MOTOR SYSTEMS II: THE BASAL GANGLIA

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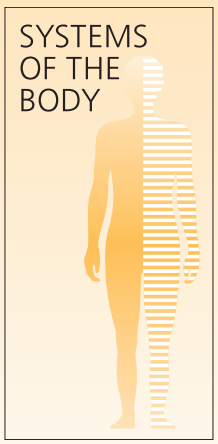

Chapter objectives

After studying this chapter you should be able to:

1. Describe the organisation of the basal ganglia and their connections with other central nervous system regions.
2. Describe the main symptoms and diseases associated with dysfunction of the basal ganglia, and their pathophysiology.
3. Outline the therapeutic management and prognosis of Parkinson's disease and Huntington's disease.
4. Treat the complications of treatment in Parkinson's disease.
5. Define the factors that may contribute to neurodegeneration.
6. Discuss the potential of cell replacement therapies in neurodegenerative diseases.

Introduction

The smooth execution of movements involving the trunk and the limbs, and the maintenance of posture, balance and normal gait, would not be possible without the coordinated activity of supraspinal centres, in particular the corticospinal neurones (the 'upper motor neurones', UMNs), the motor neurones in the ventral horn of the spinal cord (the 'lower motor neurones', LMNs) and an intact neuromuscular junction and muscle. Disturbances in the function of the major descending motor pathways are associated with paresis, paralysis or spasticity. Several other structures provide irreplaceable central input required for normal motor activity and are involved in its continuous control and coordination. The basal ganglia and the cerebellum are the main structures fulfilling these roles. They are at the interface between the intention and the execution of the movement. Neuronal activity in these structures is correlated temporally in a complex manner with motor activity. This chapter is dedicated to the basal ganglia, and illustrates how their dysfunction leads to subtle and specific alterations in motor performance, which can be ultimately severely debilitating. Disorders of the basal ganglia can lead to either hyperkinetic or hypokinetic manifestations. The cases described in this chapter illustrate both.

Motor systems II: The basal ganglia Box 1

Case history

Gavin Porter, a 57-year-old recently retired businessman, came to the doctor with his wife because of 'trembling', which affected his hands, in particular the right hand. Over the last year, the trembling had become worse, and he sometimes felt that his legs trembled very slightly too. He had also become rather slow in his movements, and sometimes sat for hours in an armchair, with a rather expressionless face. His wife found this irritating, and thought that his general mood had changed and he had become more withdrawn. He was finding it increasingly difficult to button and unbutton his shirt or tie his shoelaces. He had recently suffered two falls, one of which had resulted in a serious skin laceration on his head. When asked, he could not pinpoint a specific cause for these falls. The patient was otherwise in good health. He had taken early retirement in order to enjoy other activities, such as gardening and voluntary work for a charitable organisation. He seemed to be deeply worried about his progressive physical incapacity. In his moments of anxiety about the future, the trembling was much worse.

This case gives rise to the following questions:

① What is the cause of the symptoms (i.e. tremor, rigidity, slow movements, altered gait and balance)?
② Would the confirmation of the diagnosis require additional tests?
③ Are there any risk factors for developing this disease?

The basal ganglia: structure and organisation

General organisation

The basal ganglia consist of several subcortical interconnected nuclei that are involved in the initiation and execution of movement. They are the caudate nucleus, the putamen and the globus pallidus (in the telencephalon), the subthalamic nucleus (in the diencephalon) and the substantia nigra (in the mesencephalon). The relative locations of these structures are given in Chapter 1.

The caudate nucleus and the putamen are two nuclei that are interconnected and form the striatum. They are related structurally and have similar afferent and efferent connections. The globus pallidus has an internal (or medial) and an external (or lateral) division. The striatum receives afferents from the neocortex, the thalamus and the substantia nigra. The globus pallidus receives projections from the striatum and the subthalamic nucleus. The major output of the basal ganglia, which represents mainly projections from the globus pallidus (internal division) and substantia nigra, is directed to thalamic nuclei (in particular, the ventral anterior, ventral lateral and centromedian nuclei), which project to motor and prefrontal cortical areas. A smaller contingent of efferent fibres project to the pedunculopontine nucleus in the brainstem tegmentum, and to the superior colliculus. The substantia nigra can be subdivided into substantia nigra pars compacta and substantia nigra pars reticulata. The pars compacta contains neurones that project to the striatum, whereas the pars reticulata receives striatal input and provides the nigral output.

Circuits and neurotransmitters

The basal ganglia form a network of parallel loops and circuits that integrate the neuronal activity in cerebral regions (motor, oculomotor, limbic and associative), the basal ganglia nuclei and thalamic nuclei. Lesion or degeneration in the basal ganglia leads to diseases that present with a range of characteristic motor symptoms. Figure 10.1 summarises the functional organisation of the basal ganglia, and shows the major neurotransmitters present in afferent and efferent pathways.

The striatum is heterogeneous in structure, and consists of two main compartments: the matrix and the striosomes. These two compartments can be identified using the differential distribution of various neurochemical markers, such as the various subtypes of opioid receptors (mu (μ), delta (δ) and kappa (κ)) or acetylcholinesterase. A majority of neurones in the matrix and the striosomes are medium-sized projection neurones, which have highly collateralised axons, and dendrites endowed with dense spines. These cells are called 'medium spiny neurones'.

The cortex provides glutamatergic excitatory input to all striatal projection neurones. The cortical projections are organised somatotopically, innervating both the matrix and the striosomes. The striatum is connected with the globus pallidus and the substantia nigra through two distinct pathways (see Fig. 10.1).

