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Neurotoxicity and neuroprotection in Parkinson's disease

K. W. Lange[1], **M. B. H. Youdim**[2], and **P. Riederer**[1]

[1] Department of Clinical Neurochemistry, University of Würzburg, Würzburg, Federal Republic of Germany
[2] Department of Pharmacology, Faculty of Medicine, Technion, Haifa, Israel

Summary. Recent findings of impaired mitochondrial function, altered iron metabolism and increased lipid peroxidation in the substantia nigra in Parkinson's disease emphasize the significance of oxidative stress and free radical formation in the pathogenesis of the disease. Future research will focus on improvements in neuroprotective therapy to prevent or slow the rate of progression of Parkinson's disease. Possible neuroprotective strategies include free radical scavengers, monoamine oxidase-B inhibitors, iron chelators and glutamate antagonists.

Introduction

Parkinson's disease is characterized pathologically by loss of catecholaminergic neurones in the brainstem (German et al., 1989; Jellinger, 1991). The degeneration of the melanin-pigmented dopaminergic neurones of the substantia nigra pars compacta is the neuropathological basis of the movement disorders characterizing Parkinson's disease. When about 80% of the neurones are lost the motor symptoms appear (Riederer and Wuketich, 1976). The cause of degeneration of dopamine-containing neurones in Parkinson's disease is unknown.

The search for evidence supporting a genetic aetiology for Parkinson's disease 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 Parkinson's disease suggested that inheritance plays little or no part in the aetiology of the disease (Ward et al., 1983; Marsden, 1987; Marttila et al., 1988). A reappraisal of the twin study by Ward et al. (1983) concluded that a genetic component of Parkinson's disease cannot be ruled out (Johnson et al., 1990). Two large kindreds of familial Parkinson's disease have shown an autosomal dominant mode of transmission of clinically rather atypical, but pathologically classical

Parkinson's disease (Golbe et al., 1990). A recent study using strict diagnostic criteria has shown that familial Parkinson's disease exists and is clinically indistinguishable from sporadic Parkinson's disease (Maraganore et al., 1991). The role of genetic factors in the aetiology of sporadic cases of Parkinson's disease remains to be determined.

The incidence of Parkinson's disease increases with advancing age. However, the hypothesis that Parkinson's disease is the result of an interaction between age-related nigrostriatal dopamine loss and secondary insults has recently been challenged. Post-mortem 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 (Scherman et al., 1989). Positron emission tomography studies produced conflicting results with regard to alterations of striatal [^{18}F]fluorodopa uptake with age. In cross-sectional studies of normal volunteers both a decrease (Martin et al., 1989) and no change (Sawle et al., 1990) 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 Parkinson's disease more likely. In a longitudinal study, a reduction in dopamine uptake was observed in both normal subjects and patients with Parkinson's disease, and the rate of change was comparable in both groups (Bhatt et al., 1991). This data suggests that Parkinson's disease 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 Parkinson's disease is supported by histological studies showing that in normal brains the number of pigmented substantia nigra cells is reduced by only 4.7 to 6.0% per decade from the fifth to the ninth decade of life (Gibb and Lees, 1991). Parkinson's disease may be the result of a toxic insult during early life which reduces the number of dopaminergic neurones in the substantia nigra and the further decline of this number with ageing may finally produce the symptoms of the disease. Recent research on the pathogenesis of Parkinson's disease has focussed on the possible involvement of neurotoxins as a cause of Parkinson's disease.

Involvement of neurotoxins in Parkinson's disease

The discovery that the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces neuropathological and neurochemical alterations as well as clinical signs very similar to those of Parkinson's disease suggests that a similar chemical compound may cause Parkinson's disease (Ballard et al., 1985; Burns et al., 1985). 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 (Snyder and D'Amato, 1986). Several case-control studies have shown associations between Parkinson's disease and rural

living, well-water drinking and exposure to herbicides and pesticides (Tanner and Langston, 1990). A recent case-control study from Kansas has shown that rural residence and drinking well-water, but not farming and herbicide exposure, were increased in patients with Parkinson's disease compared with control subjects (Wong et al., 1991). Another case-control study from Calgary compared patients with Parkinson's disease with randomly selected community controls and did not find an increased risk for the development of Parkinson's disease 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 (Semchuk et al., 1991). Possible explanations for the conflicting findings are difficulties with regard to the diagnosis of Parkinson's disease, 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 the risk of developing Parkinson's disease.

