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Parkinson's Disease: Prevention or Treatment

Eric J Lien[1], James D Adams[1], Linda L Lien[2] and Meng Law[3]*

[1]Department of Pharmacology and Pharmaceutical Science, University of Southern California School of Pharmacy, USA

[2]Retired Pharmacist, Culver City, CA, USA

[3]Departments of Neuroradiology, Neurological Surgery and Biomedical Engineering, University of Southern California, USA

Abstract

Different approaches in the search for the means of prevention and treatment of Parkinson's Disease (PD) are discussed: Including dietary, folk medicine, traditional Chinese medicine and placebo controlled pilot clinical studies. Many factors appear to be involved in disease causation, such as oxidative stress and α-synuclein accumulation. Possible drug development from traditional Chinese medicines is discussed. It is concluded that prevention is the best means of dealing with PD.

Keywords: Parkinson's disease; Blood brain barrier; Traditional Chinese medicine

Introduction

Neurodegenerative disorders like Alzheimer's disease and Parkinson's Disease (PD) involve many factors as shown in Figure 1 [1,2]. PD is the second common age related neurodegenerative brain disorder after Alzheimer's disease. It affects 1% to 2% of seniors over 65 years old. Currently, PD patients are usually treated with Levodopa, dopamine receptor agonists, monoamine oxidase B inhibitors and other drugs [2]. PD treatments ameliorate symptoms in the early stages of the disease, but become less effective as the disease progresses. Thus, therapies that prevent or stop the progression of the disease are needed.

Traditional Chinese Medicine (TCM) describes PD as a deficiency in liver and kidney functions and an excess of phlegm and stasis [3]. Common symptoms of PD are tremor, slow movement, dizziness and vertigo. Tremor and slowness of movement are caused by phlegm heat and wind stirring [4]. Vertigo and dizziness are caused by deficient qi and blood [4]. The TCM approach to PD is very different from the western approach. TCM has produced useful medicines and therapies for the treatment of PD. Acupuncture has been shown in a meta-analysis to provide effective therapy for PD [5]. Tai chi and qigong provide significant improvements in movement and balance in PD according to meta-analyses [6,7].

Pathogenesis

PD is caused by several factors. Genetics are involved in about 10% of cases and may involve PARK genes and other genes [8]. However, the majority of PD is probably caused by alterations to the BBB and dopamine oxidation [9]. When the BBB is altered by atherosclerosis, the penetration of nutrients and neurotransmitter precursors into the brain may be altered. This will change brain functioning perhaps resulting in α-synuclein accumulation and changes in dopamine turnover. The BBB can be damaged by adipokines. Several of the compounds discussed in the current work may be able to protect the BBB.

Dopamine oxidation produces oxygen radicals [9]. Dopamine is oxidized by mitochondrial monoamine oxidase A inside dopaminergic neurons to produce oxygen radicals and hydrogen peroxide [10]. Another product of monoamine oxidase A is 3,4-dihydroxyphenylacetaldehyde which is oxidized by aldehyde dehydrogenase with the production of oxygen radicals [10]. A small amount of dopamine is spontaneously oxidized inside neurons to produce oxygen radicals. Many of the compounds presented in the current work are antioxidants that may protect against oxygen radical damage. Therefore, dopamine degradation produces oxygen radicals that can damage dopaminergic neurons leading to many, but not all, of the symptoms seen in PD.

Perhaps as many as 50% of PD patients also suffer from Alzheimer's Disease (AD) [9]. This implies similarities in the pathogenesis of the two diseases. It is possible that AD is caused by

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Correspondence:
James D Adams, Department of Pharmacology and Pharmaceutical Science, University of Southern California School of Pharmacy, Los Angeles, CA, 90089-9121, USA, Tel: 1-323-442-1362; E-mail: jadams@usc.edu