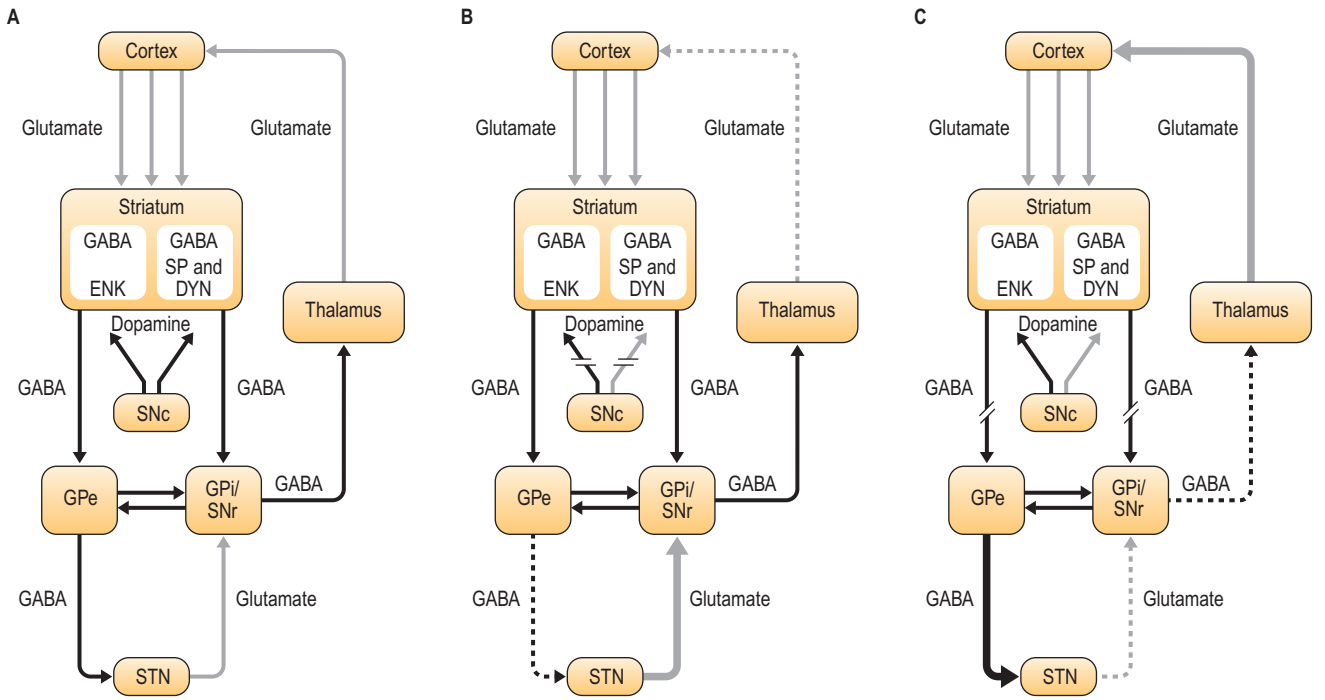

Fig. 10.1

Functional organisation of the basal ganglia. The diagrams illustrate the functional organisation of the basal ganglia circuits (A) under normal conditions, (B) in Parkinson's disease, and (C) in Huntington's disease. Broken lines indicate pathways that are hypoactive, and thick lines indicate pathways that are hyperactive. DYN, dynorphins; ENK, enkephalins; GABA, γ-aminobutyric acid; GPe, external globus pallidum; GPi, internal globus pallidum; SNc, substantia nigra compacta; SNr, substantia nigra reticulata; SP, substance P; STN, subthalamic nucleus.

1. The projection of the striatum to the globus pallidus (internal division) and substantia nigra pars reticulata is known as *the direct pathway*. The main neurotransmitter in this projection is γ-aminobutyric acid (GABA), which is co-localised with peptides such as substance P and dynorphins. The globus pallidus (internal division) or substantia nigra pars reticulata neurones project to the thalamus and are also GABAergic. The thalamic neurones, which contain glutamate, project to the cortex, thus closing the loop.
2. In the case of *the indirect pathway*, striatal GABAergic neurones (which also contain enkephalins) project to the globus pallidus (external division). The pallidal neurones are GABAergic and project to the subthalamic nucleus. The subthalamic nucleus glutamatergic neurones project to the globus pallidus (internal segment) and the substantia nigra pars reticulata. The circuit is ultimately completed through the GABAergic nigrothalamic projection, and then the glutamatergic thalamocortical projections, as in the case of the direct pathway. Another link between the direct and the indirect pathways is provided by neurones in the globus pallidus (external division), which establish contact with the globus pallidus (internal division) and substantia nigra pars reticulata through axon collaterals.

In summary, through these two pathways, the cortex can either increase (direct pathway) or decrease (indirect pathway) the excitatory thalamocortical projections. The presence of GABA as a main transmitter in the striatal efferents indicates that the striatal projection neurones will have an inhibitory effect on target cells in the substantia nigra and the globus pallidus. In contrast, the subthalamic nucleus is a source of excitation. Thus, through parallel loops and the balance between excitation and inhibition, the basal ganglia are involved in the transfer of information from the neocortex to the motor areas, in particular involving the premotor and supplementary motor areas. Finally, this results in facilitation or inhibition of the major descending motor pathways (e.g. corticospinal projection).

The substantia nigra pars compacta contains neurones that produce dopamine and project to the striatum, exerting a modulatory influence on the activity of striatal projection neurones that are involved in both the direct and the indirect pathways. Cortical input to medium spiny neurones can be controlled by dopaminergic fibres at the level of their dendrites and the dendritic spines. Dopamine appears to facilitate the activity of medium spiny neurones involved in the direct pathway, and to inhibit the activity of the medium spiny neurones involved in the indirect pathway. The striatum also contains several types of interneurone, e.g. cholinergic neurones. Nigral dopaminergic cells provide

inhibitory input to striatal cholinergic interneurones. Although the latter represent less than 10% of striatal cells, they exert important integrative functions in the striatum.

Parkinson's disease

Symptoms

Parkinson's disease (PD) was first described in 1817 by James Parkinson, a doctor with encyclopaedic interests, who was practising in the East End of London (Box 3). He based his monograph, 'An Essay on the Shaking Palsy', on the analysis of six cases. The cardinal features of this disease are motor: tremor (unilateral or bilateral), bradykinesia and rigidity. They may occur in isolation or in any combination (Box 2).

Tremor

The most prominent symptom is the resting tremor of the extremities that almost always accompanies the disease. The tremor has a characteristic frequency of 4–6 Hz and may begin in only one extremity and spread to the others. The distal joints of the limbs are preferentially affected. In the hand, the tremor is characteristic and involves the thumb and fingers rolling together. This is called a 'pill-rolling' tremor. The tremor is seen at rest and disappears during an intentional movement and during sleep. However, in the late stages of the disease, an 'active' tremor may emerge, with a frequency of 6–8 Hz. Tremor is exacerbated by anxiety. It primarily affects the hands, but it can also affect the lower limbs, jaw and lips.

Bradykinesia/akinesia

Bradykinesia is a slowing of normal movement. In the advanced stages of the disease, the patient becomes akinetic and shows almost no motor initiative. There is reduced arm-swinging when walking, reduced blinking, and various daily simple or complex tasks (e.g. washing, brushing the teeth, dressing and writing) can be affected. There is a gradual

Motor systems II: The basal ganglia Box 2

Case history

Gavin Porter was submitted to a full neurological examination. The patient was alert and oriented for time and place. Memory and general knowledge were appropriate for his age. His speech was slow and quiet, and rather monotonous, almost devoid of natural voice inflexions. His face was impassive and he rarely blinked. A mild resting tremor was present in the orofacial musculature, which diminished on speaking or swallowing.

His strength was intact, and deep tendon reflexes were normal. There was cogwheel rigidity upon passive movement of the limbs. The 'pill-rolling' 4–6-Hz tremor of the right thumb and index fingers was abolished by volitional movement. The patient's gait was rather slow. If given an abrupt push, he could not quickly restore his posture, and was at risk of falling. Cutaneous sensation and proprioception were intact.

The patient was diagnosed with Parkinson's disease and was prescribed L-dihydroxyphenylalanine (L-DOPA) with carbidopa. The doctor discussed the prognosis with the patient and his wife.

This case gives rise to the following questions:

① Why was the patient given L-DOPA with carbidopa, and are there any therapeutic alternatives?
② What is the long-term prognosis for this patient?

Motor systems II: the basal ganglia Box 3

James Parkinson (1755–1824): a physician and a radical thinker

James Parkinson was a general practitioner whose medical writings attest to his busy medical career. However, his intellectual interests were much wider. He was a respected palaeontologist and his two books 'Organic Remains of a Former World' and 'Outlines of Oryctology' were considered to be reference works by his contemporaries.

One of the most interesting aspects of James Parkinson's personality was his interest in politics and in social issues, as a member of several 'reform societies' and 'revolutionary clubs'. In his pamphlet entitled 'Revolution without Bloodshed; or Reformation Preferable to Revolt', published in 1794, he made several remarkably radical suggestions, such as the following: taxation should be in proportion to an individual's ability to pay; excise duties on the necessities of life should be abolished; workmen should not be imprisoned for uniting to obtain an increase in wages; punishment should be proportional to the severity of the crime; and provisions should be made to aid the aged and disabled who could not support themselves.

In 'An Essay on the Shaking Palsy', Parkinson gives a short definition of the disease, for which he also provides a Latin synonym—paralyis agitans: 'Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellect being uninjured.' He believed that the disease had 'escaped particular notice', and he hoped that other colleagues in the medical community would 'extend their searches' so that in the end they could 'point out the most appropriate means of relieving a tedious and most distressing malady'. Parkinson provided a graphic depiction of most of the symptoms of the disease, but apparently failed to appreciate features such as the significant muscular rigidity and the bradykinesia.