Although environmental toxins may contribute to the aetiology of Parkinson's disease, chronic intoxication by selective exposure to a specific agent is unlikely because Parkinson's disease is widespread throughout the world. Endogenous substances with neurotoxic actions similar to those of MPTP may exist; possible compounds include tetrahydroisoquinolines (Saitoh et al., 1988) and beta-carbolines (Drucker et al., 1990). It is also possible that MPTP and related agents do not cause Parkinson's disease but rather provide clues to the mechanism underlying neuronal death in this disease.

Oxidation reactions in Parkinson's disease

It has been suggested that excess free radical formation plays a role in the pathogenesis of Parkinson's disease (Graham et al., 1978; Spina and Cohen, 1989; Youdim et al., 1990). There are two theoretical concepts of how oxidation reactions and toxic oxygen species may contribute to the degenerative process underlying neuronal death in Parkinson's disease.

The first concept proposes that excess formation of free radicals occurs as a result of toxin action. The neurotoxin MPTP expresses its toxicity as a consequence of its oxidation to the 1-methyl-4-phenyl-pyridinium ion (MPP^+) by monoamine oxidase type B (MAO-B) (Chiba et al., 1984; Salach et al., 1984; Heikkila et al., 1985). Inhibition of the oxidation of MPTP to MPP^+ by MAO-B inhibitors such as deprenyl and pargyline prevents the neurotoxic effects of MPTP and the development of a parkinsonian syndrome in animal models of Parkinson's disease (Cohen et al., 1984; Heikkila et al., 1984; Langston et al., 1984b). If Parkinson's disease is caused by MPTP-like compounds, oxidation reactions may be essential for the development of Parkinson's disease. The toxic effects of MPP^+ are thought to be caused by its ability to inhibit complex I of the mitochondrial respiratory chain (Nicklas

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

– Disturbed mitochondrial respiratory function with reduction in complex I and III activities
– Altered cellular calcium homoeostasis with decrease in calcium-binding protein
– Decreased glutathione and glutathione peroxidase activity leading to a reduced ability to scavenge hydrogen peroxide derived from oxidative deamination and auto-oxidation of dopamine
– Increased iron content resulting in a potential excess of radical-generating free iron
– Increased mitochondrial superoxide dismutase activity, perhaps reflecting an attempt to compensate for oxidative stress
– Increased peroxidation of membrane lipids inducing membrane damage and cell death

et al., 1985; Vyas et al., 1986) resulting in decreased cellular adenosine triphosphate levels (Di Monte et al., 1986) and altered intracellular calcium content (Kass et al., 1988). Alterations in the homoeostasis of intracellular calcium are closely linked with altered cell function and cell death (Orrenius et al., 1989). Recent studies have shown that the calcium binding protein calbindin is selectively decreased in the substantia nigra in Parkinson's disease (Iacopino and Christakos, 1990). The inhibition of mitochondrial function may also lead to increased formation of free radical species.

The second concept concerning the importance of oxidation reactions and free radical formation in the pathogenesis of Parkinson's disease relates to the metabolism of dopamine. Dopamine can be oxidatively metabolized by the enzyme monoamine oxidase (MAO). The polymerization of auto-oxidative products of dopamine leads to the formation of neuromelanin and the characteristic pigmentation of the substantia nigra. Both auto-oxidation of dopamine and oxidative deamination by MAO result in the formation of hydrogen peroxide (H_2O_2). Under normal circumstances H_2O_2 is rather inert and never accumulates in the brain or other organs. H_2O_2 is normally cleared from the brain by the glutathione system. Glutathione peroxidase catalyzes the reaction of H_2O_2 with glutathione (GSH) to form glutathione disulfide (GSSG):

$$H_2O_2 + 2\,GSH \xrightarrow{\text{Glutathione peroxidase}} 2\,H_2O + GSSG$$

In the presence of iron, H_2O_2 can be reduced to form the toxic hydroxyl free radical (Fenton reaction):

$$H_2O_2 + Fe^{2+} \rightarrow {}^{\cdot}OH + OH^- + Fe^{3+}$$

MAO activity in the brain increases with ageing (Fowler et al., 1980) and this may lead to an increase in the formation of H_2O_2 which could exceed the capacity of the glutathione system. Similarly, a reduction in glutathione or glutathione peroxidase could prevent the clearance of H_2O_2 generated from normal dopamine metabolism. The result of either of these mechanisms could be the insufficient clearance of H_2O_2 and the production of hydroxyl free radicals which may cause damage to dopamine-containing cells.