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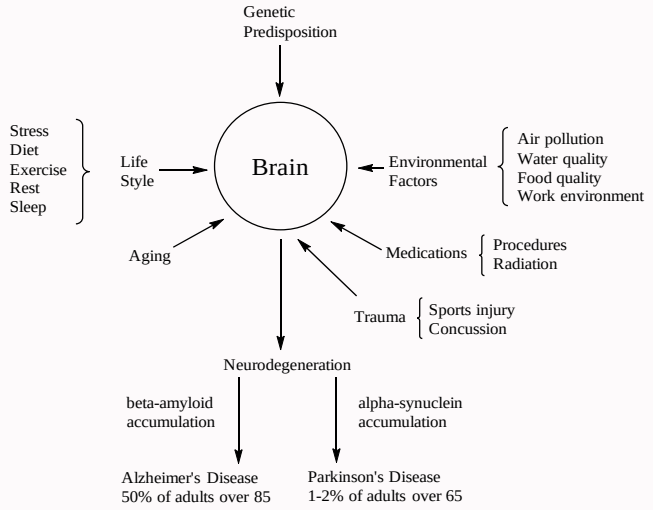

Figure 1: Various factors affecting neurodegeneration including Parkinson's disease [1,2].

alterations to the BBB by adipokines [11]. Many of the Traditional Chinese Medicines used in the treatment of AD protect the BBB [12].

A more recent theory of PD pathogenesis involves α-synuclein aggregates penetrating the BBB and activating microglial cells [13]. The activated microglial cells release tumor necrosis factor α, IL-1α and C1q that activate astrocytes. These activated, neurotoxic A1 astrocytes somehow cause the death of dopaminergic neurons. A-synuclein crosses the BBB [14]. However, damage to the BBB increases the penetration of α-synuclein into the brain [14]. The question that remains unanswered is whether α-synuclein causes PD or is a byproduct of PD.

At least 6 drugs are being tested, as of July 2018 (Michael J Fox Foundation) that bind to α-synuclein to enhance its clearance or decrease its ability to form aggregates. These drugs include PRX002/RO7046015 (Prothena/Roche), antibodies from Biogen/AstraZeneca and Takeda. A vaccine that enhances antibody formation to α-synuclein is being tested by AFFiRiS (AFFITOPE® PD01A). NPT200-11/UCB0599 may decrease α-synuclein accumulation and is being tested by Neuropore/UCB. NPT088 may decrease α-synuclein aggregation and is being tested by Proclara. A PD clinical trial of PRX002 found by neuro-imaging that α-synuclein did not decrease in the brains of patients and movement disorders did not improve [15]. This suggests that α-synuclein may not be critical to the causation of PD. The other agents are yet to be tested.

From Folk Medicines and Functional Foods to Recent Clinical Trials

In TCM, Gou Teng (*Uncaria macrophylla*, *U. rhynchophylla*, *U. hisuta*, *U. sinensis*) an herb with hook like branches, has been used to treat the "shakes" associated with PD for over 2,000 years [16]. Gou Teng has been shown to contain several indole alkaloids like [17]: rhynchophylline, corynoxine, corynoxine-B, corynoxeine, rhynchophine, isorhynchophylline and 7-isorhynchophylline [18]. Among these indole alkaloids, isorhynchophylline has been shown to activate autophagy of α-synuclein without suppressing the immune system in transplant patients (Figure 1) [16]. This may be why no apparent side effects have been reported in patients treated with Gou Teng over the past centuries [16]. This compound has been suggested to have therapeutic potential for cardiovascular and CNS diseases, including vascular dementia, amnesia and symptoms of PD [18]. Gou Teng and isorhynchophylline have not been tested in PD clinical trials in Europe or the US.

Functional foods include the popular Mediterranean diet, coffee, tea and neuro-protective natural products (herbs) which may prevent PD as well as cardiovascular disease. In 2019, US News and World Report published the Mediterranean diet as the best among 41 entries [19]. Adherence to the Mediterranean diet decreases the risk of developing PD [20]. The Mediterranean diet has seven characteristics.

1. Multiple grains and nuts are main ingredients. They contain fiber, group B vitamins, minerals including magnesium and polyunsaturated fatty acids. These are beneficial to the digestive system, stabilize blood sugar, enhance the immune system and lower cardiovascular risk.

2. Fresh vegetables and fruits (minimally processed) to provide vitamins, minerals (magnesium in chlorophyll), fiber and antioxidants (flavonoids and anthocyanins).

3. Fresh fish and seafood. Deep ocean fish like salmon provide omega-3 fatty acids, which protect cardiovascular health and brain functions due to its antioxidant properties and immune promotion. In addition, seafood provides good proteins.

