Neuroprotection in Parkinson's Disease: An Elusive Goal

William C. Koller, MD, PhD, and Maria G. Cersosimo, MD*

Address
*Department of Neurology, The Mount Sinai Medical Center, One Gustave L. Levy Place, Annenberg 1494/Box 1137, New York, NY 10029-6574, USA.
E-mail: william.koller@mssm.edu

Current Neurology and Neuroscience Reports 2004, **4:**277–283
Current Science Inc. ISSN 1528-4042

Parkinson's disease is a chronic progressive condition that causes disability and reduction of quality of life. Symptomatic treatments are effective in the early disease; however, with time, most patients develop motor complications. Neuroprotective therapies are those that can slow disease progression; unfortunately, these agents are not available. Advances in the knowledge of the possible pathogenic events that can lead to nigral cell death have increased dramatically. These mechanisms include oxidative stress, mitochondrial dysfunction, inflammation, excitotoxicity, alterations in protein degradation, and ultimately apoptosis. Based on these laboratory scientific findings, a number of agents have been studied in clinical trials. However, how to assess disease evolution and establish reliable endpoints is still an unresolved issue. The monoamine oxidase inhibitors selegiline and rasagiline have been shown to be neuroprotective in vitro and in animal models, but so far this property was not demonstrated in clinical trials. Other agents have been studied and still others are undergoing clinical investigation. These include antiexcitotoxicity drugs like riluzole, the bioenergetic agent coenzyme Q10, trophic factors, and antiapoptotic drugs. Laboratory and clinical data suggest that dopamine agonists may have a neuroprotective action, but this has yet to be proven. However, as our basic and clinical knowledge on Parkinson's disease increases, it is likely that a neuroprotective drug will be found.

Introduction

Parkinson's disease (PD) is a chronic, progressive disease of the nervous system. It is characterized clinically by tremor, bradykinesia, rigidity, and gait and balance problems, as well as by nonmotor features [1]. PD is a common condition affecting as many as 1 million people in the United States [2]. The pathologic hallmark of PD is a progressive and relatively selective degeneration of the nigrostriatal pathway with loss of dopaminergic cells of the substantia nigra [3]. The resulting dopamine deficit underlies most of the motor manifestations of PD. Another key feature is the formation of Lewy bodies in the cytoplasm of the substantia nigra neurons, which might be the result of abnormal protein aggregation [4••]. Treatment of PD is often effective in early disease. However, with advancing PD there is an increase in disability and a reduction of quality of life due to adverse effects of medications. These adverse effects include dyskinesias, motor fluctuations, and unresponsive motor and nonmotor PD symptoms [5]. Thus, PD relentlessly progresses in most patients despite current advances in medical and surgical therapies.

As our knowledge of the etiology and pathogenesis of nigral cell death in PD has increased, it has become possible to consider approaches that might stop or slow the rate of progression of PD [6,7]. Most patients do well during the first 5 to 10 years of the illness; however, if this period could be extended to 10 to 20 years, the impact of PD would be dramatically reduced. Neuroprotective therapies can be defined as those that prevent neurons from cell death. In PD, a proportion of neurons appear to be damaged and dysfunctional but not dead. Therefore, it may be possible to design neuro-rescue agents that would restore function to this defective neuronal population. There is more than one cause of parkinsonism and more than one pathway to cell dysfunction. However, there may be a common final pathway to cell death, and this may represent an opportunity for a neuroprotective intervention. This article reviews the etiology and possible pathogenetic mechanisms of PD and discusses putative neuroprotective drugs.

Etiology

The cause of PD is not known. Both genetic and environmental factors appear to be involved [8]. Families with both autosomal dominant and autosomal recessive PD have been described, and in some cases the genetic defect has been identified. For instance the genetic mutation for α-synuclein in several families with autosomal dominant PD and a mutation in the Parkin gene for juvenile onset autosomal recessive PD have been identified [9]. Epidemiologic case control studies have identified various environmental risk factors, such as rural living and exposure to herbicides and pesticides [10]. Specific chemicals, such as MPTP and rotenone, a commonly used pesticide, cause nigral striatal degeneration and a parkinsonian syndrome

