Pathogenesis of Parkinson's disease

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The importance of genetic aspects, ageing, environmental factors, head trauma, defective mitochondrial respiration, altered iron metabolism, oxidative stress and glutamatergic overactivity of the basal ganglia in the pathogenesis of Parkinson's disease (PD) are considered in this review.

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Introduction

The cause of Parkinson's disease (PD) is still unknown. The reinterpretation of twin studies had led to an increased interest in the possible role of heredity in the aetiology of PD. Selective destruction of dopaminergic neurones in the substantia nigra (SN) of humans and other primates is caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); it has therefore been hypothesized that a similar environmental toxin may play a role in the pathogenesis of PD. No such agent, however, has yet been identified. It is possible that a combination of genetic and environmental factors is the underlying cause of PD. Research on the neurotoxicity of MPTP has shown that the biochemical changes occurring in the brain in PD are similar to those produced by MPTP, namely inhibition of mitochondrial function. Furthermore, an increased iron load in the SN may contribute to the neuronal damage occurring in PD.

Genetic factors in Parkinson's disease

The search for evidence supporting a genetic aetiology for PD has long been hampered by uncertainties regarding nosology and neuropathology of the disease. Twin studies showing similar concordance rates between monozygotic and dizygotic twins with PD suggested that inheritance plays little or no part in the aetiology of the disease [1–3]. A reappraisal of the twin study by Ward *et al.* [1] concluded that a genetic component of PD cannot be ruled out [4]. Two large kindreds of familial PD have shown an autosomal dominant mode of transmission of clinically rather atypical, but pathologically classical PD [5]. A recent study using strict diagnostic criteria has shown that familial PD exists and is clinically indistinguishable from sporadic PD [6••]. If it is assumed that familial PD has a genetic basis, pedigree and segregation analysis in this study suggest autosomal dominant inheritance of a gene or genes with reduced penetrance as the most likely explanation. The similar sex ratio of patients and the excess of paternal transmission in the study by Maraganore *et al.* [6••] argue against X-linked inheritance. This is contrary to the hypothesis of a major genetic susceptibility to PD conferred by mitochondrial genes [7].

The role of genetic factors in the aetiology of sporadic cases of PD remains to be determined. Recent studies confirming the existence of familial PD suggest that the genetic hypothesis of PD should be explored further. Clinically unaffected twins of patients with PD should be carefully examined for signs of parkinsonism over a prolonged period of time as a large range of variation in age of onset and clinical features may occur within families. In view of this, [^{18}F]fluorodopa positron emission tomography scanning in asymptomatic siblings of patients with PD may detect the preclinical stage of the disease and genetic linkage studies should be performed in large kindreds consisting of a sufficient number of affected cases.

Ageing and Parkinson's disease

The hypothesis that PD is the result of an interaction between age-related nigrostriatal dopamine loss and secondary insults has recently been challenged. Postmortem measurement of striatal dopamine uptake terminals demonstrated decreasing striatal innervation with ageing, but no difference in the rate of terminal loss between young and old patients was found [8]. Positron emission tomography studies produced conflicting results with regard to alterations of striatal [^{18}F]fluorodopa

Abbreviations

AMPA—α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; **CPP**—(±)-2-carboxypiperazine-4-yl-propyl-1-phosphonic acid; **MPP$^+$**—1-methyl-4-phenyl-pyridinium; **MPTP**—1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; **NBQX**—6-nitro-7-sulphamobenzo[f]quinoxaline-2,3-dione; **NMDA**—N-methyl-D-aspartate; **PD**—Parkinson's disease; **SN**—substantia nigra.

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uptake with age. In cross-sectional studies of normal volunteers both a decrease [9] and no change [10] in striatal dopamine uptake have been found. The failure to show an age-related dopamine depletion in normal subjects makes an acute event as the cause of PD more likely. In a longitudinal study, a reduction in dopamine uptake was observed in both normal subjects and PD patients, and the rate of change was comparable in both groups [11••]. This data suggest that PD results from sudden damage of unknown origin in the past rather than from a gradual acceleration of dopamine loss. The suggestion that ageing does not contribute significantly to the evolution of PD is supported by histological studies showing that in normal brains the number of pigmented SN cells is reduced by only 4.7 to 6.0% per decade from the fifth to the ninth decade of life [12••].

Epidemiology of Parkinson's disease

Two recent studies [13•,14•] and the majority of previous investigations show that the incidence of PD is greater in men than in women. A recent Canadian study [14•] based on hospital stays compared the geographic distribution of PD. The disease displayed an uneven regional distribution in the average annual prevalence rates with a higher prevalence in the westernmost provinces of Canada. This offers support for environmental influences in the aetiology of PD and a starting point for a more involved survey comparing environmental differences between high and low prevalence provinces.