In the 19th century, important contributions to the description of this disease were made by the French neurologists Trousseau and Charcot, and their pupils. In recognition of James Parkinson's first incisive insight into this pathology, it is the eminent neurologist Jean-Martin Charcot who gave the disease the name of 'Parkinson's disease'.

Motor systems II: the basal ganglia Box 4

Case history

Gavin Porter continued to take L-DOPA with carbidopa for 6 years. Initially, the patient complained of nausea and tiredness. The drug improved his motor symptoms, especially during the first year. However, the dose administered had to be increased gradually, and during the last year he had started suffering from totally unpredictable complete immobility, although he was taking his medication regularly. Sometimes, episodes of immobility alternate with abnormal violent movement of his limbs, which he cannot control and finds extremely embarrassing. His sleep is disturbed and he complains of nightmares. He has frequent falls, and his wife finds it very difficult to lift him. He has become very apathetic and withdrawn, and has lost interest in any activities that he used to enjoy before he became ill.

The condition of this patient after 6 years of treatment raises the following questions:

① Was the prescription of L-DOPA with carbidopa the best choice when treatment was initiated?
② What could be done to alleviate the additional problems that have emerged in this case?

loss of normal facial movement and expression (Fig. 10.2). The speech is poorly articulated, and the voice is quiet and monotonous. Eating and swallowing become increasingly difficult. This may result in a tendency to drool (sialorrhoea). It is estimated that up to 70% of patients ultimately experience drooling, which may lead to dermatitis and aspiration.

Rigidity

Parkinsonian patients have increased muscle tone in flexor and extensor muscles and typically present resistance to passive movement of the limbs. This rigidity is due to inappropriate sensitivity of the muscles to stretching and an inability to obtain complete relaxation. The increased resistance to movement, combined with tremor, leads to the 'cogwheel' phenomenon. Manipulating the patient's limbs feels like manipulating a lead pipe; hence the term 'lead pipe' rigidity.

Other motor and non-motor manifestations of Parkinson's disease

Abnormalities of posture and gait are associated with this disease and tend to appear at a later stage. The gait of a parkinsonian patient becomes slow and shuffling, and the posture is flexed (see Fig. 10.2). Patients have a marked tendency to fall, which is partly due to the rigidity of limb and trunk muscles, but is also a consequence of the failure of

A B

Fig. 10.2

(A) Facial features and rigid posture of a patient with Parkinson's disease, drawn by Paul Richer, a former intern of Charcot's. From Richer (1888), in Koller WC, ed. Handbook of Parkinson's Disease. Marcel Dekker, 1987. (B) Characteristic flexed posture of a patient with Parkinson's disease. From Hauser RA, Zesiewicz TA. Parkinson's Disease—Questions and Answers. Merit Publishing International, Basingstoke, 1996.

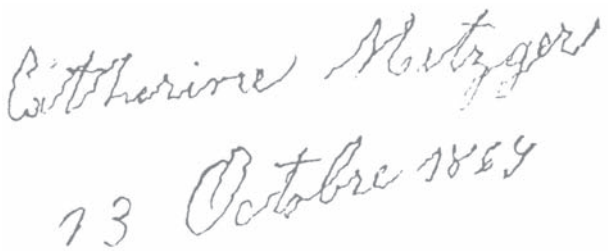

Fig. 10.3

A specimen of the handwriting of a patient with paralysis agitans under the care of Professor Charcot at the Hôpital St Louis in 1869. From Charcot (1872), in Koller WC, ed. Handbook of Parkinson's Disease. Marcel Dekker, 1987.

Table 10.1
Classification of parkinsonian syndromes

Idiopathic Parkinson's disease
Secondary parkinsonian syndromes
Infectious or post-infectious
Toxic
Drug-induced
Metabolic
Post-traumatic
Vascular
Tumour
Parkinsonian syndromes as part of other neurodegenerative disorders
Multiple system atrophy
Progressive supranuclear palsy
Corticobasal ganglionic degeneration
Diffuse Lewy body disease

postural adjustment movements, such as holding out the arms. As the disease progresses, 'freezing' also begins to appear. Patients become 'frozen' when trying to initiate walking, when passing through narrow spaces or when turning. This immobility can be overcome using sensory cues, such as drawing lines on the floor, and asking the patient to step over them.

The handwriting is altered (Fig. 10.3), and as the disease evolves it becomes small and indecipherable (micrographia). The skin may have a greasy appearance (seborrhoea), and constipation is common. Other autonomic abnormalities, such as urinary dysfunction (in particular, urinary incontinence due to bladder detrusor hyperreflexia), increased sweating and sexual dysfunction, are also encountered in parkinsonian patients.

In the late stages of the disease, many patients present with memory impairment, confusion and disorientation, and other features of dementia. Cognitive deficits represent a serious clinical problem and may be compounded by the unwanted effects of medication. It is estimated that dementia occurs in about 30% of parkinsonian patients, especially when the disease is diagnosed after the age of 70 years. Depression is also very common, at any stage of the disease, and may be reactive or part of the disease process.

The diagnosis of PD is made entirely on the basis of the symptoms, and does not involve additional laboratory investigations or imaging procedures. PD is diagnosed by: (1) finding at examination at least two out of several signs of a movement disorder (e.g. rigidity, resting tremor, bradykinesia, or problems with posture and gait); and (2) a positive response to dopamine substitution treatment.

The presentation in the patient described in Boxes 1 and 2 is typical of PD. His muscle strength is not affected, but his symptoms reflect difficulties in initiating and coordinating simple motor acts, and impaired posture and gait. The patient has no gross sensory impairment. This allows us to suggest that somatosensory pathways and cortical projection areas are intact. Furthermore, no muscle weakness, paralysis or spasticity are detected, which rules out a lesion of the UMNs or LMNs. The motor abnormalities have global effects on his performance of motor acts that form part of normal daily activities, and also his posture. This suggests an abnormality of motor systems that is not strictly localised. Furthermore, the onset of this dysfunction in motor performance is gradual, which rules out a vascular event and is suggestive of a neurodegenerative process. There is no pattern of relapse and remission, and the state of the patient is constantly deteriorating. Thus, as the pathological process may be continuous, it is important to understand the rationale of any treatment attempted and establish whether therapeutic strategies can at least slow down the neurodegenerative process and improve the patient's quality of life.

All parkinsonian syndromes (Table 10.1) are characterised by akinesia, rigidity and tremor at rest. It is important to differentiate between idiopathic PD (i.e. no detectable cause for the disease) and secondary parkinsonism, which may be due to other causes, such as vascular lesions in the basal ganglia, carbon monoxide or manganese poisoning, repeated head trauma ('boxer's parkinsonism'), or chronic blockade of dopaminergic receptors in the basal ganglia (use of neuroleptic drugs in schizophrenic patients). Idiopathic PD is an irreversible form of neurodegeneration. In the final stages of the disease, patients become bedridden, and death is due to medical complications (Table 10.2).

Pathophysiology of Parkinson's disease

The pathological hallmark of PD is the degeneration of the nigrostriatal dopaminergic pathway. Post-mortem analysis of specimens from patients with PD shows a striking absence of dopaminergic cells in the substantia nigra (Fig. 10.4). *In vivo* imaging of dopaminergic neurones, using, for example, a labelled precursor of dopamine, or markers of the dopamine neuronal reuptake system, also confirms the loss of striatal dopaminergic terminals (see below). Unfortunately, when the diagnosis is made, it is likely that more than 70–80% of dopaminergic neurones in the substantia nigra will have been already lost.

