Neuroprotection in Parkinson Disease

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Treatment of Parkinson disease has improved dramatically over the past quarter of a century and promising therapies are emerging. Although treatment with levodopa results in marked symptomatic improvement, mortality rates of the disease have remained relatively unchanged. Recent findings of abnormal protein folding, coupled with oxidative stress, provide scientific rationale for novel therapeutic strategies designed to slow disease progression. To be effective, these disease-modifying and neuroprotective therapies must be instituted early in the course of the disease and early diagnosis therefore is critical. Consequently, primary care physicians will play an increasingly important role in early institution of such neuroprotective strategies. This review is designed to highlight some of the recent advances in our understanding of the mechanisms of neurodegeneration and to draw attention to the importance of early recognition and implementation of the new therapeutic interventions.

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The fortuitous discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a “homemade” meperidine analogue, can cause degeneration of dopamine-producing neurons and induce the symptoms of Parkinson disease (PD), spawned novel hypotheses on the etiology and pathogenesis of the disease. Current theories propose complex interaction between genetic susceptibility and environmental factors, coupled with increased oxidative stress, mitochondrial dysfunction, excitotoxicity, generation of abnormal inflammatory cytokines, and abnormal processing of cellular proteins. These and possibly other mechanisms lead to dopaminergic neuronal loss in the substantia nigra pars compacta, ultimately causing symptoms of PD. Dysfunction of the ubiquitin-proteasome system, which normally serves as a clearing mechanism for abnormal proteins, is emerging as the leading mechanism of cell death not only in PD but also in other neurodegenerative diseases.

A growing understanding of processes leading to cell death elicited the notion that neuroprotection may be a reachable goal in the treatment of PD. In contrast to symptomatic therapy, which is designed to merely ameliorate the clinical features of the illness, the goal of neuroprotective therapy is to protect or rescue neurons that are vulnerable to the neurodegenerative process. If effective, neuroprotective therapy is expected to slow or even halt the underlying progression of degeneration.

Neuroprotection must be introduced early to be effective, and it is therefore essential that diagnosis be made as soon as possible after the onset of symptoms. Since primary care physicians are the “gatekeepers” of medicine, the burden of early diagnosis rests with them. By the time diagnosis is made, 50% to 80% of nigral cell loss usually has already occurred. Based on detailed pathological studies, Fearnley and Lees have hypothesized an exponential loss of nigral neurons, with greater loss occurring early in the disease, and reaching over 90% at the time of death. At the stage where most pa-
myalgia," and shoulder pain during this period.

It is also important to question family members when suspecting early PD. Family members often retrospectively report decreased arm swing on the patient's affected side, as well as decreased emotional expression and personality changes, including more introversion and inflexibility. Upon physical examination, the physician may notice loss of facial expression, decreased blink rate, impaired convergence of gaze, a positive glabellar sign, slowness of movement, tremor at rest often exacerbated during walking, and loss of arm swing. In addition, examination may reveal slow and monotonous speech, cogwheel rigidity in response to passive movements of limbs, micrographia, and slow and shuffling gait. Loss of balance and postural reflexes is usually a later sign.

If PD is suspected, the physician can perform a variety of tests during the office visit to objectively assess the mental and motor impairment. The Unified Parkinson's Disease Rating Scale is the gold standard for objective measurement of PD progression. This scale evaluates the following 6 components associated with disability in PD: behavior, activities of daily living, examination of motor skills, additional complications of the disease or therapy, Hoehn and Yahr staging, and score on the Schwab and England activities of daily living scale. Montgomery et al developed a PD battery of evaluations that includes a patient's olfaction, motor functions, and mood. Capitalizing on the finding that olfactory dysfunction and mood disorders such as depression often precede the diagnosis of PD, this study attempted to use these symptoms to discern healthy individuals from those with early PD. While individual assessments of motor function, olfaction, and mood are not sufficiently sensitive to diagnose PD, the evaluation of all 3 components has shown relatively high sensitivity (69%) and specificity (89%). In the future, early diagnosis will depend not only on clinical suspicion, but also on functional imaging. Current approaches under consideration include imaging techniques such as positron emission tomography (PET) and single-photon emission computed tomography. Both PET and single-photon emission computed tomography have generated much excitement as they have shown utility in preclinical disease detection.2,7

