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Neuroprotection for Parkinson's disease

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Summary Although still a disorder of unknown etiology, Parkinson's disease (PD) has provided a number of clues that have led to clinical trials of neuroprotection. For example, defects in mitochondrial metabolism and evidence for oxidative stress in PD have fostered therapeutic interventions aimed at slowing disease progression. More than a dozen compounds already have been tested in PD for disease modification, and others are in planning stages for clinical trials. The challenge is to find a highly effective therapy halting disease progression (beyond the relatively modest clinical effect exemplified by recent findings with coenzyme Q-10 treatment administered at 1200 mg/day). Clinical exam-based ratings and disability assessments still serve at providing the primary evidence of efficacy. However, with surrogate biomarkers such as radiotracer neuroimaging of the dopaminergic system, the pace of clinical investigation can be increased. Recent years have seen the utilization of more sensitive study methods in PD neuroprotection research, such as staggered wash-in, 2×2 factorial, and "futility" trial designs. The results of several ongoing PD neuroprotection trials are planned for release in the near future.

Introduction

For most patients with Parkinson's disease (PD) over the past four decades, highly effective symptomatic treatment with levodopa has been a routine experience. At their best, such medications have permitted most patients to achieve near-normalization of most Parkinsonian signs and symptoms. Only for some advanced cases of PD does significant disability evolve, and this typically occurs with at least some degree of continuing benefit from levodopa and other drugs that can mask most of PD's motor features. Therapeutics for Parkinsonism has capitalized on an increasingly thorough understanding of the key pathophysiology behind PD's motor deficits: a marked decrease of dopaminergic neurotransmission normally provided by neurons projecting to the striatum from the substantia nigra pars compacta (SNpc). For some fortunate patients, the relief of motor disabilities by medications can continue indefinitely. However, over time, the consistency of such benefits tends to diminish and problems such as involuntary movements can develop. Since mild PD tends to be so responsive to medication, treatment strategies to maintain this disorder in its mild stage are desirable. Such therapies, if applied to PD at its preclinical stage, might even prevent the loss of SNpc neurons and so would serve as the equivalent of a cure. Protective therapy against the progression of PD might also help to avert problems of advanced disease that are currently untreatable, such as impairments of posture, balance, and cognition.

The search for a neuroprotective therapy of PD has captured the interest of thousands of clinicians and basic neuroscience researchers. A leader in this quest has been Professor Moussa Youdim, who has contributed a wealth of ideas and discoveries to finding the cause(s) and treatments of PD. Readers of this Festschrift should be well aware of Professor Youdim's influential role at investigating the most promising directions of PD pathogenesis, including oxidative stress, apoptosis, and toxicities of iron and neuromelanin. Through his own laboratory's efforts and from numerous collaborations established throughout the world, Professor Youdim has also maintained a long-standing interest in the discovery of potential neuroprotective agents for PD. Each of his lectures on the topic (and Moussa has never been shy about placing himself in the thick of debate!) has aimed at bring together the multiple strands of the etiological puzzle into a unifying theme. The challenge is to find rational therapeutic interventions for PD in the current absence of evidence that unequivocally points to a particular cause (or causes) of PD. Contemporary efforts to slow or halt the disease are guided primarily

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by analogies to animal models and a few insights into the disorder's pathophysiology. Nonetheless, a growing list of hypothetical targets for definitive treatment of PD has been developed. Reflecting this diversity of options, a recent initiative by the National Institutes of Health considered 59 possible therapies against the progression of PD (Ravina et al., 2003) (a list that does not include the option of mercury treatment as originally proposed by James Parkinson (Parkinson, 1817)). The diversity of possible anti-Parkinsonian therapies has expanded greatly from an earlier focus limited to anti-oxidant strategies (Spencer et al., 1996). In this article, the results of several clinical trials and ongoing studies of neuroprotection in PD will be reviewed.

Although cognitive and autonomic disturbances can develop as later features in many cases of PD, the increasing severity of motor impairments generally provides the most obvious evidence for disease progression over time. These motor features can be linked to loss of the majority of dopaminergic neurons in the SNpc (Fearnley and Lees, 1991). Parkinsonian features correlate to the extent of SNpc neuronal dropout after reaching a theshold of greater than 60% of the original cellular complement. Although no biological marker unequivocally gauges these changes in the living patient, neuroimaging techniques utilizing radiotracers have shown a linear rate of decline in the striatal dopaminergic system as PD worsens (Ravina et al., 2005). These neuroimaging techniques have been utilized in clinical trials as potential surrogate markers, although their possible role in replacing or even supplementing clinical indicators is still in question.