Table 10.2
Hoehn and Yahr staging of Parkinson's disease

Stage 1
Signs and symptoms on one side only
Symptoms mild
Symptoms inconvenient but not disabling
Usually presents with tremor of one limb
Friends have noticed changes in posture, locomotion and facial expression

Stage 2
Symptoms are bilateral
Minimal disability
Posture and gait affected

Stage 3
Significant slowing of body movements
Early impairment of equilibrium on walking or standing
Generalised dysfunction that is moderately severe

Stage 4
Severe symptoms
Can still walk to a limited extent
Rigidity and bradykinesia
No longer able to live alone
Tremor may be less than earlier stages

Stage 5
Cachectic stage
Invalidism complete
Cannot stand or walk
Requires constant nursing care

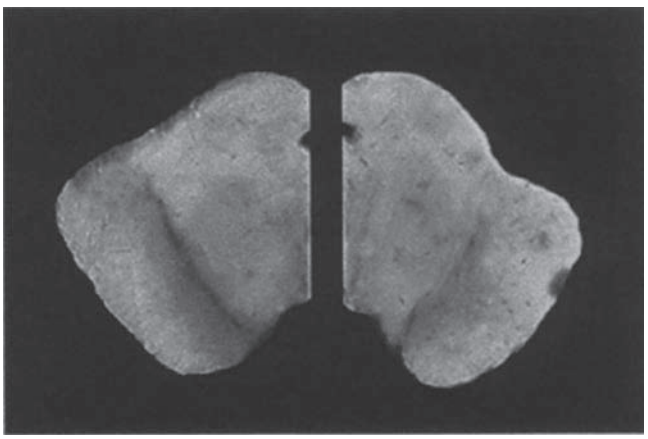

Fig. 10.4
Neurodegeneration in Parkinson's disease. Brain sections from the midbrain of a normal patient (left) and a Parkinson's disease patient (right). The Parkinson's disease hemisphere on the right shows a loss of melanised dopaminergic neurones in the substantia nigra. After Alexi et al. Progress in Neurobiology 2000; 60: 418.

Nigrostriatal dopaminergic neurones are tonically active and exert a modulatory influence on the striatum and the striatonigral and striatopallidal efferent pathways, through D_1 and D_2 receptors, respectively. According to the prevailing model, dopamine facilitates the activity of striatal projection neurones in the direct pathway through D_1 receptors, and inhibits the activity of striatal projection neurones in the indirect pathway via D_2 receptors. Under normal conditions, as a result of the activity in the two pathways, and the neuromodulatory effect of dopamine, there is adequate thalamocortical excitatory input (see Fig. 10.1A), and therefore facilitation of movement.

As illustrated in Figure 10.1B, the degeneration of the dopaminergic nigrostriatal cells leads to an imbalance in striatal output pathways. In particular, the loss of dopamine appears to lead to an increase in the activity of GABAergic striatal neurones in the indirect circuit, and a decrease in the activity of GABAergic striatal neurones in the direct circuit. The decreased inhibition in the direct pathway leads to increased activity of inhibitory GABAergic nigrothalamic projections, and diminished thalamocortical input, and therefore less activation of the motor cortex. The slowness of normal movement (bradykinesia) or lack of movement (akinesia) seen in parkinsonism is considered to be a consequence of this increased inhibition of thalamic neurones that project to the cortex. The increased activity in the indirect pathway leads ultimately to a similar consequence, through disinhibition of the subthalamic nucleus, which provides an excitatory glutamatergic projection to the substantia nigra. Therefore, in PD, the excitatory input to cortical areas involved in motor control is reduced. In other diseases of the basal ganglia, such as Huntington's disease, the opposite happens, leading to a hyperkinetic syndrome (see below). However, this is a simplified view of the functioning of the basal ganglia, and the limitations of this functional model become apparent as the disease evolves, and as complications of treatment emerge.

PD is characterised by the massive loss of nigrostriatal dopaminergic melanised cells, but the pathological examination may also reveal other abnormalities. For example, another characteristic, although not pathognomonic, finding in idiopathic PD is the presence of Lewy bodies. These are concentric eosinophilic cytoplasmic inclusions with peripheral halos and dense cores (Fig. 10.5), and are consistently immunoreactive to the proteins α-synuclein and ubiquitin. Lewy bodies are a frequent incidental finding at postmortem examination in elderly patients. In idiopathic PD, Lewy bodies and other signs of neurodegeneration can be found in the substantia nigra and also in other structures, such as the locus coeruleus, the nucleus basalis of Meynert, the pedunculopontine nucleus, the dorsal motor nucleus of the vagus, the cerebral cortex and the spinal cord. There is thus evidence that the pathophysiological neurodegenerative process in PD does not exclusively affect dopaminergic systems; as the disease evolves, significant changes in noradrenergic, serotonergic and cholinergic neurones can be detected.

Causes of Parkinson's disease

PD is one of the most common neurological disorders leading to major disability and ultimately death. It affects 1/1000 of the population and is rising in both incidence and prevalence, due to increased longevity and improvements

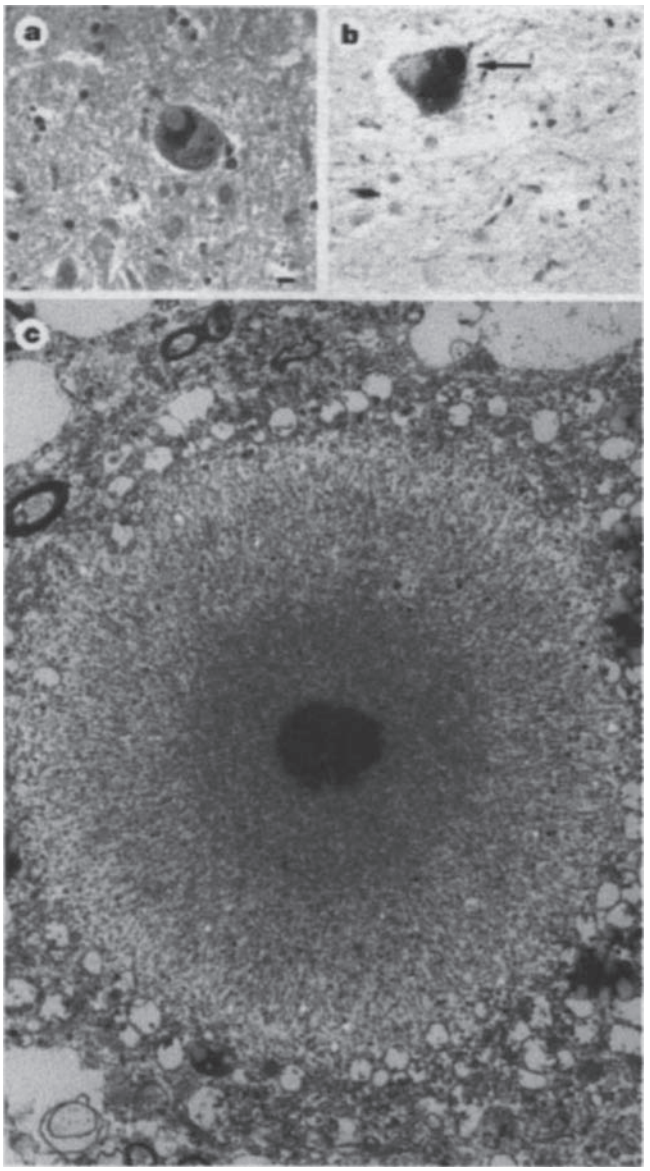

Fig. 10.5

Lewy bodies. These inclusions are visualised using (a) haematoxylin and eosin, (b) an antibody against α-synuclein, and (c) electron microscopy. After Flint Beal. Nature Reviews in Neuroscience 2001; 2: 326.