Recent research on the biochemical pathology of Parkinson's disease indicates that free radicals generated from oxidation reactions are important for the neuronal loss in the substantia nigra in Parkinson's disease (see Table 1).

Oxidative stress as a cause of Parkinson's disease

The recent discovery of complex I deficiency in the substantia nigra in Parkinson's disease (Schapira et al., 1990a) raised the possibility that the disease may be caused by a similar mechanism to MPTP-induced parkinsonism. Complex I deficiency in Parkinson's disease appears to be anatomically specific for the substantia nigra (Schapira et al., 1990b) and probably reflects some active process selectively affecting this area.

The absence of complex I deficiency in multiple system atrophy (Schapira et al., 1990b) indicates that this defect is not the result of neuronal degeneration in the substantia nigra. 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 substantia nigra, putamen and cortex of patients with Parkinson's disease (Lestienne et al., 1990). Studies using the polymerase chain reaction have shown an increase in deletion of striatal mitochondrial DNA in both Parkinson's disease and senescence (Ikebe et al., 1990; Lestienne et al., 1991). The deleted genome may therefore not be a specific property of Parkinson's disease but rather the result of ageing.

The inhibition of mitochondrial function may lead to increased formation of radical species in several ways including an overspill of superoxide radicals from the electron transport chain. Free radicals are capable of reacting almost instantaneously with membrane lipids and causing lipid peroxidation, alterations in membrane fluidity and eventually cell death. In the substantia nigra of patients with Parkinson's disease an increase in the basal formation of malondialdehyde, a stable intermediate in the peroxidative process, coupled with a decrease in the levels of polyunsaturated fatty acids, the substrate for lipid peroxidation, has been shown (Dexter et al., 1989a).

Superoxide dismutase converts superoxide, a free radical involved in MPTP neurotoxicity, to hydrogen peroxide. In the substantia nigra in

Parkinson's disease an increase in the activity of the mitochondrial form of this enzyme has been reported with no change in total or cytosolic enzyme activity (Saggu et al., 1989). This data suggests an increased formation of superoxide radicals in proximity to mitochondria inducing an increase in superoxide dismutase activity.

Iron-melanin interaction in Parkinson's disease

The brain contains a substantially higher concentration of iron than of any other metal (Youdim, 1988). Within the brain iron shows an uneven distribution with high levels in the substantia nigra, striatum and globus pallidus (Spatz, 1924; Hallgren and Sourander, 1958; Hill and Switzer, 1984; Riederer et al., 1989). Although the function of a regionally high brain iron content is unknown the homoeostasis of brain iron is believed to be necessary for normal brain function (Youdim, 1989; Youdim et al., 1989). Free tissue metal such as Fe^{2+} or Cu^{2+} can initiate the formation of cytotoxic oxygen free radicals resulting from its interaction with hydrogen peroxide and leading to promotion of membrane lipid peroxides. The mobilization of intracellular and mitochondrial calcium by iron is thought to be directly involved in cellular toxicity in oxidative stress (Braughler, 1988).

It is now generally accepted that a selective increase in iron content occurs in the substantia nigra in Parkinson's disease (Riederer et al., 1989; Dexter et al., 1989b; Jellinger et al., 1990; Sofic et al., 1991). Histochemical and biochemical analyses have shown that this increase in iron is localized in the pars compacta of the substantia nigra (Jellinger et al., 1990; Sofic et al., 1991). Iron-induced oxidative stress and lipid peroxidation can proceed optimally with either Fe^{2+} or Fe^{3+} provided mechanisms exist to facilitate the interconversion of iron between its redox states. Fe^{3+}, when formed, can be converted to Fe^{2+} in the presence of endogenous chelators such as adenosine diphosphate or melanin. Such an interaction makes Fe^{3+} even more reactive as an initiator of $^{\cdot}OH$ production. An endogenous iron chelator in the substantia nigra with a high affinity for iron is melanin. The substantia nigra pars compacta contains excessive amounts of neuromelanin produced by the autooxidation of dopamine and it is the melanin-containing dopaminergic neurones that degenerate in Parkinson's disease (Hirsch et al., 1988). Melanin is able to bind high amounts of metals but is under normal circumstances thought to participate in scavenging metal-induced free radicals as it does in the skin. However, melanin has high affinity binding sites for Fe^{3+} and increased amounts of Fe^{3+} have been found in neuromelanin of substantia nigra pars compacta neurones (Jellinger et al., 1992). Melanin-iron interaction leads to a potentiation of iron-induced basal lipid peroxidation in the presence of synaptosomal preparations of the rat brain cortex (Ben-Shachar and Youdim, 1990). The potentiation of melanin-iron-induced lipid peroxidation has been