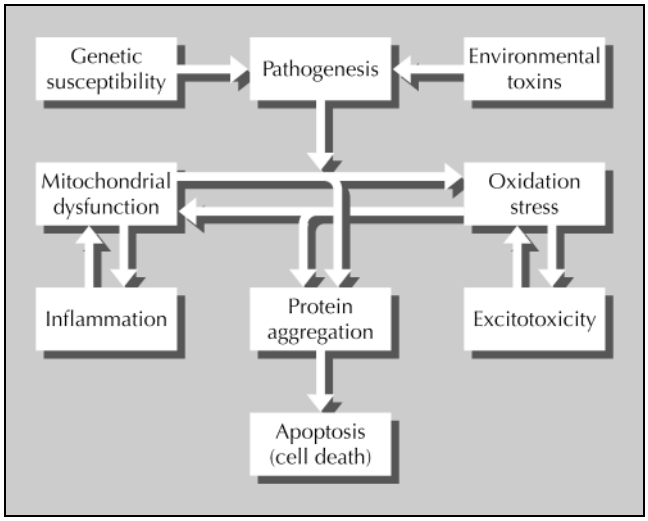

Figure 1. Causes of Parkinson's disease.

[11]. A large study of twins found no concordance for PD among monozygotic twins, which favors an environmental causation [12]. It is likely that a combination of genetic susceptibility and an environmental exposure are necessary for PD.

Pathogenesis

Parkinson's disease results in a cascade of pathogenetic events, leading ultimately to the demise of melanin-containing nigra-striatal dopaminergic neurons (Fig. 1). These include oxidative stress, mitochondrial energy abnormalities, excessive excitotoxicity, inflammatory responses, and lack of trophic factors. Exactly which of these factors is the primary event is unknown. Furthermore, one process can affect other processes (*eg*, mitochondrial dysfunction results in increased free radicals and free radicals can cause mitochondrial inhibition). Thus, a complex inter-relationship may exist among proposed pathogenetic mechanisms. Lastly, a final common pathway may occur involving protein aggregation and cell death by an apoptotic mechanism. These mechanisms are discussed.

Oxidative Stress

Oxidative stress appears to play a role in nigral cell death [13•]. This is based in part on the hypothesis that the degradation of dopamine by monoamine oxidase produces oxidative stress by generating hydrogen peroxide. Furthermore, hydrogen peroxide is converted by the Fenton reaction to produce highly toxic hydroxyl radicals. The auto-oxidation of dopamine can also form superoxide radicals and reactive quinines. It has been suggested that early compensatory changes in dopamine turnover resulting from the initiation of nigral cell death could cause an induction of oxidative metabolism, thereby enhancing oxidative stress and a hastening of nigral death. The substantia nigra pars compacta is vulnerable to oxidative stress because of its high dopamine, neuromelanin, and iron content [13•]. Also, the presence of neurofilaments and the absence of calbindin in the substantia nigra confer additional vulnerability to oxidative stress. Postmortem studies of PD brains provide further support for oxidative stress in the pathogenesis of PD [15]. Pathologic findings include increase in iron levels, decrease in growth-stimulating hormone levels, evidence of lipid peroxidation, elevated levels of oxidized proteins, and impairment of mitochondrial complex I function.

Thus, oxidative stress appears to occur in the substantia nigra in PD and may contribute to nigral cell degeneration. However, it is not known what event is the initial pathogenetic process in PD or exactly how oxidative stress is related to the other pathologic processes. Moreover, there is no evidence that oxidative stress is the initiator of cell death in PD.

Mitochondrial Dysfunction

Substantial evidence indicates that mitochondrial defects are involved in the pathogenesis of PD [16,17]. The substantia nigra neurotoxin MPTP, which causes parkinsonism in humans and animals, has its effect mediated by inhibition of respiratory complex I [18]. In postmortem studies of PD brains, there is a 30% to 40% reduction of complex I in the substantia nigra [17]. A reduction of complex I activity has also been reported in platelets of PD patients [19]. There is genetic evidence that shows some forms of familial parkinsonism have mitochondrial defects [20]. Rotenone, which is used as an insecticide, is a potent complex I inhibitor. This compound, when infused intravenously in rats, induces a progressive degeneration of nigrostriatal neurons [11]. Pathologically, there are inclusion bodies that are similar to Lewy bodies that stain for α-synuclein. Clinically, the animals have motor disturbances similar to PD, and improvement is observed after apomorphine injection. Mitochondrial damage appears to enhance oxidative stress, and oxidative stress can induce mitochondrial dysfunction. Also, mitochondrial deficits cause a loss of adenosine triphosphate (ATP)-dependent magnesium blockage of *N*-methyl-D-aspartate (NMDA) receptors, thus increasing susceptibility to excitotoxicity [20].

