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Contemporary Treatment of Parkinson's Disease

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Abstract: ***In the past the treatment of Parkinson's disease primarily comprised enhancing the dopaminergic functions of levodopa, stimulation of dopamine receptor sites directly by bromocriptine or by suppression of the cholinergic hyperactivity by anticholinergics such as trihexyphenidyl. Recently, new approaches have been applied aimed at protecting nigrostriatal neurons (Mitzuno Y, Mori H, Kondo T, 1994). These approaches involve several mechanisms: Blocking the dopamine transporter by mazindol, Blocking the NMDA-receptor by dizocilpine maleate, Improvement of neuronal survival by administration of brain-derived neurotrophic factor, Providing antioxidants such as Vitamin E, Inhibition of MAO-B by Selegiline, Except for Selegiline the other supposed neuroprotective treatment methods are still in the field of experimental studies.***

Keywords: Parkinson's disease, Levodopa, Selegiline

1. Introduction

In Parkinson's disease dopaminenergic neurons in the compact part of substantia nigra are reduced by 80-95%. Nomifensine and mazindol which are dopamine transporter inhibitors have shown they can prevent MPTP-induced Parkinsonism. The effect of the released dopamine and other neurotransmitters may be suspended by diffusion, enzymatic degradation or reuptake through a high affinity transporter. It remains to be checked whether compounds such as mazindol may have positive effects in patients with Parkinson's disease.

Numerous studies have shown that activation of corticostriatal glutamatergic system may influence the function of dopamine nigrostriatal terminals. The stimulation of excitatory amino acid receptors such as NMDA-subtype has been shown to enhance the release of dopamine synthesis in striatum which suggests that dopamine-excitatory amino acid interactions are important to the normal function of striatum. The drug amantadine is a weak antagonist of NMDA-receptors.

Vitamin E is a concept which includes a group of naturally occurring lipid-soluble antioxidants, tocopherols, and tocotrienols that are naturally found in vegetable oils such as soybean, corn, cotton, and seeds.

Alpha-tocopherol is a natural antioxidant in stabilizing unsaturated lipids against autoxidation. Free radicals generated by the normal metabolic processes or by toxic compounds taken in the body, e.g., ozone, react with the polyunsaturated fatty acids. Breakdown of these components leads to cellular damage. Tocopherol may react with free radicals and possibly with other oxidation intermediates and prevent the development of pathological processes (Bieri J, Corash L, Hubbard V, 1983). Using a newly developed system of induction of lipid peroxidation consisting of dopa and iron the susceptibility of substantia nigra to peroxidation compared to that of putamen and nucleus caudatus produced in normal animals or animals having a Vitamin E deficiency has been investigated (Tanaka M, Sotomatsu A, Kanai H, 1992). The histochemical study of lipid peroxidation has revealed that substantia nigra is far more susceptible to treatment with dopa and iron compared to putamen and nucleus caudatus. Vitamin E deficiency enhances the susceptibility of substantia nigra but has no effect on the histochemical findings observed in putamen and nucleus caudatus. It has been reported that the disease in Parkinsonian patients receiving Vitamin E runs significantly easier compared to those who do not receive it (Factor S, Sanchez-Ramos J, Weiner W, 1990).

Free radicals are normally found in the dopaminergic neurons of substantia nigra. The protective mechanisms against damage by free radicals present in the dopaminergic neurons are superoxide dismutase, glutathione peroxidase, reduced glutathione, and neuromelanin (Barbeau A, 1984). The free radical-mediated damage to substantia nigra may occur when the protective mechanisms are overburdened by the rapid formation of free radicals or antioxidant deficiency. Vitamin E may replace these protective mechanisms that are deficient in nigral neurons. It is concentrated in the hydrophobic core of cell membranes and gives a hydrogen ion to the peroxy radical interacting with the chain reaction which leads to lipid peroxidation (Halliwell B, Gutteridge J, 1).

It has been found that the use of selegiline (deprenyl) has a beneficial effect in Parkinson's disease (Cezura A, Pietscher A, 1992). A large multicenter study (DATATOP) where 800 patients with early-stage Parkinson's disease were enrolled was aimed to investigate the efficiency of selegiline 10 mg/day and alpha-tocopherol 2000/U/day. It was found that 302 of 399 patients who received active selegiline did not need to receive levodopa. Selegiline is the first highly selective MAO-B inhibitor and clinically proven to be effective in Parkinson's disease. A relatively small number of side effects are observed with it. Furthermore, it increases the activity of nigrostriatal dopaminergic neurons and inhibits the release of acetylcholine in nucleus caudatus which is indirect evidence of increased activity of nigrostriatal dopaminergic neurons. It has a neurotrophic effect on neurons, increases

the reactive astrogliosis and slows down neurodegenerative processes regardless of MAO-B inhibition. It does not change the activity of superoxide dismutase.