attributed to the ability of melanin to reduce Fe^{3+} to Fe^{2+} while H_2O_2 drives a Fenton-like reaction with liberation of cytotoxic hydroxyl radicals (Ben-Shachar and Youdim, 1990). This process is thought to occur with Fe^{3+} and not Fe^{2+} (Pilas et al., 1988). The alteration in the ratio of Fe^{2+} to Fe^{3+} from 2:1 in the substantia nigra pars compacta of control subjects to 1:1 in parkinsonian patients (Sofic et al., 1991) is compatible with optimal conditions necessary for induction of a lipid peroxidation process (Braughler et al., 1986):

$$Fe^{3+} + \text{melanin} \rightarrow Fe^{2+} + \text{melanin}^{+}$$

These findings suggest that oxidative stress induced by iron-melanin interaction is a possible mechanism in the aetiology of Parkinson's disease without involving an endogenously or exogenously derived neurotoxin (Youdim et al., 1989).

Recent findings of animal experiments support the hypothesis that iron initiates dopaminergic neurodegeneration in Parkinson's disease. Injection of iron into the substantia nigra of rats causes a selective decrease of striatal dopamine and impairment of dopamine-related behavioural responses (Ben-Shachar and Youdim, 1991). Furthermore, 6-hydroxydopamine lesions of nigrostriatal dopamine neurones can be prevented by administration of iron chelators (Ben-Shachar et al., 1991). 6-Hydroxydopamine is thought to exert its neurotoxic activity via the formation of oxygen free radicals liberated from H_2O_2 as a result of its oxidation (Heikkila and Cohen, 1972; Sachs and Jonsson, 1975; Graham et al., 1978). The prevention of 6-hydroxydopamine toxicity by iron chelators implies therefore that endogenous free iron interacts with H_2O_2 generated.

Glutathione in Parkinson's disease

The findings of altered iron metabolism, impaired mitochondrial function and increased lipid peroxidation support the importance of oxidative stress for neuronal degeneration in the substantia nigra of patients with Parkinson's disease. These alterations do not explain, however, why nigral neurones are not protected by normal detoxification mechanisms. Toxic compounds formed in the brain are normally inactivated by various protective mechanisms. These mechanisms, however, may be impaired in Parkinson's disease, e.g. reduced activity of catalase, peroxidase and glutathione peroxidase and diminished concentrations of reduced glutathione (GSH) have been found in the substantia nigra in Parkinson's disease (Ambani et al., 1975; Perry et al., 1982; Kish et al., 1985; Riederer et al., 1989). GSH in the substantia nigra and enzymes that utilize GSH for free radical detoxification, such as glutathione peroxidase and glutathione-S-transferase, probably play an important role in protecting dopamine-containing nigral neurones from damage by MPTP or from other

MPTP-like neurotoxins which may cause Parkinson's disease in humans. Reduced levels of GSH have been found in the brainstem of mice following administration of MPTP (Yong et al., 1986; Riederer et al., 1987).