The discovery that the neurotoxin MPTP induces neuropathological and neurochemical alterations as well as clinical signs very similar to those of PD suggests that a similar chemical compound may cause PD [15,16]. The chemical structure of MPTP is similar to that of many pyridines found in the environment and, in particular, to that of chemicals commonly used in agriculture [17]. Several case-control studies have shown associations between PD and rural living, well-water drinking and exposure to herbicides and pesticides [18]. A recent case control study from Kansas, USA of 19 families having two or more siblings with PD has shown that rural residence and drinking well-water, but not farming and herbicide exposure, were increased in 38 patients with PD compared with 38 control subjects [19••]. Another case-control study from Calgary compared 130 patients with PD with 260 randomly selected community controls and did not find an increased risk for the development of PD associated with a history of rural residence, farm living or well-water drinking in early childhood or at any time during the first 45 years of life [20••]. Possible explanations for the conflicting findings are difficulties with regard to the diagnosis of PD, different definitions of positive exposure or length and timing of the exposure period. An alternative explanation is that geographic variation exists in the relationship between rural environmental factors and risk of developing PD.

Head trauma in Parkinson's disease

Significant head trauma as a possible cause of PD has been established. Head trauma does not, however, appear to be a primary aetiologic agent in PD and the syndrome of post-traumatic parkinsonism is rare [21]. Recently the relationship between head trauma and PD has been investigated [22•]. PD patients reported a higher frequency of head trauma or of head injury associated with alterations of consciousness in the past than control subjects. The duration of time between head injury and the year of the survey was approximately 30 years in both groups.

Head trauma may be a risk factor in the aetiology of PD. A major possible flaw of retrospective survey studies is recall bias. Patients with chronic disease are more likely to ponder the possible connections between life events and disease onset. This view is supported by the fact that increased incidence of head trauma has been reported in other neurological disorders. The role of head trauma in the pathogenesis of PD remains unclear. Prospective studies are therefore needed.

Defective mitochondrial respiration

The discovery that the neurotoxin MPTP destroys dopamine-containing neurones in the SN and causes parkinsonian motor deficits in humans and other primate species has led to further insights into the pathogenetic processes involved in PD. MPTP itself is not the active toxin but has to be converted by monoamine oxidase B into 1-methyl-4-phenyl-pyridinium (MPP^+). MPP^+ is concentrated in mitochondria where it poisons complex I of the mitochondrial respiratory chain [23]. MPP^+ synthesis from MPTP may also induce the formation of free radical species, imposing oxidative stress with consequent lipid membrane peroxidation [24].

The recent discovery of complex I deficiency in the SN of idiopathic PD [25] raised the possibility that the disease may be caused by a similar mechanism to MPTP-induced parkinsonism. Complex I deficiency in PD appears to be anatomically specific for the SN [26•] and probably reflects some active process selectively affecting this area. The absence of complex I deficiency in multiple system atrophy [26•] indicates that this defect is not the result of neuronal degeneration in the SN. An MPTP-like substance may inhibit complex I of mitochondrial energy metabolism. Alternatively, complex I deficiency could result from a defective gene encoding abnormal complex I proteins or a factor that regulates gene transcription. Using immunoblotting analysis, mitochondrial DNA has been reported to be normal in the SN, putamen and cortex of patients with PD [27]. Studies using the polymerase chain reaction have shown an increase in deletion of striatal mitochondrial DNA in both PD and senescence [28,29•]. The deleted genome may therefore not be a specific property in PD but rather the result of ageing. Further investigations are required to clarify whether the

observed mitochondrial dysfunction is the result of enzyme inhibition by toxins, gene deletion or reduced gene expression.

Analysis of mitochondrial oxidative phosphorylation enzymes from muscle biopsies showed complex I defects in four out of six PD patients and a complex IV defect in one out of six [30•]. Mitochondrial DNA analysis revealed no deletions or insertions in any of the patients. These findings suggest that PD is a systemic disorder of oxidative phosphorylation.

Altered iron metabolism and oxidative stress

Free radicals are known to promote membrane fluidity, lipid peroxidation and alteration in cellular calcium homeostasis. Free radicals generated from oxidation reactions may contribute to the pathogenesis of PD by reacting with membrane lipids and causing lipid peroxidation, membrane damage and neuronal death. Lipid peroxidation is increased in the SN of subjects with PD [31] suggesting that free radicals are generated.