In the beginning the treatment of Parkinson's disease is generally symptomatic although there is a therapy providing neuroprotection - protection of neurons against excitotoxicity, oxidative stress, and apoptosis.

Levodopa remains the most efficient drug to relieve symptoms of Parkinson's disease but its prolonged use is often associated with motor complications and dyskinesias (Khutorskaia O, 1998, Hjermind L, Johannsen L, Blau N, et al 2006, Hauzer R, 2013, Anderson P, 2013, Thobois S, Delamarre-Damier F, Derkinderen P, 2005, Antonini A, Cilia R, 2009, Fahn S, Oakes D, Shoulson J et al 2004, Parkkinen L, O'Sullivan S, Kuoppamaki M et al 2011). Therefore, this treatment is postponed if possible. Alternatives to levodopa in early Parkinson's disease are monoamine oxidase (MAO-B) inhibitors, dopamine agonists, amantadine, etc. MAO-B inhibitors have mild symptomatic effects only. Amantadine is associated with improvement of functional disability and dopamine agonists improve symptoms and may have a neuroprotective effect. Some partial dopamine agonists - adenosine, A2A-receptor agonists, and safinamide are subject to recent research. Neuroprotective treatment involves enhancement of mitochondrial functions and anti-inflammatory therapy enables blocking of calcium channels (Boll M, Alcaraz-Zubeldia M, Rios C, 2011).

Some newer methods such as deep brain stimulation, cell and gene therapy are in the experimental phase.

Dopaminergic replacement therapy with levodopa and carbidopa has been shown to slow down PD progression and is usually assessed using the UPDRS scale.

Pharmacological alternatives to treatment with levodopa at the early stages of Parkinson's disease are most often two MAO-B inhibitors - rasagiline and selegiline (Palhagen S, Heinonen E, Hagglund J, et al 2006, Olanow C, Rascol O, Hauser R, et al 2009).

Amantadine is a drug of choice at the early stages of PD but it has some side effects such as hallucinations, occurrence of edemas, and anticholinergic effects (Castake R, Macleod A, Ives N et al 2009, Weintraub D, Sohr M, PotenzaM et al, 2010).

Dopamine agonists pramipexole and ropinerole show good efficacy in improving the symptoms of Parkinson's disease. However, they also have side effects such as hallucinations, edemas, excessive day and night drowsiness, pathological gambling (Schapira A, Barone P, Hauser R et al, 2011).

Transdermal administration of rotigotine and nicotine show good efficacy in early Parkinson's disease (Wats R, Jankovic J, Waters C et al 2007, Clinical Trials in Progress. NIC-PD, 2013).

Safinamide is a new experimental drug which improves motor symptoms and cognitive functions. Coenzyme Q10 shows a good neuroprotective effect and improves symptoms assessed using the UPDRS scale (Storch A, Vierenna J, 2007).

A meta-analysis of 7 trials has shown an overall odd ratio of PB development of 0.85 with the use of nonsteroidal anti-inflammatory drugs (NSAIDs). The use of certain antioxidants such as deprenyl and tocopherol in a cohort of 800 patients with Parkinson's disease at a dose of 10 mg deprenyl daily enables treatment with levodopa to be postponed (The Parkinson Study Group, 1993, Fahr S, 1992, Vinh Quoc Luong K, Thi Hoang Nguen L, 2012). Epidemiological studies have definitely established the link between coffee consumption and lower risk of developing Parkinson's disease (Ross G, Abbot R, Petrovitch H, et al 2000).

Treatment of psychotic symptoms that occur in Parkinson's disease is essential (Weintraub D, Cornelia C, Horn S, 2008, Reid W, Hely M, Morris J et al, 2011, Barbas N, 2006, Treatment of Parkinsons' disease 2011). Deep brain stimulation is currently used in the treatment of advanced Parkinson's disease and in the presence of complications of levodopa therapy (Espay A, Vanghan I, Marras C, et al 2010, Moreau C, Delval A, Defebre L, et al 2012).

Experimental treatment with transplantation of stem cells is also being conducted but studies are still at an early stage (Politis M, Lindvall O, 2012).

There are many national and international programs for diagnosis and treatment of Parkinson's disease (National Collaborating Centre for Chronic Conditions Parkinsons' disease 2006). They enable the conduct of up-to-date prevention and treatment of this severe neurodegenerative disease.

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