Neuroprotective Agents for Management of Parkinson's disease

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Introduction

Parkinson disease (PD), the second most common neurodegenerative disorder after Alzheimer's disease, is a movement disorder manifested by bradykinesia, rest tremor, postural instability and rigidity. It is an idiopathic, chronic and progressive syndrome that affects both physical and mental functions (1- 3).

As for the etiology of the disease, most cases are of unknown origin (idiopathic PD). Genetic, environmental factors (e.g. toxin exposure) and age related changes play a significant role in the pathogenesis of PD. In addition, free radical production causes oxidative and nitrosative stress which is linked to inflammation and leads to cell death and neuro-degeneration (1, 2, 4, 5).

Figure 1 shows how neuroinflammation and oxidative stress can damage dopaminergic neurons in patients who suffer from PD (6).

In vivo and In vitro studies show that neuroinflammation has a role in PD and serum levels of interleukin - 2, Tumor Necrosis Factor (TNF) α, interleukin- 6, nitric oxide and others are increased in these patients. Also antibodies against oxidized dopamine have been found in the sera of above patients. In addition, some oxidative factors like interleukin 6 and 1β, TNFα, osteopontin are present in cerebrospinal fluid of patients with PD. Epidemiologic studies show that individuals who take non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) have a lower risk of developing PD. This risk is also low in people who

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take two or more tablets of aspirin (6).

Neuroprotection should be considered for prevention of further loss of neurons in substantia nigra especially for patients with early clinical signs of disease (6). In the substantia nigra of PD patients, protective mechanisms are impaired and the brain is more susceptible to oxidants and reduced glutathione (GSH) -a potent antioxidant- level is seen in these patinets. The combination of excessive oxyradical formation in an environment deficient in GSH and other defense pathways may be one of the primary mechanisms of neurodegeneration in PD (4, 5, 7, 8).

A major hypothesis for the pathogenesis of PD is that neurotoxicity caused by free radicals leads to neuronal cell loss through overproduction of reactive oxygen and nitrogen species**.** Pharmacotherapy for PD improves patients' symptoms, but its influence on neuroprotection has not yet been established. At the present time, no specific drug or supplement can be recommended for neuroprotection and for controlling the progression of PD (9-11).

Our aim is to discuss agents that might have neuroprotective properties so that the selection of such drugs or supplements would be based on proper evidences.

Drugs used in Parkinson disease and their potential role in Neuroprotection

MAO B Inhibitors

Monoamine oxidase (MAO B) inhibitors (e.g. selegiline and rasagiline) have been evaluated for their neuroprotective properties. They can block free radicals formed from the oxidative metabolism of dopamine; also these agents may inhibit apoptosis (7, 11).

Selegiline: The possibility of long-term neuroprotection with selegiline has neither been confirmed nor disproven.
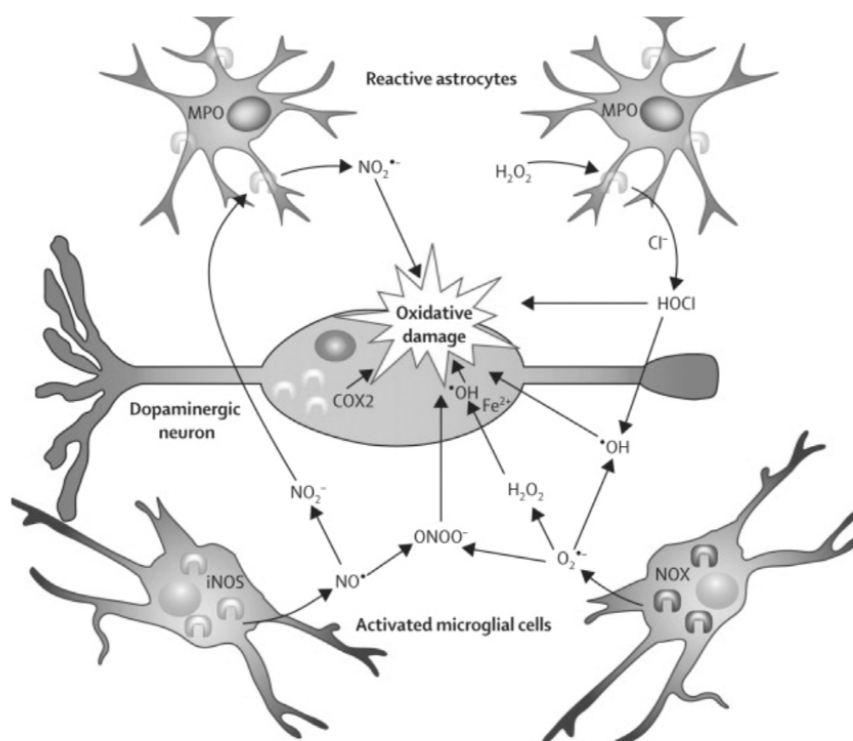
Figure 1. Damage to dopaminergic neurons caused by oxidative stress and neuroinflammation (6).