Inflammation

There is evidence that reactive glial cells, by virtue of their inflammatory properties, may play a role in the pathogenesis of PD [21]. McGeer *et al.* [22] noted that there were an increased number of positive microglial cells in the substantia nigra pars compacta of patients dying with PD. Similarly, activated microglial cells were found in the substantia nigra of drug addicts who ingested MPTP several decades earlier [23]. Supportive evidence for a role of inflammation in PD is the finding of increased cytokine levels in the striatum and cerebrospinal fluid (CSF) of PD patients, such as proinflam-

Table 1. Possible outcome variables for neuroprotective studies

Change in UPDRS motor score
Time to initiation of dopaminergic therapy
Loss of independence on ADL skills
Loss of employability
Time to institutionalization
Loss of ability to walk
Onset of dementia
Onset of freezing
Onset of postural instability
Change of fluorodopa PET scan
Change on b-CIT SPECT scan
Death

ADL—activities of daily living; PET—positron emission tomography; SPECT—single photon emission computed tomography; UPDRS—Unified Parkinson's Disease Rating Scale.

matory cytokines and tumor necrosis factor [24•]. Also, the cytokines are produced in the vicinity of dopaminergic neurons and may be involved in the pathogenesis of PD. Although the mechanism of how inflammation can cause cell death is not known, it has been reported that proinflammatory cytokines cause activation of the induction of nitrous oxide synthetase, which mediates the synthesis of nitrous oxide, which is toxic to neurons [21]. It likely that an inflammatory response may arise secondarily to more primary neuronal insults. However, a chronic inflammatory response can be harmful to neuronal cells and represent a target for potential neuroprotective therapy.

Excitotoxicity

Excessive glutamatergic stimulation with consequent excitotoxicity may contribute to neuronal death in PD [25]. The subthalamic nucleus (STN) uses the excitatory neurotransmitter glutamate and projects to various brain areas, including the globus pallidus, pars interna, the pedunculopontine nucleus, and the substantia nigra pars compacta. The neuronal activity of the STN has been shown to be increased in parkinsonian animal models and in PD patients [26]. It is possible that a vicious cycle occurs, where cell death in the substantia nigra increases subthalamic activity, which results in enhanced cell death in the nigra. NMDA glutamate receptor antagonists protect against cell death in a number of animal models of PD [25]. Interestingly, a retrospective study of the NMDA antagonist amantadine suggested that early use of this drug decreased the rate of PD progression [27].

Protein Degradation

One of the pathologic hallmarks of PD is the formation of Lewy bodies, although their role in the pathogenesis of PD is not clear. Lewy bodies are large intracytoplasmic inclusions and appear to have high levels of various proteins such as α-synuclein, torsin A, and parkin [28]. It has been suggested that Lewy bodies are simply a consequence of the pathologic process of PD or they could be involved in the pathogenetic process, perhaps even having a protective action [29]. Aggregation of nondegraded proteins could be involved in mechanisms leading to cell death. It is of interest that MPTP causes protein aggregation [4••].

There is accumulating evidence that altered protein degradation plays a role in the pathogenesis of PD. The proteasomal system and failure of ubiquitin-mediated protein degradation may be important in PD [30]. Parkin is an E-3 ubiquitin protein ligase, and mutations appear to result in decrease enzyme activity. Mutant forms of α-synuclein appear to inhibit proteasome function [31]. Also, reduced mitochondrial complex I activity leads to a decrease in cellular ATP, and this may affect the highly ATP-dependent proteasome.

Apoptosis

Cell death can occur by necrosis or by apoptosis, which is a programmed form of cell death. In apoptosis, there is a cascade of events that terminates in destruction of DNA chains [32]. It has been suggested that apoptosis could be the mechanism of neuronal death in PD. It has been demonstrated that an upregulation of proteins expressed in the apoptotic pathways, such as caspases, occurs in PD. Furthermore, considerable data indicate that MPTP causes cell death by an apoptotic mechanism [33]. However, there is still debate if apoptosis occurs in PD and whether apoptosis may occur only as an end-stage event, making therapeutic intervention impossible.

Neuroprotective Strategies and Clinical Trials

There are many potential neuroprotective agents that have been identified in animal models of PD. Which agents should be studied in humans and how to clinically assess these drugs are major unresolved issues [34]. PD is a highly variable condition, and the rate of disease progression can differ greatly among patients. Another problem is the assessment when a possible neuroprotective drug also has a symptomatic effect. Furthermore, it is not known for most drugs how long of a washout period is needed to be totally free of the drug's symptomatic effect. A number of outcome variables have been used or have been suggested (Table 1). Disease progression has traditionally been monitored by the assessment of the severity of motor signs. However, there is marked variability in individual symptom progression. The Unified Parkinson's Disease Rating Scale (UPDRS) is frequently used in clinical trials to assess changes due to drug intervention, but the rate of change over time is not well studied (*eg*, it is unclear if this scale is a sensitive tool to measure disease progression in early PD). The decision to initiate dopaminergic therapy has been used as a primary endpoint in some trials [35]. It is