Oxidative stress in Parkinson's disease

(*a*) $DA + O_2 + H_2O \xrightarrow{MAO} 3,4\text{-DHPA} + NH_3 + H_2O_2$

(*b*) $DA + O_2 \longrightarrow SQ^{\bullet} + {}^{\bullet}O_2^{-} + H^+$

$DA + {}^{\bullet}O_2^{-} + 2H^+ \longrightarrow SQ^{\bullet} + H_2O_2$

(*c*) $H_2O_2 + 2GSH \longrightarrow GSSG + 2H_2O$

(*d*) $H_2O_2 + Fe^{+2} \longrightarrow OH^{\bullet} + OH^{-} + Fe^{+3}$

Fig. 10.6

Oxidation processes in the basal ganglia. Examples of reactions involving dopamine and leading to formation of free radicals, and oxidation of protective substances such as glutathione. DA, dopamine; H_2O_2, hydrogen peroxide; 3,4-DHPA, 3,4-dihydroxyphenylacetaldehyde; OH^-, hydroxyl ion; OH•, hydroxyl radical; GSH, reduced glutathione; GSSG, oxidised glutathione; Fe^{2+}, ferrous iron; Fe^{3+}, ferric ion; $\bullet O_2^-$, superoxide radical; MAO, monoamine oxidase; SQ•, quinones.

in treatment. It affects both sexes equally, and occurs in all races. It is the second most common neurodegenerative disease, affecting 1% of the population above the age of 65 years.

The cause of primary PD is unknown. There is evidence for a role of both environmental and genetic factors. The effects of exposure to certain toxic agents, such as manganese oxide, and also the association of parkinsonism with viral encephalitis lethargica, clearly show that environmental precipitating causes cannot be ruled out. A minority of cases are associated with a clear genetic abnormality. Thus, mutations in α-synuclein are associated with autosomal-dominant PD, whereas mutations in the gene *parkin* are associated with autosomal-recessive juvenile-onset PD. However, the majority of cases of PD are not associated with a clearly defined cause. Dopaminergic cell loss in the substantia nigra occurs naturally with increasing age, but appears to be accelerated in PD. This may be due to oxidative stress, or to selective neurotoxins, which may preferentially target dopaminergic cells that are rich in neuromelanin, such as those in the substantia nigra. The oxidation of endogenous dopamine leads to the formation of H_2O_2 and highly reactive free radicals (Fig. 10.6). Neuromelanin, which gives nigral dopaminergic cells their characteristic colour, is an oxidation product of dopamine. Furthermore, post-mortem studies show evidence of oxidative damage and decreased activity of complex I of the mitochondrial electron transport chain in the substantia nigra in PD. Patients also have increased iron levels in the substantia nigra pars compacta and a reduced concentration of the binding protein transferrin, which makes iron more available for oxidation reactions. Finally, there is also evidence of increased lipid peroxidation in PD.

Observations on the development of severe parkinsonian symptoms in young drug addicts following accidental exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) also lend strength to a neurotoxic cause of PD, through exposure to environmental neurotoxins. MPTP had been produced during the illicit synthesis of the opiate pethidine. MPTP is very lipophilic, and crosses the blood–brain barrier (BBB) without difficulty. It is converted into a toxic metabolite, the 1-methyl-4-phenylpyridinium ion (MPP^+), through the action of the enzyme monoamine oxidase type B (MAO_B). MPP^+ is taken up by the plasma membrane dopamine transporter into nigral dopaminergic neurones, and selectively destroys them by inhibiting complex I of the respiratory chain in mitochondria (Fig. 10.7). The administration of MPTP in primates replicates all the clinical signs of PD, including tremor, rigidity, akinesia and postural instability.

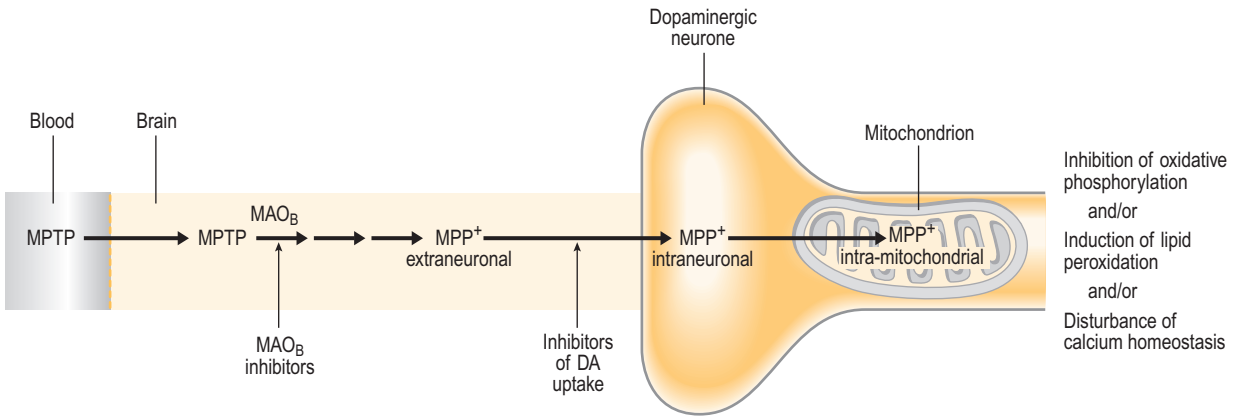

Fig. 10.7

The fate of MPTP after systemic administration, and mechanisms underlying its toxicity for dopaminergic neurones. MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP$^+$, 1-methyl-4-phenylpyridinium ion; MAO$_B$, monoamine oxidase B; DA, dopamine.

Motor systems II: the basal ganglia Box 5

Dopaminergic systems and receptors

Dopamine is a catecholamine neurotransmitter associated with numerous physiological and pathological processes, including motor activity, emotion, cognition, addiction, endocrine regulation, and cardiovascular and renal function. Because of the variety of effects induced by dopamine centrally or at the periphery, one of the major challenges is to develop dopaminergic drugs that affect selectively these processes.

In the central nervous system, dopamine-containing neurones form three main pathways (Fig. 10.8).

① The nigrostriatal pathway: cell bodies lie in the substantia nigra, and the axons innervate the caudate nucleus and the putamen. This system is mainly involved in the integration of sensory information and the control of movement.

② The mesolimbic/mesocortical pathway: cell bodies are situated mainly in the ventral tegmental area (which is medial to the substantia nigra), and the axons innervate the nucleus accumbens (considered by some authors to be the most ventral part of the striatum), the olfactory tubercle, the amygdala and the cortex (in particular the prefrontal and cingulate cortices). This system is associated with reward and reinforcement mechanisms (involved in addiction), emotional behaviour and cognition.

③ The tuberoinfundibular pathway: cell bodies are located in the arcuate nucleus in the hypothalamus, and the axons project to the median eminence. In this system, dopamine acts as a modulator of the hypothalamic–pituitary axis (for example, it inhibits prolactin secretion).

Dopamine exerts its effects through five receptor subtypes: D_1, D_2, D_3, D_4 and D_5. These can be grouped into two classes: the D_1-like receptors (this includes the D_1 and D_5 receptors) and the D_2-like receptors (this includes the D_2, D_3 and D_4 receptors). Additional complexity is conferred by the existence of multiple receptor isoforms within a receptor subtype. All dopamine receptors are G-protein-coupled receptors. They are associated with several signal transduction systems (Fig. 10.9). The two main classes of receptor may exert opposite effects on the same signalling mechanism. For example, D_1-like receptors activate adenylate cyclase, whereas D_2-like receptors inhibit this enzyme. The two families of dopamine receptors differ in their pharmacological profiles, which is reflected in shifts in the affinity of certain agonists and antagonists.