The elusive goal of disease modification

Initially, the specific goal of an effective PD neuroprotective treatment would seem to be obvious, especially if the therapeutic perspective is guided from studies of neurotoxins such as MPTP and 6-hydroxydopamine (Heikkila et al., 1990). Like the pathological outcome in PD, these neurotoxins produce a relatively selective loss of dopaminergic neurons in the SNpc. The analogy these neurotoxins have provided to the development of neuroprotective therapies has been pervasive. Sparing the further loss of dopaminergic SNpc neurons would seem to be the means to accomplish slowing of disease progression and leads to conceptualizing the appropriate treatment of PD as inhibiting a toxic mechanism. This is exemplified in some of thinking behind proposals for studying selegiline as a neuroprotective strategy, based on outcome of selegiline pre-treatment in the animal model of MPTP toxicity (Heikkila et al., 1990). However, whether there actually is a similar neurotoxicity mechanism to target in PD is not known. Another challenge ahead is the interpretation of results from a successful clinical trial. For example, a therapy associated with less worsening on clinical criteria might reflect either the halting of further neuronal dropout or else the initiation of recovery processes (such as neuronal sprouting or increased output of dopamine from remaining SNpc neurons). These alternative therapeutic mechanisms are obviously quite different though the clinical result is the same. Other challenges await the interpretation of successful disease-modifying therapies. For example, an effective treatment preventing clinical deterioration might be quite distinct from the mechanisms initiating the disorder. Intervening at a common final pathway of neurodegeneration, such as at steps in inflammatory processes observed in PD (Miklossy et al., 2006) or apoptotic mechanisms (Tatton et al., 2003) might be successful without having targeted the specific causative mechanism. For these reasons, inferring a disease process from the outcomes of clinical studies will continue to be problems, even now that more than a dozen neuroprotection trials have been undertaken (LeWitt, 2004).

Monoamine oxidase inhibitors in Parkinson's disease

As clinicians and researchers in the 1980s set their sights on more than symptomatic relief of PD, the predominant viewpoint was that this disorder was the result of unprotected oxidant stress causing progressive damage to SNpc neurons. The selective vulnerability of these neurons was thought to be partly a consequence of their dopamine metabolism. Dopamine produced by SNpc neurons can convert to quinones, semiquinones, and other byproducts of autooxidation. The action of monoamine oxidase (MAO) generates hydrogen peroxide, which can then further react to produce various reactive oxyradicals (Spencer et al., 1996; Jenner, 2003). Consequences of these processes include oxidant reactions against vital cell constituents such as lipid membranes, nucleic acids, and proteins. The unique relationship between dopamine metabolism and SNpc neurons led to speculation that blocking MAO might offer one means for slowing a plausible mechanism for progressive damage to dopaminergic neurons. With this thought in mind, a clinical trial was designed by clinicians who formed the Parkinson Study Group in North America in the mid 1980s (Parkinson Study Group, 1989a). Their study, the first large neuroprotective clinical trial in PD, incorporated a trial of a selective MAO inhibitor, selegiline (deprenyl), as one of two antioxidant strategies to be tested. Blockade of the type B species of MAO (MAO-B) was chosen to be the appropriate target since, at that time, this enzyme was thought to

be the predominant source of dopamine catabolism. Selective MAO-B can be accomplished with selegiline at 10 mg per day, the dose chosen for this study. A 2-year randomized clinical trial of 800 subjects tested whether selegiline might protect against progression of PD. This study, titled ''deprenyl and tocopherol antioxidative therapy of Parkinsonism'' (DATATOP), was also conducted with a biologically active form of vitamin E, alpha-tocopherol. The study was a 2×2 factorial randomization between for treatment arms, including placebo and a combination of alpha-tocopherol and selegiline (Parkinson Study Group, 1989a, b; 1993). Otherwise untreated PD subjects were followed to a primary endpoint defined as the need for symptomatic treatment of worsening parkinsonism. Other secondary endpoints included the unified Parkinson disease rating scale (UPDRS), other clinical and neuropsychological assessments, and measurement of CSF homovanillic acid and other neurochemicals as biomarkers of change over time in dopamine metabolism (Parkinson Study Group, 1995; LeWitt et al., 1992).