relatively defined and measurable. Functional variables, such as loss of ambulation, ability to perform activities of daily living (ADL), or institutionalization, represent other possible endpoints. Another possibility that has been suggested is the achievement of certain disease milestones that are known to occur in mid disease, such as the occurrence of postural instability or dementia. In addition to clinical markers, neuroimaging of the dopaminergic system with fluorodopa positron emission tomography (PET) or β-CIT single photon emission computed tomography (SPECT) scan may be able to monitor disease progression [35]. This is an objective measure that has been shown to change with disease progression. It is estimated that in PD there is a change of approximately 10% per year compared with about 1% in control subjects [36]. However, the possibility that drugs might have a regulatory action on the imaging measure is a potential confounding factor. Therefore, the value of neuroimaging in following disease progression has been questioned. However, it seems that neuroimaging could provide a valuable adjunct to clinical measures in the assessment of potential neuroprotective agents.

Monoamine Oxidase Inhibitors

The knowledge that the catabolism of dopamine by monoamine oxidase (MAO) could produce potentially toxic byproducts and that MAO inhibitors prevent the conversion of MPTP to its active toxin MPP+ led to the hypothesis that MAO inhibitors could be neuroprotective in Parkinson's disease. There are substantial basic science data regarding MAO inhibitors (*eg*, selegiline and rasagiline are neuroprotective in a variety of laboratory settings and in animal models of Parkinson's disease) [37–39]. Selegiline also protects against ischemic changes in animal models, increases the survival of fetal dopaminergic cells, and protects against apoptotic cell death. These actions are independent of the drug's ability to inhibit MAO.

This knowledge led to the first large neuroprotective trial performed by the Parkinson's Disease Study Group (PSG) that evaluated the potential protective actions of selegiline and tocopherol (vitamin E) in a 2 x 2 factorial design [40]. The dosage of selegiline was 10 mg/d and vitamin E was 2000 U/d. The primary endpoint was when the patient became symptomatic enough to require levodopa therapy. The study was designed to last 2 years. However, it was stopped because of a major treatment effect that occurred early in the study. At a mean of 12 ± 5 months after the onset of selegiline therapy, comparison between placebo and selegiline groups revealed 176 of 401 subjects in the placebo-treated group and only 67 of 396 subjects in the selegiline-treat group reached endpoint. This was highly statistically significant. Kaplan-Meier analysis of the sequential occurrence of endpoints revealed that selegiline treatment reduced the risk of reaching endpoint by approximately half the rate occurring in the placebo group. In contrast, a 2-year analysis showed no evidence of a neuroprotective action with vitamin E. Initial interpretation was that selegiline might have a neuroprotective action. However, analysis of the data showed that selegiline produced a small but measurable symptomatic effect. This was a confound regarding a possible neuroprotective action. An interesting feature of this study was that selegiline was associated with a decreased risk for freezing of gait [41].

Another study compared selegiline and bromocriptine in a prospective, double-blind study [42]. This trial attempted to control for selegilines's symptomatic effects. Patients with untreated PD were randomized to selegiline or placebo in addition to treatment with either carbidopa/levodopa or bromocriptine. Thus, there were four treatment groups. The primary endpoint was the change in the UPDRS motor score between baseline and the final visit performed 2 months after the withdrawal of selegiline and 7 days after withdrawal of carbidopa/levodopa or bromocriptine. The study found that the deterioration of the UPDRS score was significantly less in the patients randomized to the selegiline group than those receiving placebo, regardless of whether they received carbidopa/levodopa or bromocriptine. The authors interpreted these findings to be consistent with the hypothesis that selegiline has a neuroprotective effect that could not be explained by a symptomatic action of the drug.

There have been other double-blind studies comparing selegiline with placebo [43–45]. These studies also found that selegiline delayed the primary endpoint of time to require levodopa therapy. However, these studies were also confounded by the fact that a significant clinical effect was noted. The PSG also studied the MAO inhibitor rasagiline [46]. This drug was shown to have efficacy, and it reduced the UPDRS motor score in mild PD. Rasagiline has yet to be studied in a neuroprotective paradigm.

Antiexcitotoxicity

Riluzole, a blocker of the presynaptic release of glutamate, is approved for the treatment of amyotrophic lateral sclerosis. A multicenter, randomized, placebo-controlled trial of riluzole was undertaken to test the drug as a possible neuroprotective agent in PD [47]. The trial was stopped because of lack of efficacy that was determined at an interim analysis. Remacemide, a NMDA channel blocker, was evaluated in PD for safety and tolerability in a double-blind, placebo-controlled trial [48]. There was no symptomatic effect of the drug, and severe adverse reactions did not occur. Remacemide failed to show neuroprotection in Huntington's disease [49]. The drug has not been studied for neuroprotection in PD.