4. Dairy products and 1-2 eggs/day. These foods supply protein, vitamins and calcium.

5. Olive oil instead of animal oil. Monounsaturated fatty acids prevent cardiovascular diseases.

6. Low intake of red meat and processed food products.

7. Spices in lieu of salt. Decreased use of salt and oil in cooking is beneficial since many spices contain antioxidant ingredients.

Specific factors that decrease the risk of developing PD include: regular exercise, tobacco, caffeine, black tea, ibuprofen, calcium channel blocking agents, high blood urate levels and eating a diet high in fruit, vegetables and fish [21,22]. Exercise causes muscles to release myokines, including brain derived neurotrophic factor that may be beneficial [23]. Pesticides, melanoma, traumatic brain injury and consumption of a diet too high in dairy products may increase the risk of developing PD [21,22]. Interestingly, type 2 diabetes and obesity do not increase the risk.

L-Dopa Containing Foods and Herbs

Functional foods like broad beans (*Vicia faba*) are natural sources of L-dopa [24]. The amount of L-dopa in the beans is pharmacologically active in the treatment of PD. It has been suggested that *V. faba* can potentially be incorporated into dietary strategies to manage PD motor oscillations [25].

Other L-dopa containing herbs include [26]: *Vigna aconitifolia*, *Vigna unguiculata*, *Vigna vexillata*, *Prosopis chinensis*, *Pileostigma malabarica*, *Phanera vahlis*, *Parkinsonia aculeata*, Macaroons, *Canvalia gladiata*, *Cassia floribunda*, *Cassia hirsute* and *Dalbergia retusa*. Besides L-dopa containing herbs, a *Ginkgo biloba* extract showed protective effects *in vivo* and *in vitro*. An ethanolic extract of *Plumbago zeylonica* was effective in a rat PD model [25].

Table 1: Jia Wei Liu Jun Zi Tang components.

Chinese name	Pharmaceutical name	Percent present
Dang Shen	Dried root of *Condonopsis pilosula* (*Campanulaceae*)	13.39
Sheng Di	Dried root of *Rehmania glutinosa* (*Scrophulariaceae*)	13.39
Fu Ling	Dried sclerotium of fungus *Poria cocos* (*polyporaceae*)	10.71
Gou Teng	Dried hook-bearing brainches of *Uncaria rhynchophylla* (*Rubiaceae*)	10.71
Bai Zhu	Rhizome of *Atractylodes macrocephala* (*Compositae*)	8.93
Dang Gui	Dried root of *Angelica sinensis* (*Umbelliferae*)	8.93
Fa Ban Xia	Dried tuber of *Pinellia ternata* (*Araceae*)	8.04
ChuanXiong	Dried rhizome of *Ligusticum chuanxiong* (*Umbelliferae*)	8.04
HuaiNiu Xi	Dried root of *Achyranthes bidentata* (*Amaranthaceae*)	8.04
Chen Pi	Dried pericarp of *Citrus reticulate* (*Rutaceae*)	5.36
Sheng Gan Cao	Dried root and rhizome of *Glycyrrhiza uralensis* (*Fabaceae*)	4.46