The DATATOP trial was halted prior to its planned two-year duration because of initial findings suggesting a neuroprotective effect from selegiline. A major treatment effect, observed at a mean of $12 \pm$ five months after start of selegiline, was that 170 of 401 subjects receiving placebo but only 97 of 399 receiving selegiline reached the study endpoint. The two treatment arms had a highly significant difference ($p < 10^{-8}$) and led to initial conclusions of a disease modifying effect that could evolve rapidly following the start of selegiline treatment (Parkinson Study Group, 1989b). A Kaplan-Meier analysis of subjects reaching the need-for-levodopa endpoint demonstrated reduction in the risk by approximately half in the selegiline-treated group. No benefit occurred for the alpha-tocopherol-treated group, however (Parkinson Study Group, 1993). Although exciting in its implications for the hypothesis of oxidant stress as a mechanism for PD, subsequent analysis of the DATATOP study revealed that the rate of reaching endpoint did not differ from placebo if the assessment was evaluated just a few months later. Furthermore, there was an alternative explanation for the apparent reduction in rate of progression. Unsuspected at the design of the study was a small symptomatic effect exerted by selegiline. Although these symptomatic actions against mild Parkinsonism didn't necessarily account for all of the clinical improvements found in the selegiline-treated group, as compared to placebo, any further analysis of the study data was compromised by this confound. The DATATOP study has continued to be a challenge for interpretation of its findings (Ward, 1994; Maki-Ikola and Heinonen, Goetz et al., 2002) and emphasizes the complexities implicit in clinical research for neuroprotection against PD (Clarke, 2004). It has offered researchers considerable information on the natural history of untreated PD and yielded the unexpected finding that selegiline treatment was associated with decreased risk for eventually developing ''freezing'' of gait (Giladi et al., 2001).

The DATATOP trial provided useful insights into the development of study designs for neuroprotection in PD. Although the ''need for levodopa'' endpoint may appear unduly subjective and imprecise for studying the progression of PD (LeWitt et al., 1997), this endpoint, along with DATATOP findings from UPDRS scores have found their way to guide subsequent neuroprotection clinical trials. The expectation that CSF homovanillic acid (derived from CNS dopamine metabolism) would provide a useful biomarker of disease progression was not supported by comparisons of homovanillic acid concentrations measured before and after the study was completed. Furthermore, the CSF findings also demonstrated that selegiline treatment did not completely block the oxidative deamination of dopamine as was initially hypothesized (LeWitt et al., 1992). As one of the largest clinical studies ever carried out with PD patients, the DATATOP trial provided the groundwork for future studies of MAO-B inhibitors (Parkinson Study Group, 1996, 2002) and other potential neuroprotective therapies.

Selegiline has been studied in several smaller investigations using study formats similar to the DATATOP trial. In 2 of them, also using selegiline as a monotherapy (10 mg/day) in 54 PD subjects, progression and delay to the need for levodopa was demonstrated (Tetrud and Langston, 1989; Myllylä et al., 1991). Other studies attempted to assess for symptomatic effects of selegiline by prolonging drug washout for eight weeks, and concluded that this drug may have conferred a neuroprotective effect (Palhagen et al., 1998). One study found that the ability of selegiline-treated subjects remained milder than placebo for up to 12 months, although as in the DATATOP study, the apparent protective action was lost by 12 months after the start of treatment (Myllylä et al., 1991). In another study, conducted over five-years with a randomized and placebo-controlled format involving selegiline together with levodopa therapy, an attempt was made to discern neuroprotective form the symptomatic actions of the MAO-B inhibitor (Larsen et al., 1999). The statistically significant slower rate of PD progression found in the selegiline-treated group provided evidence for a possible protective effect. In the background of studies suggesting that selegiline might be disease-modifying were laboratory

findings indicating that, beyond inhibition of MAO, the drug's metabolite desmethylselegiline might offer neuroprotective actions including anti-apoptotic effects (Tatton et al., 2003).