In Parkinson's disease the surviving neurones of the nigrostriatal pathway exhibit an increased dopamine turnover (Hornykiewicz and Kish, 1986). This could theoretically be associated with oxidative stress as a consequence of increased production of hydrogen peroxide during the oxidative deamination of dopamine by MAO. In the mouse, a reserpine-induced increase in presynaptic dopamine turnover caused a rise in the level of oxidized glutathione (glutathione disulfide, GSSG). The formation of GSSG could be blocked by the MAO-A inhibitor clorgyline (Spina and Cohen, 1989). Oxidative metabolism of dopamine in the brain is associated with the production of hydrogen peroxide and may be reflected by oxidation of GSH to GSSG (Sies, 1983; White et al., 1986). A recent study has shown that the concentration of GSH is reduced in the substantia nigra of patients with Parkinson's disease compared with control subjects while the concentration of GSSG is unaltered (Sofic et al., 1992). The decreased concentration of nigral GSH in Parkinson's disease could be the result of neuronal loss, since a positive correlation has been found between the GSH content and the severity of neuronal depletion in the parkinsonian brain (Riederer et al., 1989). However, neuronal degeneration does not appear to be the only explanation for the GSH reduction observed, since GSSG was not decreased to the same extent as GSH and the percentage of GSSG of the total glutathione was slightly increased (Sofic et al., 1992). The reduction in GSH levels may provide a target for therapeutic intervention.

Neuroprotective strategies in Parkinson's disease

The biochemical alterations in Parkinson's disease such as increased lipid peroxidation, altered iron metabolism and impairment of mitochondrial function point to oxidative stress as an important factor contributing to neuronal loss in the substantia nigra in Parkinson's disease. Protection against such oxidative damage could be provided by scavengers of free radicals and antioxidants such as MAO-B inhibitors, alpha-tocopherol (vitamin E), ascorbic acid (vitamin C), glutathione and iron chelators (see Table 2).

Treatment with ascorbic acid in the mouse has been reported to reverse the decrease in striatal dopamine levels caused by the systemic administration of MPTP or focal injection of MPP^+ into the striatum (Sershen et al., 1985; Wagner et al., 1985, 1986). Alpha-tocopherol has been shown to prevent nigral cell loss in MPTP-treated mice (Perry et al., 1985) and has been reported in an open-label study to retard the clinical progression of Parkinson's disease in therapeutically naive patients (Fahn, 1989). Another open study showed that parkinsonian patients taking alpha-tocopherol had less severe deficits than those not taking the substance (Factor et al., 1990). The ongoing DATATOP

Table 2. Neuroprotective strategies in Parkinson's disease

Biochemical alterations in the substantia nigra	Possible neuroprotective therapies
Formation of hydrogen peroxide	MAO-B inhibitors (e.g. L-deprenyl)
Increased iron content	Iron chelators
Formation of toxic oxygen free radicals	Free radical scavengers (e.g. vitamin C, vitamin E)
Alteration in the homeostasis of intracellular calcium	Calcium entry blockers (e.g. nimodipine)
Excess activity of excitatory amino acids (?)	Excitatory amino acid antagonists

study (Parkinson Study Group, 1989) compares the effect of alpha-tocopherol and placebo on disease progression in a prospective, double-blind trial.

The findings of a selective increase in oxidative stress and in Fe^{3+} content in the substantia nigra in Parkinson's disease suggest that iron chelators may be able to prevent the retardation of the dopaminergic neurodegeneration. The dopaminergic neurotoxic effect of 6-hydroxydopamine is thought to involve the generation of oxygen free radicals (Heikkila and Cohen, 1972; Sachs and Jonsson, 1975; Graham et al., 1978) presumably initiated by a transitional metal. The administration of the iron chelator desferrioxamine in the rat protects against the 6-hydroxydopamine-induced reduction in striatal dopamine content and the development of dopamine-related behavioural changes (Ben-Shachar et al., 1991). The ability of iron chelators to retard dopaminergic neurodegeneration in the substantia nigra may indicate a new neuroprotective approach in Parkinson's disease. Iron chelators such as amino steroids have shown protective activity in animal models of trauma and ischaemia and are able to cross the blood-brain barrier and to inhibit iron-dependent lipid peroxidation (Braughler et al., 1987; Hall, 1988; Hall and Yonkers, 1988).