It also has a mild symptomatic benefit. The DATATOP (Deprenyl and Tocopherol Antioxidant Therapy of PD) study found that 10 mg daily selegiline delayed the onset of disability of Parkinson's disease in previously untreated patients by at leastnine months (12).

Studies found that treatment of early PD patients that haven't been on drug therapy with selegiline resulted in reduction of later freezing and possible neuroprotection. But this treatment did not reduce the occurrence of subsequent levodopa-associated motor fluctuations in this population; there was no persistent, long-term benefit in slowing the progression of PD with selegiline. Thus a 2002 report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN) suggested that there is insufficient evidence to recommend the use of selegiline for a neuroprotective effect. The 2006 report did not change this conclusion (7, 11).

Rasagiline: This drug showed neuroprotective properties in animal models. Human trials such as TEMPO (TVP-1012 in Early Monotherapy for Parkinson's Disease Outpatients) showed that rasagiline could slow progression of Parkinsonian disability. In this trial 440 patients diagnosed with early PD received 1 or 2 mg daily of rasagiline or placebo and the results showed that both dosages were effective in possible slowing of PD's progression (12). Early treatment with rasagiline

monotherapy had a smaller increase in mean adjusted total Unified Parkinson Disease Rating Scale (UPDRS) score than those who were initially assigned to placebo for six months before starting rasagiline. But because of rasagiline's symptomatic benefits might be responsible for the outcomes (7, 11). An extension of the TEMPO trial published in 2009, showed a statistically significant slower progression of PD (measured by the UPDRS score). This result can show the neuroprotective and disease modifying effect of the drug (7). ADAGIO trial showed that early treatment with 1 mg daily rasagiline might have neuroprotective effects (7). The 2006 AAN practice parameter concluded that there is insufficient data to confirm or disprove rasagiline's neuroprotection in patients with PD (11).

Dopamine (receptor) agonists

Dopamine agonists (DAs) are antioxidants and free radical scavengers in laboratory studies. This led to the hypothesis that early treatment with DAs may slow progression of neurodegeneration. Other studies with radiographic markers of basal ganglia function supported the possible neuroprotective effects of DAs (7, 11).

Pramipexole: The CALM-PD study, using SPECT B-CIT scans as a surrogate marker of neuroprotection, evaluated 82 patients with early PD. The results showed

that patients with 0.5 mg three times per day Pramipexole had lower decline in striatal B-CIT uptake compared with those treated with 25/100 mg three times per day carbidopa-levodopa. The length of the follow-up was four years. No difference in the UPDRS scores of the two groups from baseline was detected (7).

Ropinirole: A randomized trial studied 162 patients treated with either ropinirole or levodopa , using positron emission tomography (PET) scanning and the dopa decarboxylase ligand 18 F-fluorodopa (18) F-dopa. There was significantly less decline in (18) F-dopa uptake in patients assigned to ropinirole compared with those assigned to levodopa (6). Another randomized trial studied 45 patients who were assigned to ropinirole or levodopa. After two years, the ropinirole treatment group showed less reduction in the primary endpoint of putamenal (18) F-dopa uptake compared with placebo, but the difference was not statistically significant (13 versus 18 percent, respectively) (7).

Amantadine: Based on one Class IV study each, the benefit of amantadine cannot be determined (9). Amantadine has N-methyl-D-aspartate (NMDA) receptor antagonist properties that may account for its therapeutic effect by interfering with excessive glutamate neurotransmission in the basal ganglia (13).

Bromocriptine: It protects nigral neurons in rats exposed to 6-OHDA and can serve as a free radical scavenger. Studies show that initial treatment with bromocriptine did not reduce   long-term mortality or motor disability, and the initial reduction in motor complications associated with bromocriptine was not sustained. Similarly, there was no sustained benefit for early dopamine agonist treatment in a 15 year follow-up study of patients from another early trial comparing bromocriptine with levodopa (8).