The initial reports of possible neuroprotective benefits from selegiline prompted consideration of other MAO inhibitors. The next compound to be investigated was lazabemide, a reversible inhibitor of MAO-B with greater selectivity and no amphetamine metabolites. The possibility of fully washing out the drug in a short period of time offered a better opportunity to sort out symptomatic from neuroprotective actions. Lazabemide provided a similar degree of mild anti-Parkinsonian action to the effects of selegiline (LeWitt et al., 1994). In a randomized placebo-controlled study of 321 subjects lasting up to one year, the results were strikingly similar to those of the DATATOP trial. In addition to small symptomatic effects, a Kaplan-Meier analysis revealed that the several might reduce the risk for reaching the ''need for levodopa'' endpoint by 51% ($p = 0.008$) (Parkinson Study Group, 1996). With lazabemide, a disease-modifying effect linked to inhibition of MAO-B was starting to appear all the more likely. However, further opportunities for the study of this drug were halted despite the promising results.

Selective inhibition of MAO-B was the target of rasagiline, another compound that was developed for a trial of neuroprotection for PD. Rasagiline is, like selegiline, a propylpargyline structure that is an irreversible inhibitor of MAO-B (Akao et al., 2001). In laboratory research conducted by Professor Youdim and his colleagues, it has demonstrated a number of properties beyond MAO-B inhibition that show promise for achieving neuroprotection (Maruyama et al., 2002; Mandel et al., 2003; Youdim et al., 2003). Rasagiline at 1 and 2 mg/day was studied in a randomized, placebo-controlled clinical trial of 404 otherwise untreated PD subjects. In addition to a secondary endpoint of ''need for levodopa'', the primary measure of efficacy was a magnitude of change in total UPDRS from baseline to 26 weeks. A ''staggered start'' study design was utilized in an effort to minimize the potentially confounding effect of an insufficient drug washout. Results of the trial (termed the TEMPO study) revealed that both doses of rasagiline produced small but potentially meaningful improvements, as compared to placebo ($p < 0.001$) (Parkinson Study Group, 2002). The magnitude of this effect (approximately 4 points improvement in total UPDRS scores as compared to placebo) was comparable to the results of selegiline in the DATATOP study (Parkinson Study Group, 1989). Statistically significant improvement in UPDRS activities of daily living scores and in a quality-of-life measure indicated improvements were more than derived from motor improvements. However, Kaplan-Meier survival analysis showed no statistically significant changes between placebo and rasagiline in delayed need for the start of symptomatic treatment (Parkinson Study Group, 2002).

Dopaminergic agonists and levodopa

Medications that have symptomatic effects against PD have also been studied as to their possible role as neuroprotective agents. For many years there have been hypotheses that an exogenous source of dopaminergic stimulation may lessen the progression of PD. Although this line of reasoning has rested upon more intuitive than experimental evidence, laboratory research has in fact supported a potential neuroprotective role for several dopaminergic agonists. For example, dopaminergic agonists such as apomorphine and pramipexole have been shown to exert free radical scavenging properties that might be beneficial if an oxidant stress mechanism is demonstrated to be involved in the progression of PD (Grunblatt et al., 2001; Le and Jankovic, 2001). Other evidence has also connected dopaminergic agonists currently in use for PD with experimental properties in support of neuroprotection. The ergoline compound pergolide, when administered chronically to Fischer 344 rats, leads to diminished age-related attrition of dopaminergic nigrostriatal neurons (Felten et al., 1992). Another dopaminergic compounds, pramipexole, has been studied in a number of models in which neuronal damage has been produced, including methamphetamine, 6-hydroxydopamine, 3-acetylpyridine, and MPTP (Hall et al., 1996; Vu et al., 2000; Sethi et al., 1997; Cassarino et al., 1998; Kitamura et al., 1998; Zou et al., 2000; Le et al., 2000; Carvey et al., 1997; Ling et al., 1999; Anderson et al., 2001). The protective actions noted with pramipexole, as suggested by studies of cultured dopaminergic mesencephalic neurons, may be related to inactivation of specific dopaminergic receptors (Ling et al., 2002) or by anti-apoptotic actions (Abramova et al., 2001, 2002). Protection against 6-hydroxydopamine-induced damage of dopaminergic nigrostriatal projections in mice has also been demonstrated with ropinirole, another dopaminergic agonist (Takata et al., 2000, 2001). These and other results from studies with dopaminergic compounds have supported the notion that various agonists in clinical use might also add to their value by neuroprotective actions.