Neuroprotective action of L-deprenyl

The selective MAO-B inhibitor L-deprenyl was initially employed as an adjunct to L-DOPA, based on the hypothesis that inhibition of dopamine metabolism would increase dopamine availability. MAO-B inhibitors increase brain levels of dopamine and phenylethylamine (Neff et al., 1974; Riederer et al., 1984) and L-deprenyl potentiates the anti-parkinsonian action of L-DOPA (Birkmayer et al., 1975; Elizan et al., 1991). Retrospective studies showed that patients who received both L-DOPA and L-deprenyl lived longer than patients who were treated with L-DOPA alone (Birkmayer et al., 1985). Two

randomized, prospective, double-blind studies have compared L-deprenyl with placebo in otherwise untreated subjects with early Parkinson's disease (Parkinson Study Group, 1989; Tetrud and Langston, 1989). Both studies demonstrated that L-deprenyl produced a prolongation of the period before systematic therapy was required. L-deprenyl appears to delay the onset of disability and to have a neuroprotective effect by slowing the rate of progression of Parkinson's disease in newly diagnosed patients. For the first time a drug has been found that may influence the underlying neuropathology of the disease. A major argument against the neuroprotective action of L-deprenyl in the trial of the Parkinson Study Group (1989) has been the short wash-out period of one month. It has been argued that the symptomatic effects of the drug may still have been apparent (Landau, 1990). However, an increase in the concentration of amines is observed only following MAO inhibition of about 80% (Green and Youdim, 1976). The symptomatic effect of an MAO inhibitor is lost relatively rapidly as the enzyme recovers from total blockade. New protein synthesis to levels of enzyme protein that sufficiently metabolize the amine appears within the first two weeks following cessation of an irreversible MAO inhibitor. Furthermore, urinary phenylethylamine concentrations, which accumulate by 20 to 90-fold following L-deprenyl administration, drop to normal excretion levels within a few days following L-deprenyl withdrawal (Elsworth et al., 1978). The design of the L-deprenyl study (Parkinson Study Group, 1989) appears adequate for the assessment of neuroprotective properties of the drug.

L-deprenyl may decrease the generation of hydrogen peroxide associated with dopamine catabolism through its action as an MAO-B inhibitor and slow the progression of Parkinson's disease by reducing the death of substantia nigra neurones induced by endogenous neurotoxic free radicals. A neuroprotective role of L-deprenyl has been demonstrated in the mouse. L-Deprenyl reduced oxidative stress associated with an increased turnover of dopamine induced by haloperidol and limited the accumulation of GSSG in the striatum (Cohen and Spina, 1989).

The neuroprotective effects of L-deprenyl may partly be mediated by the antagonistic occupation of the polyamine binding site of the N-methyl-D-aspartate (NMDA) receptor by N-acetylated polyamines such as N-acetylputrescine, N-acetylspermidine and N-acetylspermine. These substances are highly selective MAO-B substrates (Youdim, unpublished observation) and their concentrations in the brain may be increased following L-deprenyl treatment. L-Deprenyl may therefore exert a neuroprotective function by a reduction of excessive calcium influx into neurones following antagonistic modulation of the polyamine binding site of the NMDA receptor.

The inhibition of MPTP-induced neurotoxicity by L-deprenyl given prior to the toxin is well established. It has recently been shown that L-deprenyl increases the survival of substantia nigra neurones in the mouse even when the drug is administered days following the MPTP treatment (Tatton and Green-

wood, 1991). This finding suggests a neuroprotective mechanism that is independent of MAO-B activity. It can rather be related to the stimulation of neurotrophic factors or regenerative processes.

Neuroprotective activity may be a generalized feature of both MAO-A and MAO-B inhibitors. The selective reversible MAO-A inhibitor moclobemide (p-chloro-N-[2-morpholinoethyl]benzamide) has been reported to have neuroprotective effects due to the inhibition of generation of hydrogen peroxide via MAO-A reactions (Da Prada et al., 1990).

Anti-glutamatergic neuroprotection

Excitatory amino acids such as L-glutamate are neurotransmitters in the central nervous system of mammals (Fonnum, 1984). Excessive activity of excitatory amino acids has been postulated to play a role in a variety of neurodegenerative diseases including Parkinson's disease (Olney, 1989). This hypothesis is based on findings showing neurotoxic properties of both L-glutamate (Olney, 1969) and substances exciting the main glutamate receptor subtypes, i.e. N-methyl-D-aspartate (NMDA), quisqualate or alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainate. Microinjections of many excitatory amino acids into various brain areas can produce an acute reaction that selectively destroys certain neurones in the area (McGeer et al., 1978; Rothman and Olney, 1987).