D_1 and D_2 receptors are the predominant dopamine receptor subtypes in the central nervous system. They are present at moderate to high densities in the projection areas of the dopaminergic pathways. Dopamine receptors can be located postsynaptically or presynaptically. In the latter case, they may act as autoreceptors, which regulate dopaminergic signalling, but also as heteroreceptors, through their location on non-dopaminergic terminals.

There are already indications that the diversity in dopamine receptors will not be limited to the five subtypes characterised so far. Further information on the structural and transductional properties of each receptor type, as well as their specific roles in signalling, will be essential in order to develop drugs with fewer unwanted effects than those available at present.

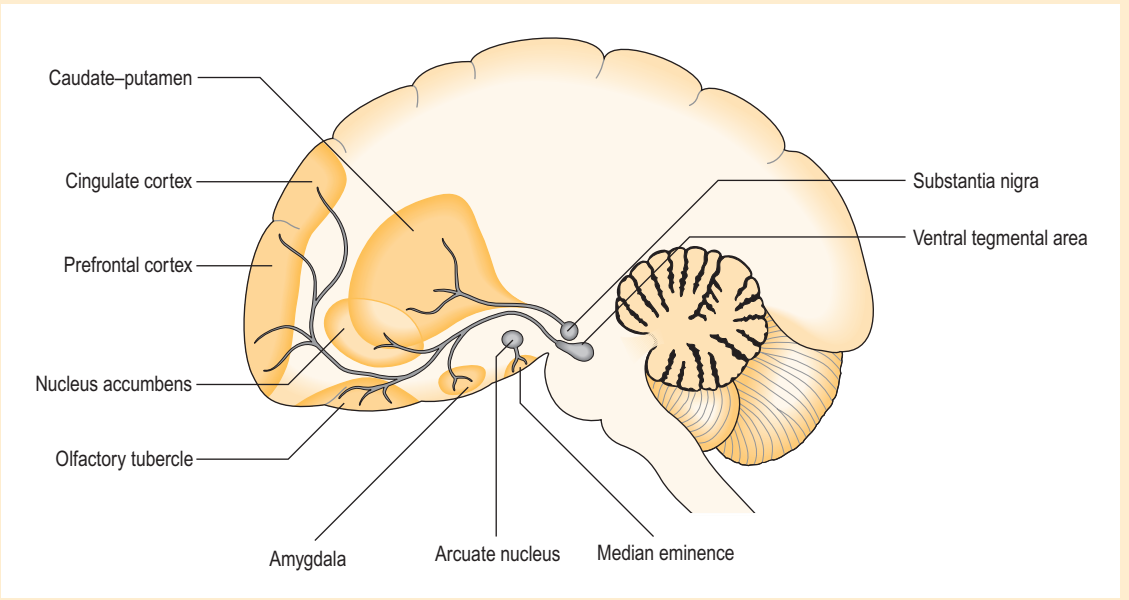

Fig. 10.8

Dopaminergic projections in the central nervous system.

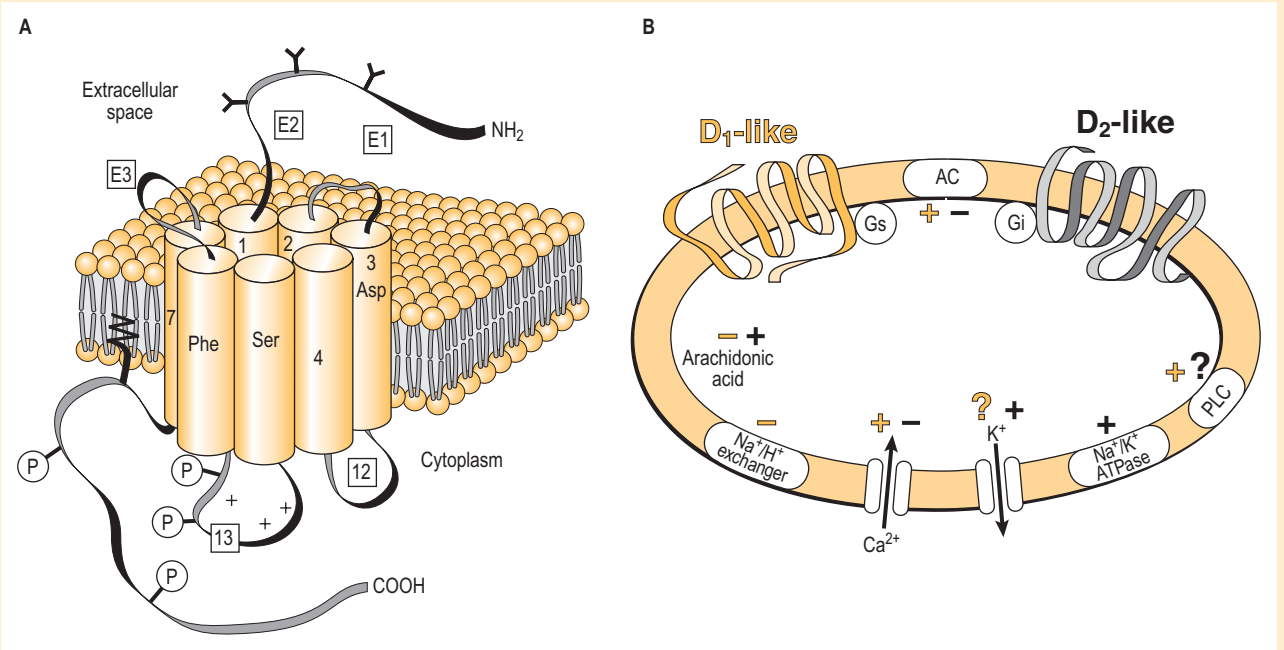

Fig. 10.9

(A) Dopamine receptor structure. The diagram represents the structural features of D_1 receptors. Residues involved in dopamine binding are highlighted in the transmembrane domains. Potential phosphorylation sites are represented on the third (I3) intracellular loop and on the COOH terminus of the receptor. Potential glycosylation sites are represented on the NH_2 terminal. E1–E3, extracellular loops; 1–7, transmembrane domains; I2–I3, intracellular loops. After Missale et al. Physiological Reviews 1998; 78(1): 92. (B) Signal transduction pathways of dopamine receptors. AC, adenylate cyclase; PLC, phospholipase C; Gs and Gi, G-proteins. After Missale et al. Physiological Reviews 1998; 78(1): 198.

Treatment of Parkinson's disease

The pharmacological treatment of PD attempts to compensate for the loss of nigral dopaminergic cells and the imbalance in input thus created in the striatum (Box 5). Dopamine replacement therapy has been the major treatment for PD for the last three decades.

Dopaminergic medication

L-DOPA

Dopamine does not cross the blood–brain barrier (BBB), so direct systemic supplementation with dopamine is not therapeutically useful. L-DOPA (or levodopa), a precursor in the biosynthetic pathway of dopamine (Fig. 10.10), can be used in order to increase dopamine concentrations in the deficient areas. After oral administration, L-DOPA is absorbed into the systemic circulation through the energy-dependent saturable activity of a neutral amino acid transporter in the duodenum. The same transporter also facilitates the passage of L-DOPA across the BBB. In the brain, L-DOPA is taken up into dopaminergic neurones and can be converted into dopamine in the remaining cells in the substantia nigra. Conversion of L-DOPA into dopamine is catalysed by an aromatic amino acid decarboxylase (also called DOPA decarboxylase). This conversion occurs not only in the brain but also at the periphery. The conversion at the periphery can be blocked by co-administration of a DOPA decarboxylase inhibitor such as benserazide or carbidopa. L-DOPA can also be metabolised at the periphery by catechol-*O*-methyl transferase (COMT). More recently, it has been shown that the use of L-DOPA with COMT inhibitors, such as entacapone, significantly improves the central bioavailability of the precursor (Fig. 10.11) and leads to smoother kinetics. It is also important to be aware that, as other amino acids compete with L-DOPA for intestinal absorption through the same transporter, dietary protein intake can change the bioavailability of L-DOPA.