Bioenergetics

The mitochondrial defect in PD raised the possibility that bioenergetic drugs could be neuroprotective. A variety of compounds, including coenzyme Q10, creatine, riboflavin,

and nicotinamide, are potential candidates. A preliminary study of coenzyme Q10 has been performed [50•]. De novo PD patients were randomized to treatment with placebo or doses of 300, 600, or 1200 mg/d of coenzyme Q10 for 10 months. There was a dose-dependent reduction in the UPDRS score; however, this was not statistically significant, perhaps because of the small sample size. Therefore, a larger trial with higher doses and a longer evaluation period is currently underway. A preliminary study of creatine has recently been completed. The results are not yet available.

Trophic Factors

The lack of trophic factors may be involved in the pathogenesis of PD [51]. Therefore, agents with trophic properties have been studied as potential neuroprotective drugs in PD. Glial cell line–derived neurotrophic factor (GDNF) is a protein that does not cross the blood-brain barrier. It is effective in laboratory models and is able to restore function to the nigrostriatal system of MPTP-lesioned monkeys, even when treatment is delayed for several weeks [52]. GDNF was initially studied when administered by intracerebroventricular injection on a monthly basis [53]. There was no clinical effect and many adverse reactions occurred. It is likely that the drug failed to penetrate the basal ganglia. Other approaches to deliver GDNF have been attempted. In MPTP-treated monkeys, GDNF was delivered using a modified lente virus to the striatum and substantia nigra [54••]. There was dramatic histologic and behavioral improvement. In clinical studies, GDNF was delivered by infusions through indwelling catheters implanted in the putamen. Initial results show the procedure and drug are well tolerated, and some clinical efficacy has been noted [55]. There are ongoing trials with this approach.

Another neurotrophic substance, AMG-474 (which is a neuroimmunophyllin), was studied in 200 de novo PD patients in dosages ranging from 800 to 4000 mg/d in a randomized, placebo-controlled study lasting for 6 months. The drug's effect was similar to placebo. However, AMG 474 is currently being studied in a larger multicenter trial with a longer duration of follow-up.

Dopamine Agonists

Dopamine agonists are important symptomatic drugs used in the management of PD either as monotherapy or as adjuvants to L-dopa. Used as monotherapy, they have less risk of motor complications as compared with L-dopa treatment. Both laboratory and clinical data suggest that dopamine agonists may be neuroprotective. Dopamine agonists are able to protect dopaminergic neurons in various in vitro and in vivo models [56]. Dopamine agonists have the capacity to enhance the growth of cultured dopamine neurons in tissue culture and to protect them from a variety of toxic agents. In in vivo systems, dopamine agonists protect nigrostriatal neurons from toxins and toxic insults, including 6-hydroxydopamine, MPTP, and ischemia. These protective effects have been observed with many dopamine agonists, and it is unclear if one agonist might have more neuroprotective benefit than another. Dopamine agonists could provide neuroprotection by a levodopa-sparing effect, with reduction of free radicals by a direct antioxidant effect, or by reduction of STN-mediated excitotoxicity,

Clinical data also suggest a neuroprotective effect of the dopamine agonists. Neuroimaging represents a surrogate marker for the integrity of the nigrostriatal system. Two prospective, randomized clinical trials using fluorodopa PET and β-CIT SPECT scans have compared a dopamine agonist versus levodopa treatment. In the Comparison of the Agonist Pramipexole versus Levodopa on Motor Complications of Parkinson's Disease (CALM-PD) study [57], patients received pramipexole, L-dopa, or both drugs. There was a significantly slower rate of decline in striatal β-CIT SPECT uptake with pramipexole compared with levodopa after 2 and 4 years of treatment [57]. The Requip as Early Therapy versus L-dopa Positron Emission Tomography (REAL-PET) study [58] demonstrated that patients randomized to ropinerole had a reduced rate of decline with fluorodopa PET than levodopa. The data from these studies are difficult to interpret because there was no placebo group and because of the possibility that the study drugs could affect regulation of imaging markers. Nonetheless, the results are consistent with a neuroprotective action of dopamine agonists.