It is generally accepted that an increase in iron content occurs in the SN in PD [32•,33••–35••]. There is histochemical and biochemical evidence that in PD the total iron content and the iron (III) content are selectively increased in the SN pars compacta but not in the SN pars reticulata [33••]. The increased iron content may contribute to the selective elevation of basal lipid peroxidation in the SN. Free iron may be available and may participate in auto-oxidation of dopamine resulting in generation of H_2O_2 and oxygen free radicals.

Hydrogen peroxide is normally cleared from the brain by the glutathione system. In the presence of iron or superoxide free radical, H_2O_2 can be reduced to form the toxic hydroxyl free radical. The activity of striatal monoamine oxidase B, which catalyzes the oxidation of dopamine, increases with age [36]. Increased dopamine metabolism could increase the formation of H_2O_2 and exceed the capacity of the glutathione system. Glutathione and glutathione peroxidase activity have been reported to be decreased in the SN of PD patients [37] and erythrocyte glutathione peroxidase has been shown to be lower in advanced cases of PD than at early stages of the disease [38•]. Evidence supporting a state of oxidative stress in PD is summarized in Table 1.

The progression of PD may therefore be retarded by neuroprotective agents including selective monoamine oxidase B inhibitors, selective calcium-channel antagonists and iron chelators [44••].

Table 1. Evidence supporting a state of oxidative stress in the substantia nigra in Parkinson's disease.

Findings	Reference
Disturbed mitochondrial respiratory function with reduction in the activity of complexes I and III	[25,26•,27,39,40]
Altered cellular calcium homeostasis with resulting decrease in calcium-binding protein	[41,42]
Decreased glutathione and glutathione peroxidase activity leading to a reduced ability to scavenge hydrogen peroxide derived from oxidative deamination and auto-oxidation of dopamine	[37]
Increased iron content resulting in a potential excess of radical-generating free iron	[32•,33••–35••]
Increased mitochondrial superoxide dismutase activity, perhaps reflecting an attempt to compensate for oxidative stress	[43]
Increased peroxidation of membrane lipids inducing membrane damage and cell death	[31]

Excitatory amino acids and Parkinson's disease

Dopamine has been shown in animals to be of less importance in the regulation of psychomotor functions than was previously believed, for example, clear behavioural activation can be produced in rodents following suppression of glutamatergic neurotransmission even in the absence of brain dopamine [45,46••]. Cortical excitatory glutamatergic pathways innervate the putamen, caudate nucleus and subthalamic nucleus and dopaminergic projections originating in the SN terminate in the putamen and caudate nucleus.

The degeneration of the dopaminergic nigrostrial neurones in PD leads to profound alterations in the neuronal activity within the basal ganglia–thalamo-cortical circuit. The ultimate result of dopamine loss appears to be an increased inhibitory output from the basal ganglia to the thalamus. The action of dopamine seems to be different on two subpopulations of striatal output neurones; dopamine depletion therefore leads to different effects. In the MPTP model of PD in the monkey, there is a tonic increase in the neuronal activity of the globus pallidus internus, the subthalamic nucleus and the SN pars reticulata, whereas the activity of the globus pallidus externus, decreases [47]. Overactivity of the glutamatergic projection neurones in the subthalamic further enhances neuronal activity in the basal ganglia output nuclei, globus pallidus internus and SN pars reticulata. The increased globus pallidus internus output results in an increased inhibition of the ventrolateral thalamus and thalamocortical neurones. The resulting reduction of cortical activation accounts for akinesia and rigidity (Fig. 1).

According to the simplified functional model of the motor circuit, an equilibrium exists between the glutamatergic system projecting from the cortex via the subthalamic nucleus to the basal ganglia output nuclei and the γ-aminobutyric acid (GABA)ergic striatopallidal and