Clinical trials have provided intriguing findings suggesting possible protective actions of dopaminergic therapy. Two clinical trials have been carried out in which radio-

tracer neuroimaging techniques have helped to gauge the progression of PD over time as a surrogate of degeneration in the dopaminergic nigrostriatal system. Imaging the presynaptic dopamine nerve terminal with a positron emission tomography [PET] ligand, [^{18}F]-dihydroxyphenylalanine (fluorodopa), has permitted the comparison of long-term outcomes from ropinirole to levodopa therapy in PD patients (Brooks et al., 2003; Marek et al., 2002). Survival of dopaminergic nerve terminals is a correlate of remaining neurons based in the SNpc. In the clinical trial termed REAL-PET (Whone et al., 2003), 86 mildly affected PD patients were randomized to monotherapy with either ropinirole or carbidopa/levodopa. The PET data indicated less loss of dopaminergic nerve terminals at two years from ropinirole treatment as compared to levodopa. Overall uptake of fluorodopa in the putamen showed a 13% loss in the ropinirole group, as compared to a 20% reduction in the group randomized to levodopa ($p = 0.034$). In addition, statistical parametric mapping detected slower progression of dopaminergic loss in the putamen and the substantia nigra (which showed a +3% change in the ropinirole treated PD patients as compared to a −8% loss in the levodopa treated group ($p = 0.035$).

Another randomized clinical trial comparing outcomes of pramipexole and levodopa has also concluded that the dopaminergic agonist conferred an apparent neuroprotective action, as judged by less change in a biomarker of striatal dopaminergic terminals (Parkinson Study Group, 2000a and b, 2002). This study used single proton emission computed tomography (SPECT) with the ligand imaging the dopamine transporter, [^{123}I]-2β-carboxymethoxy-3β(4-iodophenyl)tropane (β-CIT). The 82 PD patients in this study (a subset of the CALM-PD trial) were followed up to 46 months after baseline assessments with two β-CIT SPECT studies. The data in this investigation, which showed linear decline in imaging of the dopamine transporter for both treatment arms, showed significantly less loss of transporter sites in the pramipexole-treated group compared to patients randomized for levodopa. Changes from baseline scan showed $16.0 \pm 13.3\%$ decline versus $25.5 \pm 14.1\%$ decline in the pramipexole group compared to levodopa ($p < 0.01$). The similar direction of results with both pramipexole and ropinirole point to a ''class'' effect of dopaminergic agonists in conferring protection against the advance of PD. Since these clinical studies did not involve washout of the dopaminergic drugs to permit assessment of a drug-free state, the clinical relevance of the neuroimaging changes has not been determined.

Although levodopa has been thought of as nothing more than the amino acid precursor of dopamine, the possibility that chronic treatment might promote disease progression remains at the background of interpreting the dopaminergic agonist studies. There is little evidence in support of the latter assertion and some evidence supports the possibility that levodopa might confer an anti-oxidative neuroprotectant effect (Camp et al., 2000). A formal investigation of this matter was recently conducted to study disease progression and possible relation to levodopa dose. This was explored in a 40-week clinical trial of levodopa treatment in which baseline UPDRS status was compared to Parkinsonian state following a 2-week drug washout (Fahn et al., 2004). For the 361 mildly-affected PD subjects, randomized assignment to levodopa regimens of 150, 300, and 600 mg/day was compared to placebo treatment. This study (the ELLDOPA trial) was complemented with a SPECT study of β-CIT comparing baseline and post-washout status at 42 weeks in a subset of 142 subjects. The clinical results showed that all levodopa regimens yielded improvement even after washout, with the greatest effect at levodopa intake of 600 mg/day. In contrast, the placebo group showed some deterioration. While the UPDRS findings were compatible with a protective effect (and not indicative of increasing the rate of disease progression as compared to placebo), the outcome of striatal β-CIT uptake showed significantly more decline in the levodopa-treated groups. β-CIT measures the integrity of the dopamine transporter located in the nigrostriatal nerve terminals in the striatum and has been proposed to be a correlate of progressive loss in dopaminergic SNpc neurons. Since long-term PD treatment effects might confound the analysis of dopaminergic nigrostriatal projections, the validity of using β-CIT (and other radiotracer imaging in this and other studies) still remains questionable (Ravina et al., 2005).