Antiapoptotic Drugs

Apoptosis may be the cause of cell death in PD. The putative neuroprotective actions of propargylamines like selegiline may be due to an antiapoptotic action of the drugs. Other similar drugs are undergoing trials in PD. TCH346, a novel compound that is structurally similar to selegiline but does not inhibit MAO, prevents neuronal loss in MPTP-treated monkeys and inhibits the protein GAPDH, which is important in apoptosis [59]. Prospective, double-blind studies are currently evaluating the safety and efficacy of this compound. Clinical studies are also evaluating CEP-1347, an inhibitor of kinase-3, which is involved in the signaling pathway in apoptotic cell death [60]. This drug prevents cell death in animal models, and clinically the drug appears to be free of serious side effects and has no symptomatic effects.

Conclusions

The first major advance that was a quantum leap in the treatment of PD was the introduction of L-dopa therapy. There have been many other advances in the management of PD, but these have been only incremental. Moreover, there is no doubt that patients with PD have a much better quality of life now than 10 years ago. Nonetheless, many

patients, despite improvement of treatment, have substantial disability with advanced disease. The next major advance in PD will be the development of neuroprotective therapies. Our knowledge of the etiology and pathphysiology of PD will continue to increase. There are many potential agents that have been identified in the laboratory that need to be tested in clinical trials. How to conduct these studies in humans remains problematic. The development of generally accepted clinical endpoints needs to be achieved, and much work remains to be done. To date, we have not been able to prove an agent to be neuroprotective, and this goal remains elusive. Also, it may be necessary to use more than one drug to adequately interfere with the cascades of the various events that occur at multiple pathogenetic levels. Therefore, a combination therapy may be needed. Nevertheless, we predict that in the next 10 years there will be a neuroprotective drug for general use in PD. This discovery will have a profound impact on the management of PD and will result in a dramatic reduction of the disability associated with the disease.

Acknowledgment

Dr. Cersosimo can be contacted at the Program of Parkinson's Disease and Movement Disorders, Hospital de Clinicas, in Buenos Aires, Argentina.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Olanow CW, Watt RL, Koller WC: **An algorithm (decision tree) for the management of Parkinson's disease: treatment guideline.** *Neurology* 2001, **56(suppl 5):**51–88.
2. Rajput AH, Rajput A, Rajput M: **Epidemiology for Parkinsonism.** In *Handbook of Parkinson's Disease,* edn 3. Edited by Pahwa R, Lyons KE, Koller WC. New York: Marcel Dekker; 2003:17–42.
3. Gibb WR, Lee AJ: **Anatomy, pigmentation, ventral and dorsal subpopulation of the substantia nigra and differential cell death in Parkinson's disease.** *J Neurol Neurosurg Psychiatry* 1991, **54:**388–396.
4. •• McNaught K, Olanow CW: **Proteolytic stress: a unifying concept for the etiopathogenesis of Parkinson's disease.** *Ann Neurol* 2003, **53(suppl 3):**573–586.

This paper reviews the role of protein aggregation and degradation in PD. Dysfunction of the ubiquitin-proteasome system and the genesis of Lewy bodies are discussed .

5. Hoehn MM, Yahr MD: **Parkinsonism: onset, progression and mortality.** *Neurology* 1967, **17:**427–442.
6. Marsden CD, Olanow CW: **Neuroproctection in Parkinson's disease. The causes of Parkinson's disease are being unraveled and rational neuroprotective therapy is close to reality.** *Ann Neurol* 1998, **44:**189–196.
7. Stocchi FS, Olanow CW: **Neuroprotection in Parkinson's disease: clinical trials.** *Ann Neurol* 2003, **53(suppl 3):**587–599.
8. Warner T, Schapira AV: **Genetics and environmental factors in the cause of Parkinson's disease.** *Ann Neurol* 2003, **53(suppl 3):**516–525.
9. Fahn S, Sulzer D: **Neurodegeneration and neuroprotection in Parkinson's disease.** *Neuro Rx* 2003, **1:**139–154.
10. Koller WC, Vetere-Overfield B, Gray C, *et al.*: **Environmental risk factors in Parkinson's disease.** *Neurology* 1990, **40:**1218–1221.
11. Betarbet R, Sherer TB, MacKenzie G, *et al.*: **Chronic systemic pesticide exposure reproduces features of Parkinson's disease.** *Nat Neurosci* 2000, **3:**1301–1306.
12. Tanner CM, Ohman R, Goldman SM, *et al.*: **Parkinson's disease in twins: an etiologic study.** *JAMA* 1999, **281:**341–346.
13. • Jenner P: **Oxidative stress in Parkinson's disease.** *Ann Neurol* 2003, **53(suppl 3):**526–538.

Data implicating oxidative stress in the pathogenesis of PD are reviewed.