It is uncertain whether these imaging studies reflect changes in the underlying pathology of PD or differential pharmacologic "regulatory" changes directly attributable to the drugs themselves. Therefore, these findings raise the possibility that dopamine agonists are neuroprotective, but confirmation is required in additional clinical studies, including prospective data in untreated patients (7). The 2006 AAN practice parameter noted that significance of the studies evaluating pramipexole and ropinirole is uncertain and that there is insufficient evidence to support or refute the use of pramipexole or ropinirole for neuroprotection in patients with PD (11).

Levodopa

Accumulating clinical trial data suggest that levodopa either slows the progression of PD or has a prolonged benefit even after the drug has been stopped. In one Class I study, levodopa is possibly neuroprotective for at least 9 months and does not accelerate disease progression. The significance of the dyskinesias at the highest levodopa dose is unclear (7, 11). The 2006 American Academy of Neurology (AAN) practice parameter concluded that levodopa is possibly neuroprotective for at least nine months and does not accelerate disease progression. An additional concern with the early use of levodopa in PD patients is its putative neurotoxicity concerning mitochondrial function (11). But, the statements regarding levodopa's possible neurotoxicity has been modified to state that this drug does not accelerate disease progression (14).

Potential Neuroprotective therapies
NSAIDs and COX2 inhibitors

As mentioned before Epidemiologic studies show that individuals who take non-aspirin non-steroidal anti-inflammatory drugs have a lower risk of developing PD and therefore the hypothesis of using these drugs for neuroprotection is tempting. These drugs have not been tested in PD but trials on Alzheimer's disease show no positive effect in this matter. Also because of adverse effects of these agents in long term use currently they are not advised in this matter (6).

Amantadine

Today amantadine is mainly characterized as a noncompetitive NMDA (N-methyl D-aspartate) receptor antagonist and is used widely for treating PD and also manages levodopa induced dyskinesia. Some studies show that the use of this drug slows the severity of PD and delays the onset of PD dementia (12).

Valproic Acid

Recently there have been studies showing a probable role for valproic acid in neuroprotection (it activates signal transduction pathways and inhibiting proapoptotic factors). In animal models treatment with valproic acid showed alpha-synuclein alterations caused by neurotoxins but no results are yet available for patients with PD (12).

Coenzyme Q10

Coenzyme Q10 has been evaluated for restoring dysfunctional mitochondria and prevention of nigral dopaminergic neurons' injury (2, 7). A small clinical trial evaluated 80 patients with early PD who were assigned to three dosage groups of coenzyme Q10 or to placebo, and were followed for progression of disease as measured by the Unified Parkinson Disease Rating Scale (UPDRS). Treatment with coenzyme Q10 at the highest dosage (1200 mg daily) was associated with a lower rate of disability progression over 16 months compared with placebo but it is not clear whether the benefit of coenzyme Q10 was due to neuroprotection or to symptomatic improvement. Another trial found no symptomatic benefit at three months for coenzyme Q10 compared with placebo. The 2006 AAN practice parameter concluded that there is insufficient evidence to support or refute the use of coenzyme Q10 for neuroprotection in patients with PD

(2, 7, 11).

Vitamin E

The results of the DATATOP trial showed that there was no beneficial effect of vitamin E compared with placebo for neuroprotection. Based on a sufficiently powered Class I study, vitamin E probably does not delay the need for levodopa therapy. This reflects lack of neuroprotection. The 2006 AAN practice parameter concluded that vitamin E should not be considered for neuroprotection (2, 7, 11).

The reason for possible role of vitamin E in neuroprotection was that some studies showed that vitamin E deficiency increases MPTP toxicity. It also shows antioxidant properties and is believed to reduce iron accumulation induced oxidative stress in brain. But overall no protective effect was seen with supplementation with this agent. Studies show that there was no difference in serum and cerebrospinal fluid levels of vitamin E between PD patients and healthy subjects (15).

Riluzole

Studies found no beneficial effect of riluzole compared with placebo as measured by change in the UPDRS. However, these studies were not sufficiently powered to exclude a modest neuroprotective effect of riluzole (7, 11).

One study on animal models showed that riluzole was effective in reducing progressive

neurodegeneration and relieved several clinically relevant PD symptoms(16).