Neuroprotection by enhancement of mitochondrial metabolism

The only identified systemic biochemical marker of PD is and alteration in the mitochondrial chain of electron transport (Shults et al., 1999). The finding of diminished complex I activity in PD brain prompted clinical investigation of coenzyme Q-10, which serves as an antioxidant as well as electron acceptor. Impaired mitochondrial function is a biologically plausible mechanism of slow neuronal damage as well as oxidative stress. On this basis, a clinical trial was carried out to test supplementation with coenzyme Q10 in order to enhance complex I activity. This placebo-controlled study involved doses of 300, 600, and 1200 mg per day for 16 months in 80 otherwise untreated PD subjects (Shults et al., 2002). Total adjusted mean UPDRS

scores for the highest dose indicated an improvement of 6.69 points ($p = 0.0416$). Improvements were not seen for the lower doses. Most of the benefit on total UPDRS was attributable to less decline in the activities of daily living component of this scale, rather than change in motor features of Parkinsonism. This study has prompted a second clinical trial investigating the use of coenzyme Q-10 at 2400 mg per day. Although the latter study will be conducted as a ''futility'' trial (see below) (Elm et al., 2005), it should provide some indication whether the initial trial's positive findings represented a dose threshold affect. The beneficial outcome of the first trial, however small, is intriguing but does not necessarily point to enhancement of mitochondrial metabolism as the only explanation.

Enhancing impaired mitochondrial metabolism is the theme behind another clinical trial targeting the defect in mitochondrial complex I in PD. Creatine is a precursor for the formation of phosphocreatine, an energy intermediate that serves to transfer phosphoryl groups in the synthesis of mitochondrial ATP. The mechanism by which increase dietary intake of creatine might be beneficial through enhancing phosphocreatine production includes an overall reduction in mitochondrial oxidative stress (through stabilizing creatine kinase). Creatine kinase acts to inhibit opening of the mitochondrial transition pore, a step in the initiation of apoptosis, which, in turn, has been hypothesized to be a possible contributing factor to neurodegeneration in PD (Tarnopolsky and Beal, 2001). Laboratory studies have suggested the potential for dietary supplementation with creatine to spare MPTP-induced SNpc degeneration in mice (Matthews et al., 1999). To test the hypothesis that the progression of otherwise untreated PD might be slowed by daily supplementation with 10 grams of creatine, a clinical trial in a ''futility'' study format (see below) has been carried out. The results of the study, conducted by a North American research consortium under the direction of the National Institutes of Health (Ravina et al., 2003), are planned to be released shortly.

Neuroprotection from glutamate antagonism

For a number of neurodegenerative disorders, excitotoxicity via activation of glutamate receptors has been hypothesized (Wu et al., 2002). In PD, the possibility that activation of NMDA receptors might be a pathway for neurodegeneration has led to a search for compounds potentially blocking endogenous glutamate stimulation (Matthews et al., 1999). Many of the pharmacological agents achieving glutamatergic blockade confer their own neurotoxicity. However, riluzole has been well tolerated in its clinical application for slowing progression of amyotrophic lateral sclerosis. Riluzole was studied in conventional doses as a possible means for slowing the progression of otherwise untreated PD in a multicenter clinical trial. Because of lack of efficacy determined in an interim analysis, this trial was halted before its planned duration (Rascol et al., 2002).

Neuroprotection by inhibition of microglial activation

In the PD brain, activation of microglial is a prominent feature suggesting an inflammatory component to the pathogenesis of neurodegeneration in this disorder (Vila et al., 2001). Similar findings can be produced from experimental lesioning of dopaminergic SNpc neurons. Attempts to block microglial activation have been explored using the tetracycline compound minocycline. In rodent models of Parkinsonism induced by the neurotoxins MPTP and 6-hydroxydopamine, increased survival of dopaminergic SNpc neurons has been achieved by administration of minocycline (Du et al., 2001; Wu et al., 2002; He et al., 2001). The beneficial effects of minocycline may also be due to its properties of blocking caspases 1 and 3 as well as other factors that mediate apoptosis (Du et al., 2001). On the basis of these effects as well as its action against microglial activation, a clinical trial of minocycline at 200 mg per day has been carried out as a futility study (in the same 2×2 factorial study also investigating creatine, discussed above). The results of the study are planned for reporting shortly.

Neuroprotection by neurotrophin-like compounds

In the past 15 years there have been several studies investigating compounds with neurotrophin-like properties. One of these, GM1-ganglioside, has shown promise against MPTP-induced Parkinsonism in nonhuman primates (Schneider, 1992; Schneider et al., 1998) and has undergone limited human testing. Another clinical trial involved oral administration of AMG-474, a compound designated as a *neuroimmunophyllin* and an analogue of the immunosupressant FK-506 (which selectively enhances regeneration in damaged nerves). Although lacking the immunosuppressive actions of FK-506, AMG-474 attached to the same binding proteins and showed effectiveness at promoting recovery from animal models of neurotoxin-induced Parkinsonism. AMG-474 (also designated as NIL-A) penetrates the blood-brain barrier and was investigated in a 24-week clinical trial at 800 or 4000 mg per day. This placebo-controlled study enrolled 300 PD patients.