There is evidence indicating that excitatory amino acids are involved in the neurotoxic effects of MPTP. Systemic administration of MPTP to humans and non-human primates causes parkinsonian motor deficits associated with a selective destruction of dopamine-containing neurones in the substantia nigra pars compacta and a marked reduction in striatal dopamine content (Davis et al., 1979; Langston et al., 1983, 1984a; Burns et al., 1983). Neurotoxicity appears to be due to the formation of 1-methyl-4-phenylpyridinium ion (MPP^+) (Sanchez-Ramos et al., 1988; Lange, 1990) which is the result of the metabolism of MPTP by monoamine oxidase type B (MAO-B). MPP^+ is subsequently transported by the dopamine uptake process to accumulate within dopaminergic neurones and to be temporarily stored in a releasable pool (Javitch et al., 1985). The toxicity of MPP^+ apparently occurs as the result of inhibition of complex I of the mitochondrial respiratory chain (Nicklas et al., 1985).

It has been shown that glutamate antagonists, which block the NMDA subtype of receptor, protect dopaminergic nigral neurones against destruction by MPP^+ injected directly into the substantia nigra of rats (Turski et al., 1991). Since rats are less sensitive to MPP^+ than primates, the doses of the toxin needed to produce brain damage are very high and could cause unspecific toxic effects. In the mouse, the non-competitive NMDA-receptor antagonist (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclo-hepten-5,10-imine maleate (MK-801) has

been shown to be ineffective in preventing the dopamine depletion induced by systemic administration of MPTP (Sonsalla et al., 1989). Recent studies in monkeys, however, have demonstrated that glutamate antagonists are able to modulate the neurotoxicity of MPTP. The competitive NMDA antagonist 3-((±)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP) protects tyrosine hydroxylase-positive neurones in the substantia nigra from degeneration induced by systemic treatment with MPTP in the common marmoset (Lange et al., 1992). The non-competitive NMDA antagonist MK-801 prevents the development of the parkinsonian syndrome in the cynomolgus monkey (Zuddas et al., 1992) and protects nigral tyrosine hydroxylase-positive neurones in cynomolgus monkeys (Zuddas et al., 1992) and marmosets (Lange et al., unpublished observation) from degeneration following the administration of MPTP.

The neuroprotective action of NMDA receptor antagonists against MPTP toxicity supports the hypothesis that NMDA receptor-mediated events are involved in the neurotoxicity of MPTP and MPP^+. MPP^+ interferes with mitochondrial respiration and depletes cell energy resources (Nicklas et al., 1985). Neuronal energy deprivation could alter the normal functioning of cell membranes and cause a partial depolarization leading to a relief of the voltage dependent Mg^{2+} block of NMDA receptor ion channels (Nowak et al., 1984). Removal of the Mg^{2+} block enables excitatory amino acids to excite their receptors persistently, to open the ion channels and to become neurotoxic (Novelli et al., 1988).

The neurotoxic effects of excitatory amino acids may be involved in the pathogenesis of Parkinson's disease (Calne et al., 1986). Other forms of parkinsonism have been linked with toxic action of excitatory amino acids on dopaminergic cells in the substantia nigra. The amyotrophic lateral sclerosis-parkinsonism-dementia complex of Guam is thought to be caused by the amino acid β-N-methylamino-L-alanine (Spencer et al., 1987) which has been shown to activate glutamate receptors (Weiss and Choi, 1988). Concussive brain injuries are associated with increased extracellular excitatory amino acid concentrations (Faden et al., 1989) and can cause nigrostriatal degeneration and parkinsonism in boxers with dementia pugilistica (Mawdsley and Ferguson, 1963).

The findings demonstrating neuroprotective effects of competitive and non-competitive NMDA antagonists in MPTP-treated monkeys suggest that the clinical trial of NMDA antagonists in patients with Parkinson's disease should be performed. The 1-amino-adamantanes amantadine and memantine, which are in use as anti-parkinsonian drugs, have been shown to be non-competitive NMDA antagonists (Kornhuber et al., 1991). Whether or not these compounds have neuroprotective properties and whether they may be able to delay the progression of Parkinson's disease is unknown. If neuroprotective effects of NMDA antagonists can be shown in humans, then a novel strategy for the neuroprotective or even preventive therapy of Parkinson's disease could be available.

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Authors' address: Prof. P. Riederer, Department of Clinical Neurochemistry, University of Würzburg, Füchsleinstrasse 15, D-W-8700 Würzburg, Federal Republic of Germany