14. Jenner P: **Oxidative damage in neurodegenerative disease.** *Lancet* 1994, **344:**796–798.
15. Sian J, Dexter DJ, Less AJ, *et al.*: **Glutathione-related enzymes in brains of Parkinson's disease.** *Ann Neurol* 1994, **36:**356–361.
16. Schapira AV: **Evidence for mitochondrial dysfunction in Parkinson's disease-a critical appraisal.** *Mov Disord* 1994, **9:**123–138.
17. Schapira AV, Cooper JM, Dexter D, *et al.*: **Mitchondrial complex I deficiency in Parkinson's disease.** *J Neurochem* 1990, **54:**823–827.
18. Nicklas WJ, Vyas I, Heikkila RE: **Inhibition of NADH-linked oxidation in brain mitochondria by 1-methyl-4-phenyl-pyridine, a metabolite of the neurotoxin 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine.** *Life Sci* 1985, **36:**2503–2508.
19. Parker WP, Boyson SJ, Parks JK: **Abnormalities of the electron transport chain in idiopathic Parkinson's disease.** *Ann Neurol* 1989, **26:**719–723.
20. Beal MF: **Bioenergetic approaches for neuroprotection in Parkinson's disease.** *Ann Neurol* 2003, **53(suppl 3):**539–548.
21. Hunot S, Hirsch EC: **Neuroinflammatory processes in Parkinson's disease.** *Ann Neurol* 2003, **53(suppl 3):**549–560.
22. McGeer PL, Itagaki S, Boyes BE, McGeer EG: **Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains.** *Neurol* 1988, **38:**1285–1291.
23. Langston JW, Forno LS, Tetrud J, *et al.*: **Evidence of active nerve cell degeneration in the substantia nigra of humans years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure.** *Ann Neurol* 1999, **46:**598–605.
24. • Iravani MM, Kashefi K, Mander P, *et al.*: **Involvement of inducible nitric oxide synthetase in inflammation-induced dopaminergic neurogeneration.** *Neurol Sci* 2002, **110:**49–58.

Potential neuroprotective drugs and clinical assessment are reviewed.

25. Rodriguez MC, Obeso JA, Olanow CW: **Subthalamic nucleus mediated excitotoxicity in Parkinson's disease: a target for neuroprotection.** *Ann Neurol* 1998, **44:**175–188.
26. Feger J, Hassani LN, Mouroux M: **The subthalamic nucleus and its connections new electrophysiological and pharmacological data.** *Adv Neurol* 1997, **74:**31–44.
27. Uitti RJ, Rajput AH, Ahlskog JE, *et al.*: **Amantadine treatment is an independent predictor of improved survival in Parkinson's disease.** *Neurology* 1996, **46:**1551–1556.
28. McNaught K, Shashidharan P, Perl DP, *et al.*: **Aggresome-related biogenesis of Lewy bodies.** *Eur J Neurosci* 2002, **16:**2136–2148.
29. Olanow CW, Tatton WG: **Etiology and pathogenesis of Parkinson's disease.** *Ann Rev Neurosci* 1999, **22:**123–144.
30. McNaught KS, Jenner P: **Proteasomal function is impaired in substantia nigra in Parkinson's disease.** *Neurosci Lett* 2001, **297:**191–194.
31. Masliah E, Rockenstein E, Veinbergs I, *et al.*: **Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders.** *Science* 2000, **287:**1265–1269.
32. Tatton WG, Chalmer-Redman R, Brown D, Tatton N: **Apoptosis in Parkinson's disease: Signals for neuronal degradation.** *Ann Neurol* 2003, **53(suppl 3):**561–572.
33. Przedborksi S, Vila M: **MPTP: a review of its mechanism of neurotoxicity.** *Clin Neurosci Res* 2001, 407–418.
34. Ravina BM, Fagan SC, Hart RG, *et al.*: **Neuroprotective agents for clinical trials in Parkinson's disease: a systematic assessment.** *Neurology* 2003, **60:**1234–1240.
35. Kieburtz K: **Designing neuroprotection trials in Parkinson's disease.** *Ann Neurol* 2003, **53(suppl 3):**S100–S109.