Although the results of this investigation were not been formally reported, it was discontinued after the sponsor (Amgen) reported that the study results were negative. AMG-474 returned to neuroprotection study in PD under the sponsorship of Guilford Pharmaceuticals and designated as GPI-1485. This compound is undergoing investigation as part of the NET-PD futility study (as one of the treatments in a multicenter, placebo-controlled 2×2 factorial study together with Coenzyme Q-10).

Another compound recently studied for its neuroprotective potential is CEP-1347 (a synthetic compound also designated as KT7515). This small molecule acts to inhibit mixed lineage kinase-3, which is a major component of the transcription factor c-Jun-mediated terminal kinase signaling pathway involved in apoptotic cell death (Harris et al., 2002; Saporito et al., 2002). With the hypothesis that SNpc neuronal loss in PD might be spared by use of CEP-1347, a randomized placebo-controlled clinical study has been carried out to determine feasibility for a larger scale investigation (Schwid et al., 2002). With the finding of good tolerability and safety at 100 mg per day, more extensive testing has been underway in a randomized clinical trial termed the PRECEPT study by the Parkinson Study Group.

Clinical trials have been carried out with TCH346 (also designated in laboratory research reports as CGP3466 and as CGP 3466B), a small molecule with structural similarities to selegiline but without MAO inhibitory properties. TCH346 was developed to target a key step in programmed cell death involving the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Inhibition of GAPDH is also a property of rasagiline (see above) and other interventions by other neurotrophic-like compounds. Studies in cultured PC12 cells and in MPTP-treated monkeys have supported the neuroprotective potential for TCH346 (Ishitani et al., 1996; Kragten et al., 1998; Andringa et al., 2000). A large-scale randomized clinical trial in early PD was carried out and its results will be reported shortly.

Discussion

There has been an expanding range of therapeutic options for halting the progression of PD since the first neuroprotection study, the DATATOP trial, was conducted almost 2 decades ago. This study, which focused upon anti-oxidative treatment strategies, was instrumental in developing techniques and learning the pitfalls involved in clinical trials. Its influence continues to current investigations and has also generated concern as to whether clinical trials can provide proof of neuroprotection in PD (Clarke, 2004). To answer the simple question of whether a drug is neuroprotective or not requires dozens (if not hundreds) of PD patients and careful attention to placebo effects, the choice of clinical endpoints, and clinically meaningful outcomes. Clinical trials that investigated outcomes from inhibitors of MAO-B have not a final answer as to whether this is an appropriate target for neuroprotection. Since both selegiline and rasagiline treatments have anti-apoptotic effects and additional pharmacological actions, the question remains unanswered as to whether these properties beyond MAO-B inhibition provide the basis for the observed clinical results.

One recent development that has impacted upon accelerating the pace of neuroprotection investigation in PD is the incorporation of *futility trial* study designs. This methodology, utilized in the ongoing NET-PD studies (Ravina et al., 2003), serves as a screening tool for promising therapies. If a study does not demonstrate a futility outcome, then it would be appropriate to plan and conduct a study designed for clinical benefit. In contrast, futility trials are powered only to indicate whether a treatment would be futile to extend into a larger scale study and, as a result, involve fewer patients and often require shorter study duration (Elm et al., 2005). The guidance from a futility analysis can help to prioritize utilization of the limited resources of funding, time, and available PD patients, especially when there is a long list of possible protective therapies in need of testing.

Other issues needing resolution by further research include the possible intermingling of symptomatic and neuroprotective actions, the value and limitations of surrogate biomarkers, and ways to differentiate compensatory responses from genuine reversal of the disease process. In particular, there is a need for SPECT and PET radiotracer neuroimaging to be validated, if possible, as to how well these techniques correlate to progression of PD. The ultimate target of neuroprotection is, of course, the relief of disability and improvement in quality of life, whose ideal rating methodology has been elusive. Fortunately, with the tremendous productivity of recent research, the PD patient is entitled to take an optimistic stance towards a future in which curing the disease may become a reality.

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