. Neurosci. Abstr.* 13, 1362

89 Haber, S. N., Kowall, N. W., Vonsattel, J-P., Bird, E. D. and Richardson, E. P. (1986) *J. Neurol. Sci.* 75, 225–241

90 Gerfen, C. R. and Young, W. S. (1988) *Brain Res.* 460, 161–167

91 Reiner, A. (1986) *Brain Res.* 371, 155–161

92 Bannon, M. J., Elliott, P. J. and Bunney, E. B. (1987) *Mol. Brain Res.* 3, 31–37

93 Li, S. J., Sivam, S. P., McGinty, J. F., Huang, Y. S. and Hong, J. S. (1987) *J. Pharm. Exp. Ther.* 243, 792–798

94 Miller, W. C. and DeLong, M. R. (1988) in *Control Determinants of Age-Related Declines in Motor Function* (Joseph J. A., ed.), pp. 287–302, New York Academy of Sciences

95 Filion, M., Tremblay, L. and Bédard, P. J. (1989) in *Neural Mechanisms in Disorders of Movement* (Crossman, A. R. and Sambrook, M. A., eds), pp. 157–164, John Libbey

96 Pan, H. S. and Walters, J. R. (1988) *Synapse* 2, 650–659

97 Waters, C. M., Peck, R., Rossor, M., Reynolds, G. P. and Hunt, S. P. (1988) *Neuroscience* 25, 419–438

98 Agid, Y., Javoy-Agid, F. and Ruberg, M. (1987) in *Movement Disorders 2* (Marsden, C. D. and Fahn, S., eds), pp. 166–230, Butterworth

99 Leigh, R. J. and Zee, D. S. (1983) *The Neurology of Eye Movements* pp. 39–68, F. A. Davis

100 Hikosaka, O. and Sakamoto, M. (1986) *Exp. Brain. Res.* 63, 659–662

101 Leigh, R. J., Newman, S. A., Folstein, S. E. and Lasker, A. G. (1983) *Neurology* 33, 1268–1275

102 Lasker, A. G., Zee, D. S., Hain, T. C., Folstein, S. E. and Singer, H. S. (1987) *Neurology* 37, 364–370

103 Lasker, A. G., Zee, D. S., Hain, T. C., Folstein, S. E. and Singer, H. S. (1988) *Neurology* 38, 427–431

104 White, O. B., Saint-Cyr, J. A., Tomlinson, R. D. and Sharpe, J. A. (1983) *Brain* 106, 571–587

105 Hikosaka, O. and Wurtz, R. H. (1985) *J. Neurophysiol.* 53, 266–291

106 Hikosaka, O. and Wurtz, R. H. (1985) *J. Neurophysiol.* 53, 292–308

107 Kita, H. and Kitai, S. T. (1987) *J. Comp. Neurol.* 260, 435–452

108 Deng, S-Y., Goldberg, M. E., Seagraves, M. A., Ungerleider, L. G. and Mishkin, M. A. (1986) in *Adaptive Processes in Visual and Oculomotor Systems* (Keller, E. L. and Zee, D. S., eds), pp. 201–208, Pergamon

109 Bollen, E. L. *et al.* (1988) *J. Neurol. Neurosurg. Psychiatry* 51, 1081–1083

110 Lange, H., Thorner, G., Hopf, A. and Schroder, K. F. (1976) *J. Neurol. Sci.* 28, 401–425

111 Uhl, G. R., Navia, B. and Douglas, J. (1988) *J. Neurosci.* 8, 4755–4764

112 Aldridge, J. W., Anderson, R. J. and Murphy, J. T. (1980) *Can. J. Physiol. Pharmacol.* 58, 1192–1201

113 Crutcher, M. D. and DeLong, M. R. (1985) *Exp. Brain Res.* 53, 233–243

114 Crutcher, M. D. and DeLong, M. R. (1985) *Exp. Brain Res.* 53, 244–258

115 Caan, W., Perrett, D. I. and Rolls, E. T. (1984) *Brain Res.* 290, 53–65

116 Lidsky, T. I., Manetto, C. and Schneider, J. S. (1985) *Brain Res. Rev.* 9, 133–146

117 Hikosaka, O., Sakamoto, M. and Usui, S. (1989) *J. Neurophysiol.* 61, 780–798

118 Hikosaka, O., Sakamoto, M. and Usui, S. (1989) *J. Neurophysiol.* 61, 799–813

119 Hikosaka, O., Sakamoto, M. and Usui, S. (1989) *J. Neurophysiol.* 61, 814–832

120 Alexander, G. E., DeLong, M. R. and Strick, P. L. (1986) *Annu. Rev. Neurosci.* 9, 357–381

121 Alheid, G. F. and Heimer, L. (1988) *Neuroscience* 27, 1–40

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