36. Brooks D: **Imaging end points for monitoring neuroprotection in Parkinson's disease.** *Ann Neurol* 2003, **53(suppl 3):**S110–S119.
37. Jenner P, Olanow CW: **Understanding cell death in Parkinson's disease.** *Ann Neurol* 1998, **44:**S72–S84.
38. Finberg JP, Takeshima T, Johnston JM, Commissiong JW: **Increased survival of dopaminergic neurons by rasagiline, a monoamine oxidase B inhibitor.** *Neuro-Report* 1998, **9:**703–707.
39. Fineberg JP, Lamensdorf I, Commission JW, Youdim MD: **Pharmacology and neuroproctective properties of rasagiline.** *J Neural Transm* 1996, **48(suppl):**95–101.
40. Parkinson Study Group: **Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease.** *N Engl J Med* 1993, **328:**176–183.
41. Giladi N, McDermott MP, Fahn S, *et al.*: **Freezing of gait in PD: prospective assessment in the DATATOP cohort.** *Neurology* 2001, **56:**1712–1721.
42. Olanow CW, Hauser RA, Gauger L, *et al.*: **The effect of deprenyl and levodopa on the progression of signs and symptoms in Parkinson's disease.** *Ann Neurol* 1995, **38:**771–777.
43. Tetrud JW, Langston JW: **The effect of deprenyl (selegiline) on the natural history of Parkinson's disease.** *Science* 1989, **245:**519–522.
44. Palhagen S, Heinonen EH, Hagglund J, *et al.*: **Selegiline delays the onset of disability in he de novo parkinsonian patients. Swedish Parkinson Study Group.** *Neurology* 1998, **51:**520–525.
45. Myllylä VV, Sotaniemi KA, Vuorinen JA, Heinonen EH: **Selegiline as a primary treatment of Parkinson's disease.** *Acta Neurol Scand* 1991, **136(suppl):**70–72.
46. Parkinson's Study Group: **A controlled trial of rasagiline in early Parkinson's disease, the TEMPO Study.** *Arch Neurol* 2002, **59:**1937–1943.
47. Rascol O, Olanow CW, Brooks D, *et al.*: **A 2-year multicenter placebo-controlled, double-blind parallet group study of the effect of riluzole in Parkinson's disease.** *Mov Disord* 2002, **17:**39.
48. Parkinson Study Group: **A multicenter randomized controlled trial of remacemide hydrochloride as monotherapy for PD.** *Neurology* 2000, **54:**1583–1588.
49. Huntington's Disease Study Goup: **A randomized, placebo-controlled trial of coenzyme Q10 remacemide in Huntington's disease.** *Neurology* 2001, **57:**397–404.
50.• Schuls CW, Oakes D, Kieburtz K, *et al.*: **Effect of coenzyme Q10 in early Parkinson's disease: evidence of slowing of the functional decline.** *Arch Neurol* 2002, **59:**1541–1550.

Initial pilot study of the bioenergetic drug coenzyme Q10 is reported.

51. Collier T, Sortwell CE: **Therapeutic potential of nerve growth factors in Parkinson's disease.** *Drugs Aging* 1999, **14:**261–287.
52. Hebert AA, Hoffer BJ, Zhang Z, *et al.*: **Functional effects of GDNF in normal and parkinsonian rats and monkeys.** In *CNS Regeneration: Basic Science and Clinical Advances.* Edited by Tuszynski M, Kordower JH. New York: Academic Press; 1999:419–436.
53. Nutt JG, Burchiel KJ, Comella CL, *et al.*, for the ICV GDNF Study Group: **Randomized double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD.** *Neurology* 2002, **60:**69–73.
54.•• Kordower JH, Emborg ME, Bloch J, *et al.*: **Neurodegeneration prevented by lentiviral vector delivery of GDNF in primate models of Parkinson's disease.** *Science* 2000, **290:**767–773.

It is reported that lentivirus vector delivery of GDNF is effective in animal models of PD.

55. Gill SS, Patel NK, Hotton GR, *et al.*: **Direct brain infusion of glial derived neurotrophic factor (GDNF) in Parkinson's disease.** *Nature Med* 2003, **9:**589–595.
56. Olanow CW, Jenner P, Brooks P: **Dopamine agonists and neuroprotection in Parkinson's disease.** *Ann Neurol* 1998, **44:**5167–5174.
57. Parkinson Study Group: **Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression.** *JAMA* 2002, **287:**1653–1661.
58. Whone AL, Remy P, Davis MR, *et al.*: **The REAL-PET study: slower progression in early Parkinson's disease treated with ropinirole compared with L-dopa.** *Neurology* 2002, **58:**82–83.
59. Kragten E, Lalande I, Zimmerman K, *et al.*: **Glyceraldehyde-3-phosphate dehydrogenase, the putative target of the antiapopotic compounds CGP 3466 and R-(-)-deprenyl.** *J Biol Chem* 1998, **273:**5821–5828.
60. Schwid SR, for the Parkinson Study Group: **CEP-1347 in Parkinson's disease: a pilot study.** *Paper presented at the 7th International Congress of Parkinson's disease and Movement Disorders.* Miami, November 10–14, 2002.