NEUROPROTECTION

Although levodopa is considered the gold standard for treatment of PD, multiple complications such as motor fluctuations, hallucinations, and psychosis arise from long-term therapy (Table).10,11 It is thought that these symptoms are due to both long-term levodopa therapy and disease progression. Furthermore, the degradation of levodopa generates many toxic metabolites that can cause oxidative stress in the neuron. Cultured dopaminergic neurons have undergone necrosis or apoptosis when exposed to levodopa,12 suggesting that levodopa becomes toxic at a certain threshold. Another hypothesis is that levodopa preferentially exerts toxic effects in neurons previously damaged.13 No in vivo evidence that levodopa causes neurotoxicity currently exists.11 Nevertheless, there is a theoretical possibility of in-
creased oxidative stress associated with levodopa, and it has been observed that levodopa therapy is associated with the development of motor complications in most patients within 5 years after onset of therapy. This has led to the belief that treatment with levodopa should be delayed as long as possible and has provided the impetus for evaluation of new drugs to treat PD. Research has focused on levodopa-sparing drugs, such as monoamine oxidase (MAO) inhibitors and dopamine agonists, that not only provide symptomatic benefit but also may have neuroprotective effect by allowing a reduction in levodopa dosage and by other mechanisms.

**MAO INHIBITORS**

N-methyl-4-phenylpyridinium (MPP+), the oxidation product of MPTP, is normally taken up by the dopaminergic terminal and enters with the cell's mitochondrial function, ultimately leading to the death of the neuron. Selegiline hydrochloride (also referred to as L-deprenyl), a selective, irreversible MAO-B inhibitor, prevents MPTP toxicity by blocking the oxidation of MPTP to MPP+. Additionally, selegiline potentiates the effect of levodopa, decreasing the amount of the drug necessary to control symptoms. Selegiline has been found to have a modest beneficial effect on symptoms of PD and to help smooth out levodopa-induced motor fluctuations.14

Many laboratory and clinical studies have provided evidence that selegiline exerts neuroprotective effects not only through its antioxidant and levodopa-sparing properties, but also because of its anti-apoptotic effects.10 The DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) clinical trial examined the neuroprotective effects of selegiline and α-tocopherol (vitamin E).15 While the study clearly showed that selegiline delayed the need for levodopa therapy by about 9 months, the interpretation of this finding was confounded by the symptomatic effects of selegiline, and it was not possible to conclude that selegiline exerted any neuroprotective effects. Nevertheless, patients treated with selegiline showed significantly less deterioration than those treated with placebo, with prolonged survival.16 Although the exact neuroprotective mechanism of selegiline is unclear, more and more data suggest that it is independent of its ability to block MAO-B. Selegiline has been shown not only to prevent oxidative damage from occurring, but also to rescue cultured neurons from oxidative damage caused by MPP+.17 These and other studies suggest that selegiline's neuroprotective effect may be related to some trophic effect. This is the case for its analogue TCH 346, which, by binding to glyceraldehyde 3-phosphate dehydrogenase, prevents its translocation to the cell nucleus and thereby prevents apoptosis.18

**DOPAMINE AGONISTS**

Dopamine agonists directly stimulate dopamine receptors by decreasing presynaptic dopamine synthesis and the amount of levodopa necessary to control the disease. Although dopamine agonists have been used to provide symptomatic relief in PD for 30 years, attention is now focused on putative neuroprotective effects of these medications. Preclinical studies have shown that dopamine agonists may be neuroprotective through a variety of mechanisms.19,20 Dopamine agonists decrease dopamine metabolism, exert a levodopa-sparing effect, and delay the onset of levodopa toxicity. In addition to down-regulating dopamine turnover by stimulating dopamine auto-receptors, dopamine agonists may also have direct antioxidant effects due to their ability to scavenge free radicals.19 Pretreatment of cultured and in vivo nigral cells with ergot (eg, bromocriptine and pergolide) and nonergot (eg, pramipexole and ropinirole) dopamine agonists protected the cells from death by oxidative damage.20,21 Preincubation also protected cells from glutamate-induced toxicity.20 Studies of ropinirole have suggested that its neuroprotective effects may involve activation of glutathione, catalase, and superoxide dismutase.21 Further support for the neuroprotective effects of dopamine agonists has come from 2 recent studies evaluating disease progression via functional imaging. The Parkinson Study Group used single-photon emission computed tomography to compare the effects of pramipexole vs levodopa on PD progression. The results of the 46-month study showed that patients taking pramipexole had reduced dopaminergic neuronal loss, compared with patients taking levodopa.22 The Requip as Early Therapy versus L-dopa–PET (REAL-PET) study used PET scans to assess PD progression in patients taking ropinirole hydrochloride (Requip; SmithKline Beecham Pharmaceuticals, Uxbridge, England) vs levodopa. This 2-year, double-blind study concluded that treatment with ropinirole, when compared with levodopa, results in a significantly slower decline in fluridopa uptake.23 Although not conclusive, these studies provide crucial evidence supporting the role of dopamine agonists as disease-modifying and possibly neuroprotective agents.