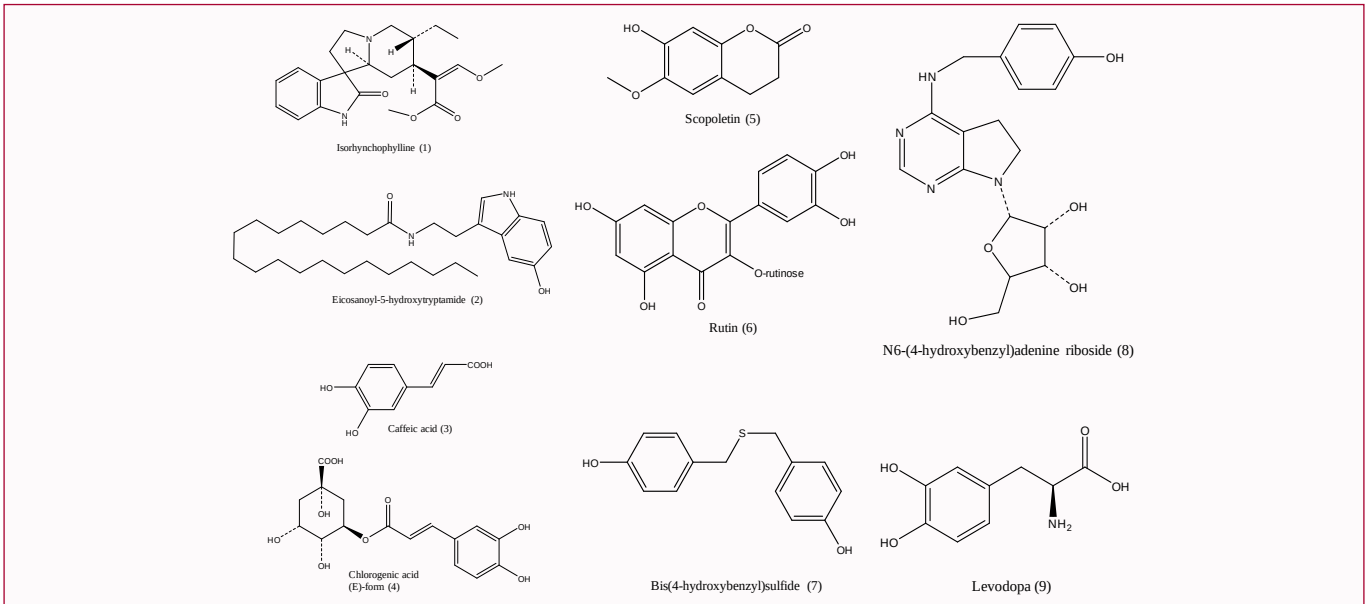

Figure 2: Structural formulas of neuroprotective compounds.

Coffee and Tea

The CNS stimulant caffeine is known to inhibit cyclic nucleotide phosphodiesterase resulting in higher concentrations of c-AMP, a key intracellular regulator. It is well known that freshly brewed coffee and tea contain polyphenols that are effective antioxidants. Recently, it has been reported that caffeine and a waxy coating on the bean may team up to fight PD (Figure 2) [24]. Eicosanoyl-5-hydroxytryptamide (2), an indole derivative, has been shown to protect the brains of mice against abnormal protein accumulation associated with PD and Lewy body dementia (due to abnormal deposits of α-synuclein). When caffeine and (2) were given together, they boosted the activity of a catalyst that helps prevent the accumulation of harmful proteins in the brain. Further research is needed to determine the doses and ratios of (2) and caffeine required for the protective effect in humans [24]. Caffeine binds to brain adenosine A2a receptors that have a neuroprotective role [27].

A Pilot Clinical Study of Eleven Herbs from TCM on Idiopathic Parkinson's Disease

Kum et al. [28] of the Hong Kong Baptist University in 2011 reported a randomized, placebo-controlled pilot study of a Chinese herbal formula (Jia Wei Liu Jun Zi Tang, JWLZT) on motor and non-motor symptoms, and on complications of conventional therapy in idiopathic PD. Significant improvements in communication abilities were reported at weeks 12 and 24 [28]. The herbs present in the herbal formula are shown in Table 1.

Among these 11 herbs, Gou Teng has been extensively studied for PD. Gou Teng has also been reported to have potent anti-aggregation effects on Alzheimer's β-amyloid proteins [29].

Objectively Selected Compounds for Further Study

In 2003, the committee to Identify Neuroprotective Agents in Parkinson's of the National Institute of Neurological Disorders and Stroke (NINDS) reported a list of 12 compounds as attractive candidates for further clinical trials in PD [30]. They were selected from 59 potential compounds based on specific criteria like scientific rationale, Blood-Brain Barrier (BBB) penetration, safety and tolerability, and evidence of efficacy in animal models or humans (from previous trials or epidemiologic data).

The list includes: Caffeine, co-enzyme Q10, creatine, estrogen (17β-estradiol) or a non-feminizing analog, GM-1 ganglioside,

minocycline, nicotine, GPI-1485, Rasagiline/selegiline (monoamine oxidase-B inhibitors), ropinirole and pramipexole (antioxidants). Many of these compounds have been tested and found ineffective in clinical PD trials including caffeine, creatine, coenzyme Q10, nicotine, GPI-1485 and ropinirole [31-36]. Rasagiline has been shown to be effective in the treatment of PD [37].