Prior to the introduction of L-DOPA into clinical use, the life expectancy following diagnosis was about 10 years. L-DOPA has increased the quality of life, particularly in the early years of treatment, and has improved survival. L-DOPA remains the most efficacious anti-parkinsonian drug, and almost all patients respond to this drug. However, the use of L-DOPA is associated with a wide range of unwanted effects and long-term additional drug-induced problems: nausea, vomiting, postural hypotension, hallucinations and paranoid delusions, and complex acute and delayed motor complications, such as dyskinesias (abnormal involuntary movements) and the 'on–off' effect (Table 10.3).

The nausea and vomiting are due to conversion of L-DOPA into dopamine at the periphery and activation of dopamine receptors in the chemoreceptor trigger zone (in the area postrema in the medulla), which is outside the BBB. This can be largely prevented by co-administration of L-DOPA with DOPA decarboxylase inhibitors (in this example, L-DOPA is given to the patient with carbidopa). Nausea can also be treated with domperidone, which is a dopamine receptor antagonist that does not cross the BBB. Hallucinations are due to the increased production of dopamine in mesolimbic dopaminergic neurones. They can be treated with neuroleptics such as clozapine.

Table 10.3
Complications of L-DOPA therapy

Motor fluctuations (end-of-dose deterioration, 'on–off' phenomenon, delayed or no 'on' responses)
Dyskinesias ('on'-period dyskinesia, biphasic dyskinesias, 'off'-period dystonias)
Non-motor complications (tingling, pain, akathisia, autonomic dysfunction)
Neuropsychiatric complications (hallucinations, delirium, mood changes, hypersexuality, sleep fragmentation, nightmares)

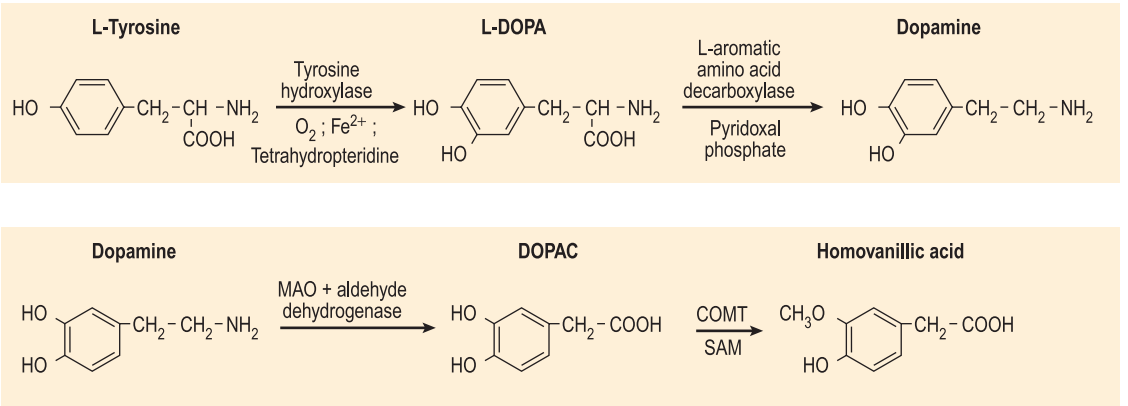

Fig. 10.10

Biosynthesis and metabolism of dopamine. L-DOPA, L-dihydroxyphenylalanine; DOPAC, dihydroxyphenylacetic acid; COMT, catechol-***O***-methyltransferase; SAM, ***S***-adenosylmethionine; MAO, monoamine oxidase.

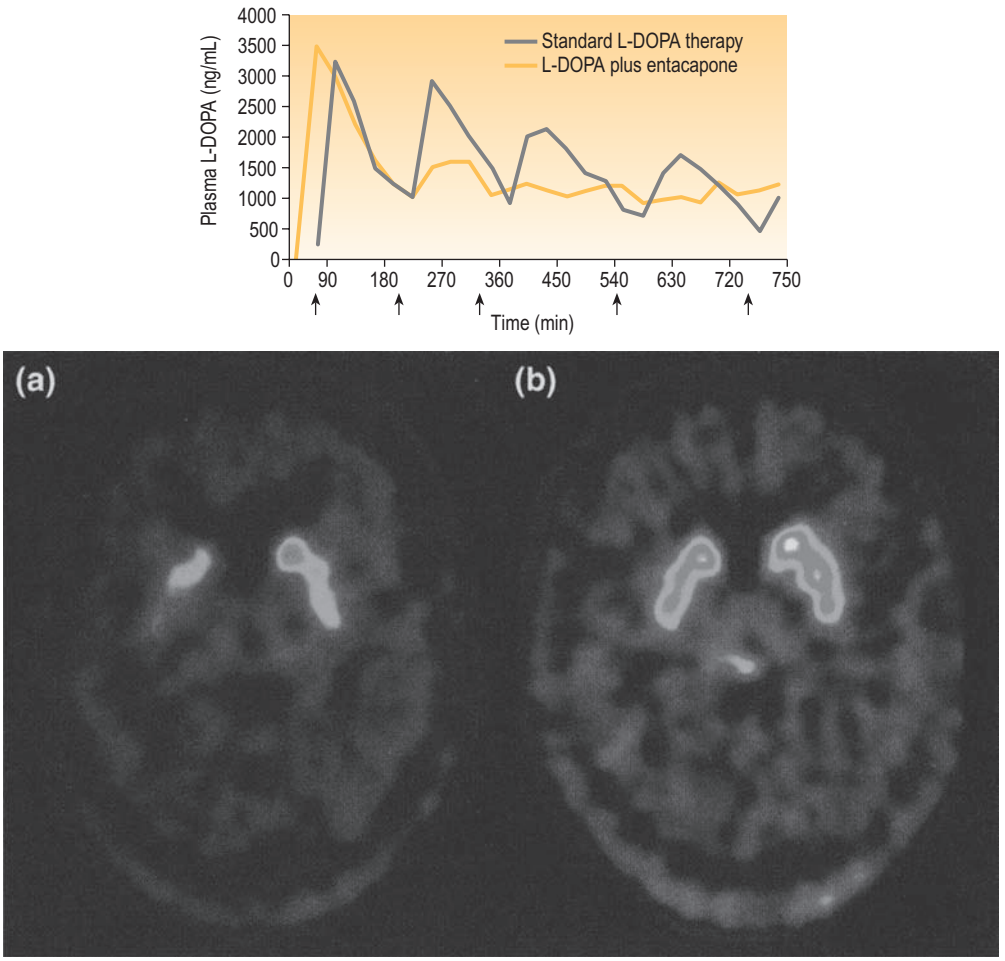

Fig. 10.11

Top: Plasma L-DOPA levels in a patient with fluctuating Parkinson's disease, with or without entacapone. In this patient, the addition of entacapone permitted a 30% reduction in the dose of L-DOPA and almost total elimination of 'off' time. After Olanow et al. Trends in Neurosciences 2000; 23(10 Suppl): S123. Bottom: PET studies on [^{18}F]6-L-fluorodopa accumulation in a subject with Parkinson's disease (Hoehn and Yahr stage 3): (a) a scan after administration of L-DOPA without entacapone; (b) a scan at the same level after administration of L-DOPA with entacapone. Note that striatal uptake of fluorodopa is enhanced in the presence of entacapone. After Olanow et al. Trends in Neurosciences 2000; 23(10 Suppl): S123.