**NMDA ANTAGONISTS**

Since neuronal damage resulting from glutamatergic toxicity is one of the leading hypotheses for neurodegeneration, N-methyl-D-aspartate (NMDA) glutamate receptor antagonists are becoming increasingly important candidates for neuroprotective clinical trials. Although amantadine, a partial NMDA antagonist, has been used in PD for over 30 years, its role in neuroprotection is currently being investigated. Not only is amantadine a levodopa-sparing drug, but patients treated with amantadine have shown increased survival times, which suggests a neuroprotective effect.24 Furthermore, amantadine and other NMDA antagonists have been shown to be useful in the treatment of levodopa-induced dyskinesias.25

**ANTIAPOPTOTIC THERAPY**

Although the mechanisms of cell death in PD are not fully understood, increased levels of pro-apoptotic signaling proteins have been found in nigral neurons of patients with PD. Agents designed to modify these proteins and alter the
pathways that lead to apoptosis would be expected to exert neuroprotective effects in PD and other diseases associated with apoptosis. Drugs that act as caspase inhibitors or immunomodulators, as well as other antiapoptotic agents, are currently investigated in PD centers around the world.\textsuperscript{26-28}

CURRENT THERAPEUTIC GUIDELINES

The most important therapeutic strategy in PD is to tailor treatment to the needs of each patient.\textsuperscript{18} While the time of therapy initiation and the order in which drugs should be initiated remain controversial, most parkinsonologists support the idea of delaying the use of levodopa until other medications (eg, selegiline, anticholinergics, amantadine, and dopamine agonists) have failed to adequately control symptoms. In our practice, patients diagnosed with PD and never previously treated are usually given selegiline first because of its ability to delay the need for levodopa. The goal of selegiline and other prelevodopa drugs is not to completely control all symptoms, but to diminish them so that the patient is able to function at home and at work. Once selegiline has been therapeutically exhausted, the choice of the next medication depends on the age of the patient. Patients younger than 65 years and cognitively intact may begin treatment with either amantadine or anticholinergics (Figure).\textsuperscript{18} Amantadine may decrease all the cardinal parkinsonian signs, and it has one of the best risk-to-benefit ratios of all antiparkinsonian medications. In addition, it has been shown to decrease levodopa-induced dyskinesias. Anticholinergics (eg, trihexyphenidyl) are particularly useful in patients with troublesome tremor, but side effects such as dry mouth, urinary retention, constipation, and cognitive impairment typically limit their use. After the addition of amantadine or anticholinergics to selegiline, trying dopamine agonists is recommended. Many studies now support the notion that monotherapy with dopamine agonists, particularly pramipexole, ropinirole, and pergolide mesylate, can delay the use of levodopa by several years. Levodopa should be used once treatment with all other medications is no longer effective. Patients older than 65 years or those who show even mild cognitive impairment should not be prescribed anticholinergics, as any symptomatic benefit is usually annulled by side effects. It is generally accepted that older patients may begin levodopa therapy earlier than younger patients. Unless absolutely necessary because of troublesome symptoms that interfere with social or occupational activities, young patients should almost never be prescribed levodopa because they are at a particularly high risk of developing motor complications early. Once levodopa is added, the dosage should be kept at a minimum and should be supplemented with dopamine agonists and catechol-O-methyltransferase inhibitors (eg, entacapone), particularly when its effect is wearing off and other motor complications emerge. Surgery (eg, pallidotomy or deep-brain stimulation) may be an option for patients who are functionally impaired despite optimal medical therapy.\textsuperscript{29}

While conclusive evidence of pharmacologic neuroprotection in PD is lacking, the role of primary care physicians in the treatment of PD is becoming better defined. If neuroprotective therapy favorably alters the course of the disease, then disease-modifying agents have to be prescribed early. In this review we attempted to summarize the current notions about the rationale for therapeutic strategies, but it is important to emphasize that as our understanding of the mechanisms of neurodegeneration changes, so will the therapeutic guidelines. Early diagnosis is critical not only to maximize potential benefits from prompt neuroprotective intervention, but also to educate the patient about novel and emerging therapies. Primary care physicians should become familiar with the regional centers with expertise in experimental therapeutics of PD so that they can refer patients for evaluation as potential subjects in clinical trials. Currently, at least a dozen novel and promising therapeutic strategies are being investigated in various academic centers, most of which are members of a consortium of clinical researchers—the Parkinson Study Group (http://www.Parkinson-study-group.org). Future success in treatment of PD will depend on a close collaboration between clinical researchers and primary care physicians.

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