Uric acid

Uric acid (urate) has antioxidant properties, suggesting that it may prevent oxidative damage and cell death in PD. In addition, patients with a history of gout appear to have a lower risk of PD than those without gout. Nonetheless, the finding of an association between uric acid concentration and the risk of PD does not prove that urate is neuroprotective. Furthermore, the therapeutic utility of urate (and diets designed to increase plasma uric acid) is likely to be limited by adverse effects with regard to the risk of developing gout and renal disease (7).

Creatine and Minocycline

Creatine is a dietary supplement marketed for performance enhancement. Similar to the theory for efficacy of CoQ10, creatine plays a role in mitochondrial energy production and has been shown to protect from MPTP-induced dopamine depletion in animal models. Minocycline is a second-generation tetracycline used to treat various infections, but has also been shown to display anti-inflammatory effects, which have resulted in improvements in chronic inflammatory conditions such as rheumatoid arthritis. An inflammatory response occurs

with loss of dopaminergic neurons in PD, and minocycline has been shown to be protective in MPTP animal models of PD (2, 7, 11).

Both creatine and minocycline were examined for use in PD in a trial. 10 g/day creatine and 200 mg/day minocycline were compared to placebo. After 12 months, the mean change in the total UPDRS was 5.6 units in the creatine group, 7.09 in the minocycline group, and 8.39 in the placebo group. Although it is too early to recommend either agent for use, future studies will likely proceed based on the encouraging results of this study (2, 7, 17).

N-acetyl-cysteine (NAC)

NAC was tested in animal models to evaluate its role in reducing oxidative stress, neurotoxicity and restoring low levels of glutathione in the substantia nigra in early PD patients. The results showed a neuroprotective effect for oral NAC which may be due to lowering of SNCA levels (alpha-synuclein, a protein primarily expressed in neural tissue and a mutation in its gene coding happens in some cases of PD) (17).

Zonisamide

This drug blocks sodium and calcium voltage channels and is a dopaminergic and GABAergic modulator; hence it has potential effectiveness in various neurologic disorders including PD (2).

Studies show that 25-50 mg zonisamide per day improves motor functions and wearing-off of levodopa without worsening dyskinesia in advanced cases of Parkinson disease. In addition zonisamide affects levels of glutathione and manganese superoxide dismutase expression and, it ameliorates reduction in the number of dopaminergic neurons in animal models treated with 6hydroxydopamine (6-OHDA). Zonisamide might have neuroprotective properties in patients with PD (12, 14).

Iron-Chelating Drugs

Some iron-chelating agents (M30 and HLA20) showed neuroprotective properties in vitro and in vivo in PD and Alzheimer's disease by preventing oxidative stress but further studies are definitely needed for recommending these drugs (5).

Surgery

One study showed a potential of neuroprotective effectiveness of thalamotomy but its benefit of could not be determined (11).

Other therapies

There is no place for drugs like biperiden or trihexyphenidyl (11).

Conclusion

The ultimate goal of treatment of PD is not achieved

until by some means the progression f the disease and continued damage to dopaminergic neurons can be controlled. The limitations in this matter are that up to now animal models do not closely mimic the process of disease in humans and no known biomarker correctly indicates the damage caused by neuroinflammation (6).

In conclusion, first we discuss levodopa therapy. This drug is a great agent in treating PD symptoms and increasing the quality of life of these patients. As mentioned before there is concern on this drug's use in PD since some studies showed neurotoxic effects in long term use (e.g. by enhanced production of free radicals), but. There is still no clear answer to this question but overall it seems that levodopa use does not accelerate disease progression but there is no long term evidence to recommend levodopa for neuroprotection (7, 11, 12, 14).

Past studies suggested that creatinine, minocycline and rasagiline are the most promising neuroprotective agents in PD but they are still in Phase III trials. Other agents like vitamin E, NSAIDs and CoQ10 show limited or inconsistent results when it comes to neuroprotection. Moreover studies show that doses 400 IU and more of vitamin E increases all cause mortality, there for we do not recommend this supplement in this case. Uric acid might be promising but the results in male and female population are controversial (15, 18, 19).

There is insufficient evidence to support or refute the use of riluzole, coenzyme Q10, pramipexole, ropinirole, MAO B inhibitors, amantadine, or thalamotomy for neuroprotection [9]. But dopamine agonists show potential neuroprotective properties but still further studies are needed in this matter (12, 20, 21).

At last until new strategies for evaluation of neuroprotective properties have not been developed and actual neuroimage markers and known serum oxidative biomarkers are not present, recommending an agent for neuroprotection in PD cannot be made.

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