The motor complications of long-term therapy with L-DOPA are particularly disabling. The pathogenesis of late complications is only partly understood. They occur in 75–80% of patients who have received L-DOPA for more than 4–5 years, and can occur in patients who have received it for less time than this. They do not appear immediately after initiation of L-DOPA therapy, but require chronic exposure to L-DOPA, with intermittent dosing. Dyskinesias can be subdivided into chorea-like movements (hyperkinetic, purposeless dance-like movements) and dystonias (intense and sustained muscle contractions). Peak-dose dyskinesia and wearing-off dystonias are due to fluctuations in the level of dopamine produced intracerebrally after each dose of L-DOPA. The 'on–off' effect refers to dramatic fluctuations in motor performance, which are not always related to the intake of L-DOPA. Patients experience normal mobility ('on') followed suddenly by total 'freezing' ('off'). This has been likened to switching a light on and off. It is clear now that a majority of patients treated with L-DOPA for several years also experience an increasingly rapid wearing-off of the clinical benefit after each dose of precursor (also called 'end-of-dose deterioration'). This may be due to the altered pharmacokinetics of L-DOPA, with exacerbations of peaks and troughs in the concentration of dopamine produced, and changes in the sensitivity of dopaminergic receptors. In patients with marked motor fluctuations, benefit may be derived from controlled-release forms of L-DOPA/carbidopa or L-DOPA/benserazide. Their bioavailability is 70–80% that of normal L-DOPA/carbidopa or L-DOPA/benserazide combinations. In extreme cases, L-DOPA may also be administered continuously by the intravenous or intraduodenal routes. Surgical intervention may also be attempted to relieve

L-DOPA-induced dyskinesia and dystonia (see below). Furthermore, several new drugs are at present under development to specifically treat L-DOPA-induced dykinesias. These include α_2-receptor antagonists, glutamate receptor antagonists (acting at 4-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-D-aspartate (NMDA) and metabotropic glutamate receptors), 5-HT_{1A} receptor antagonists and D_4 receptor antagonists. If proven successful, they may in future make the benefit of L-DOPA prescription less short-lived.

Dopaminergic agonists

Dopamine agonists, such as bromocriptine, pergolide, lisuride, pramipexole and ropinirole, can be used when adequate control of the symptoms can no longer be achieved with L-DOPA/carbidopa, or significant unwanted effects of this combination (dystonia and dyskinesia) have developed. A significant number of patients may improve on dopaminergic agonists alone, especially at the beginning of the disease. It has also been suggested that the early introduction of dopaminergic agonists might be beneficial in delaying the onset of dyskinesia and 'on–off' effects seen with L-DOPA. These agents do not have the same efficacy as L-DOPA, so ultimately L-DOPA must be prescribed. Dopamine agonists can induce nausea and vomiting, which can be treated with domperidone. They can also induce hallucinations, cardiac arrhythmias and postural hypotension. Their potential for causing dyskinesia and dystonia is much less than that of L-DOPA/carbidopa (Fig. 10.12). Furthermore, agonists with longer half-lives, such as cabergoline (Table 10.4), appear to be the best, and avoid the peaks and troughs in plasma concentration seen with short-acting compounds such as L-DOPA and other agonists. A pulsatile profile of stimulation of receptors is considered to be at least partly responsible for the onset of dyskinesias after the administration of short-acting compounds. Possible changes underlying dyskinesia are summarised in Figure 10.13. Apomorphine is an agonist that can be used subcutaneously (intermittent or continuous administration) in patients who experience major loss of efficacy of L-DOPA. Agonists in clinical use at present do not discriminate between D_1 and D_2 receptors, or have a slightly higher affinity for D_2 receptors. New agonists (e.g. cabergoline) also have affinity for D_3 receptors.

Monoamine oxidase B inhibitors

MAO_B is an isoform of monoamine oxidase that is involved in dopamine metabolism (see Fig. 10.10). The inhibition of MAO_B by selegiline (alternative name deprenyl) can

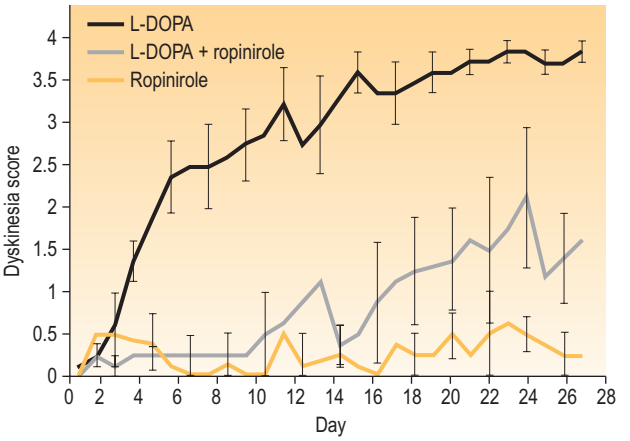

Fig. 10.12

Dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys. Frequency of dyskinesia in MPTP-treated marmosets treated with L-DOPA, ropinirole, or L-DOPA with ropinirole. Note the significantly higher dyskinesia score in L-DOPA-treated animals. After Olanow et al. Trends in Neurosciences 2000; 23(10 Suppl): S120.

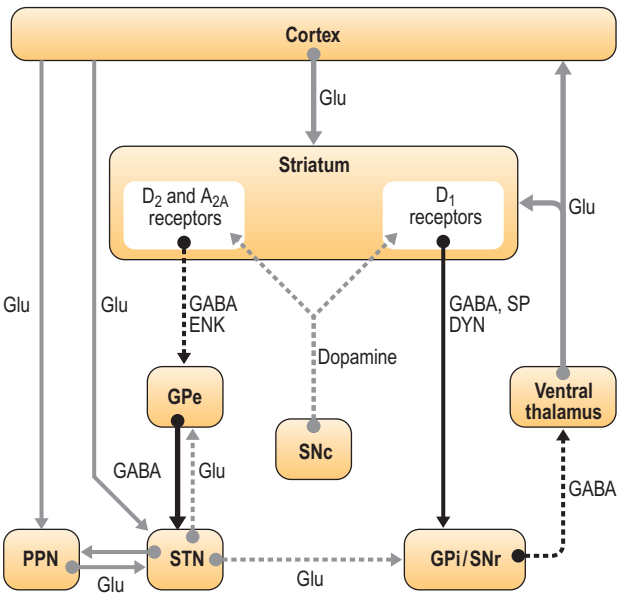

Fig. 10.13

Basal ganglia connectivity in Parkinson's disease with dyskinesia. Thickened lines indicate abnormally increased neurotransmission, and dotted lines indicate abnormally decreased neurotransmission. A_{2A}, adenosine A_2 receptors; DYN, dynorphins; ENK, enkephalins; GABA, γ-aminobutyric acid; Glu, glutamate; GPe, external globus pallidum; GPi, internal globus pallidum; PPN, pedunculopontine nucleus; SNc, substantia nigra compacta; SNr, substantia nigra reticulata; SP, substance P; STN, subthalamic nucleus. After Brooks. Trends in Neurosciences 2000; 23(10 Suppl): S102.

Table 10.4
Half-life of dopaminergic drugs

L-DOPA/carbidopa	1–1.5 h
Bromocriptine	12–15 h
Pergolide	7–16 h
Ropinirole	6–8 h
Pramipexole	8–12 h
Cabergoline	>24 h