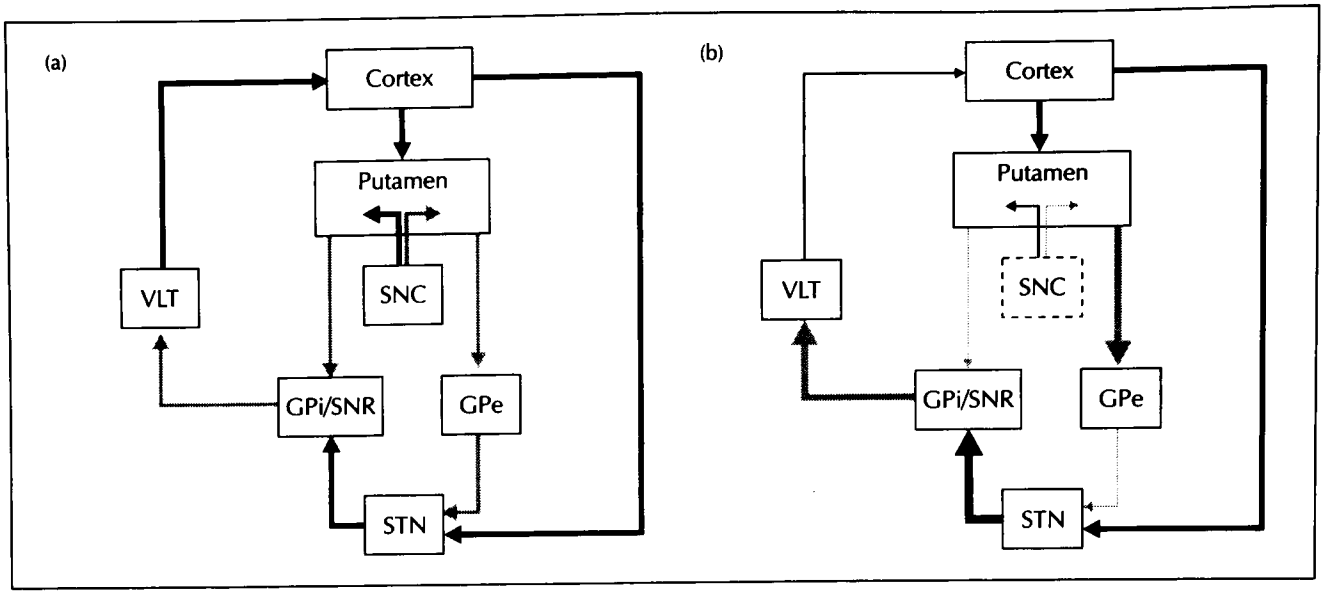

Fig. 1. Simplified diagram of the basal ganglia–thalamo-cortical circuit, with black arrows indicating excitatory connections and shaded arrows representing inhibitory connections. Alterations in the activity of connections are indicated by changes of arrow width. (a) Normal: the nigrostriatal projections are postulated to have differential effects on the two striatal output systems. The putamen is connected with the globus pallidus internus (GPi) by direct and indirect projections. (b) Alterations after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment: the substantia nigra pars compacta (SNC) is damaged, the result of which is increased subthalamic nucleus (STN) and GPi activity leading to increased inhibition of the thalamo-cortical projection and ultimately parkinsonian motor deficits. GPe, globus pallidus externus; SNR, substantia nigra pars reticulata; VLT, ventrolateral thalamus. Published with permission [48].

striatonigral projections to these nuclei. In PD the equilibrium is shifted towards the side of the glutamatergic system. In this model, excessive output from the subthalamic nucleus is postulated to play a critical role in the pathophysiology of PD. This hypothesis was recently confirmed by the finding that both lesions of the subthalamic nucleus [48] and local blockade of excitatory amino acid transmission in the globus pallidas internus [49••] can reverse parkinsonism in MPTP-treated monkeys.

Systemic administration of glutamate antagonists may also be effective in the treatment of PD. The synaptic responses of glutamate are mediated by different receptor subtypes, three of which are coupled to ionophores. They are activated preferentially by N-methyl-D-aspartate (NMDA), kainate, quisqualate or α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA). The selective AMPA antagonist 6-nitro-7-sulphamobenzo[f]quinoxaline-2,3-dione (NBQX) and the competitive NMDA antagonist (±)-2-carboxypiperazine-4-yl-propyl-1-phosphonic acid (CPP) are not effective in animal models of PD when given alone but ameliorate the parkinsonian symptoms when co-administered with a threshold dose of levodopa [49••]. These synergistic effects of NBQX and CPP were observed both in the rat with unilateral 6-hydroxydopamine lesions of the SN and in MPTP-treated common marmosets [50••].

The finding that antiglutamatergic treatment improves the parkinsonian state in experimental animals supports the hypothesis that glutamatergic overactivity in the basal ganglia as a result of striatal dopamine loss is an important pathogenetic mechanism during the course of the disease. This indicates the potential efficacy of new pharmacological strategies for the treatment of patients with PD [51•,52•].

Conclusion

Research on MPTP neurotoxicity has identified a mechanism by which selective destruction of the dopamine-containing neurones in the SN can be brought about and this process may be responsible for the neuropathological alterations occurring in PD. Further investigations are needed to establish whether changes of the mitochondrial energy metabolism and oxidative stress are specific to PD, whether they occur at early stages of the disease and whether they can be influenced by drug therapy. Novel pharmacological strategies may be introduced aimed at preventing or slowing the rate of progression of the disease, protecting against free radical damage and antagonizing central overactivity of excitatory amino acids.

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