Epidemiologic evidence suggests that smokers have a substantially reduced risk of PD compared to nonsmokers. It should be pointed out, however, that the composition of tobacco smoke is highly complex. Besides nicotine, it contains many chemicals including carcinogenic polycyclic aromatic hydrocarbons, nitrosamines, aldehydes, and many other organic and inorganic compounds. Nicotine is an important modulator of acetylcholine neurotransmission. In addition, tobacco smoke also contains polyphenols like caffeic acid (3), chlorogenic acid (4), scopoletin (5) and rutin (6, Figure 2). These may contribute to the antioxidant neuroprotective activity. They may be better candidates than nicotine for clinical study.

Nicotine has been tested in a PD clinical trial and was found to not improve motor deficiencies [34]. Caffeic acid has not been tested in clinical trials but can decrease microglial cell activation in the brain [38]. Chlorogenic acid may be neuroprotective by inhibition of neuronal apoptosis [39]. Scopoletin is a monoamine oxidase A and B inhibitor that should be tested in PD clinical trials [40]. Oral rutin attenuates neuro-inflammation in the brains of rats [41].

Mechanisms of Action for Traditional Chinese Medicines

Li et al. [2] have reported six mechanisms of action for Traditional Chinese Medicines underlying the prevention and treatment of PD.

1. The inhibition of oxidative stress in the CNS.
2. The regulation of mitochondrial dysfunction.
3. The reduction of toxic excitatory amino acid neurotransmitters (glutamate, aspartate), reflected in the activation of corresponding receptors (NMDA-R, AMPA-R, KA-R) which mediate acute osmotic swelling or delayed injury of nerve cells.
4. The inhibition of neuroinflammation.
5. The inhibition of neuroapoptosis.
6. The inhibition of abnormal protein aggregation.

Huang et al. [42] have isolated two new active compounds with neuroprotective activity from the Chinese herb Gastrodiaelata (Tien Ma), bis(4-hydroxybenzyl) sulfide (7) and N6-(4-hydroxybenzyl) adenine riboside (8), both containing phenolic groups. Bis(4-hydroxybenzyl) sulfide (7) is a histone deacetylase inhibitor [43]. N6-(4-hydroxybenzyl) adenine riboside is a sedative with no known neuroprotective mechanism.

Neuroimaging and Therapeutics

There has been considerable pre-clinical and human work on imaging the BBB and radio-tracer development in AD and PD. Gray et al. demonstrated increased permeability of the striatal BBB to hemoglobin and fibrin in PD [44]. Our group has recently also demonstrated significant increases in permeability of the BBB in the mouse AD model and in the hippocampus of patients with mild cognitive impairment and AD [45-47]. Now that we can effectively image the BBB *in vivo*, clinical trials of natural and other compounds which may stabilize the BBB may allow an objective means of studying the therapeutic effects. Many AD and PD clinical trials using cognitive function or brain Magnetic Resonance Imaging (MRI) volumes as therapeutic endpoints have failed in part because of a lack of efficacy but also because perhaps the end points were not objective or incorrect.

Flouro-Deoxy-Glucose (FDG PET) and more recently amyloid/tau PET imaging have been tracers used in the diagnosis of AD. Unfortunately the clearance of amyloid-beta on PET imaging in clinical trials of anti-amyloid agents has not demonstrated clinical efficacy. Dopamine Transporter (DAT) imaging can be performed for the differential diagnosis of PD and other degenerative Parkinsonism from essential tremor, vascular Parkinsonism, and drug-induced Parkinsonism. DAT is the plasma membrane carrier specific to dopamine neurons that is responsible for re-uptaking dopamine from the synaptic cleft back into the nerve ending. DAT binding might reflect striatal presynaptic dysfunction or DAT expression in PD patients. DAT imaging during therapeutic interventions has been applied for several antiparkinsonian drugs. Ikeda et al. [48] reviews the progressive changes and therapeutic modification of DAT binding by anti-PD medications in PD patients. We now have the opportunity to study some novel and alternative therapeutics for two debilitating diseases with objective neuroimaging approaches.

Conclusion

For neurodegenerative diseases like PD and Alzheimer's disease, prevention is the best treatment, such as eating a healthy diet and performing regular exercise. So far there has been no single drug available for the cure of either disease. The pros and cons of disease prevention, the empirical Traditional Chinese Medicine approach, and randomized, placebo-controlled clinical trials have been reported by Adams and Lien [49].

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