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Education Section

Mitochondrial Nutrition as a Strategy for Neuroprotection in Parkinson's Disease—Research Focus in the Department of Alternative Medicine and Experimental Therapeutics at Hokuriku University

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Department Overview

The Department of Alternative Medicine and Experimental Therapeutics employs a wide array of experimental models of neurodegenerative and stress-related diseases, such as Parkinson's disease (PD) and depression, in order to establish the neuroprotective and anti-stress strategies that can be applicable for both normal humans and patients with the diseases.

A central theme of our Department is to verify the alternative medical approaches to prevent and/or treat neurodegenerative and stress-related diseases in animal models. To achieve this goal, we focus on three nonpharmacological approaches: nutrition, exercise and control of mental environment. In addition to investigating the usefulness of these nonpharmacological strategies, we elucidate detailed action mechanisms of alternative medical approaches to clearly demonstrate neuroprotective effect and improvement of emotional abnormality.

In this section, background for the nutritional research in our Department is summarized.

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Research Background

PD is a progressive neurodegenerative disorder characterized by the core symptom bradykinesia, rest tremor, rigidity and postural stability (1). Currently, pharmacotherapy and surgical approaches for the treatments of PD can only improve the neurological symptoms. Although these symptomatic therapies can provide benefit, intervention that can slow or halt the progression of PD is an important consideration of overall treatment. Post-mortem examination of parkinsonian brains reveals a number of neurochemical and histological abnormalities. The most striking phenomenon is the loss of nigrostriatal dopaminergic neurons. This manifests as a loss of pigmented cells in the substantia nigra and of dopamine (DA) in the caudate and putamen of the dorsal striatum. Extensive degeneration of these neurons is required for clinical deficits. Indeed, even patients with relatively mild symptoms have striatal DA depletions of 80% (2,3). Therefore, neuroprotective therapies using pharmacological and nonpharmacological approaches may delay the progression of pathogenesis in PD.

Neuroprotection Exploratory Trials in Parkinson's Disease (NET-PD) sponsored by the National Institute of Neurological Disorders and Stroke in the United States were begun to test whether several possible neuroprotective agents could prevent the progression of PD. NET-PD is a series of clinical research studies conducted at many centers in an effort to find drugs to slow the progression of PD. For this trial, several neuroprotective agents were identified through a systematic assessment by a group comprising experts in PD,

clinical trials and clinical pharmacology (4). If promising results for potential neuroprotective agents are found in these pilot studies, the agents will be evaluated in larger, more definitive Phase III trials. The preliminary study in NET-PD shows that creatine and minocycline may warrant further study in PD (5). On the other hand, Olanow and colleagues recently reported the results of a clinical trial of the propargylamine TCH 346 (*N*-methyl-*N*-propargyl-10-aminomethyl-dibenzo[b,f]oxepin) as a neuroprotective drug in early PD (6). TCH346 provides neuroprotection in animal models of PD through interaction with a glycolytic enzyme GAPDH (7,8). GAPDH protein expression is substantially increased after exposure to various toxins long before the appearance of the classic markers of apoptosis (9) and blocking expression of GAPDH is anti-apoptotic (10). In the clinical trial, there were no significant differences between the drug-treated group and placebo with respect to the primary outcome measure of time to require dopaminergic treatment or the secondary outcome measures, including changes in clinical scores or quality-of-life measures (6).

Mitochondrial Function as a Therapeutic Target in PD

The cause of PD remains unknown, but our understanding of mechanisms of nigral dopaminergic neuronal death was advanced by the discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that selectively damages the nigrostriatal dopaminergic system and cause a parkinsonian syndrome in humans, monkeys and mice (11–14). The discovery that MPTP acts through inhibition of complex I of the electron transport chain stimulated study of mitochondrial function in the brains from patients with PD. Schapira *et al.* (15) reported that complex I activity was selectively reduced in the substantia nigra of patients with PD. Parker *et al.* (16) reported a significant reduction in complex I activity in platelets from patients with relatively advanced PD. Platelets mirror certain biochemical processes that occur in the brain. For example, platelets have been shown to take up dopamine, and they contain monoamine oxidase B and α-synuclein.

Mizuno *et al.* (17) proposed that energy crisis is the most important mechanism of nigral cell death in PD. In addition, oxidative stress has also been implicated as an important contributor to nigral cell death in PD, but it's a secondary phenomenon on respiratory failure, because respiratory failure will increase oxygen-free radical and consume glutathione. On the other hand, exposure of nigral neurons to a high risk for oxidative damage because of its high dopamine content may be the reason for more pronounced nigral complex I deficiency compared with systemic organs. Oxidative stress and mitochondrial failure produce a vicious cycle in nigral neurons.

The processes leading to death of dopaminergic neurons in PD are not fully understood. Current evidence suggests that cell death in PD occurs by either apoptosis or necrosis or both (18). Whether mitochondrial dysfunction contributes to necrosis in chronic forms of the neurodegeneration is less clear. However, it is at least theoretically possible that defects in mitochondrial electron transport could be severe enough to compromise total cellular ATP production and thereby result in necrosis. Therefore, mitochondria could be an important target for neuroprotection even if the destruction of neuron appears to be apoptotic, necrotic or intermediate between the two extremes (19,20).

Mitochondrial Nutrition for the Treatment of PD

Coenzyme Q_{10} (CoQ_{10}) is an essential cofactor of the electron transport chain where it accepts electrons from complexes I and II. Coenzyme Q also serves as an important antioxidant in both mitochondria and lipid membranes. It is particularly effective within mitochondria. Substantial data have implicated mitochondrial dysfunction and excessive production of reactive oxygen species in the pathogenesis of PD. Furthermore, a significant reduction (33%) in the level of CoQ_{10} in mitochondria has been reported in PD patients compared with that in age/gender matched control subjects (21). The central role of CoQ_{10} in two areas implicated in the pathogenesis of PD, mitochondrial dysfunction and oxidative damages, suggest that it may be useful in slowing the progression of PD. Parkinson Study Group conducted a phase II study of CoQ_{10} in patients with early untreated PD in North America and found that, particularly at the highest dosage studied, 1200 mg/day, it appeared to reduce the functional decline in the patient, as measured by the change in the total score on the Unified Parkinson Disease Rating Scale (UPDRS) (22). Although the benefit was found in all three parts of the UPDRS [part 1 (mention, behavior and mood), part 2 (activities of daily living) and part 3 (motor examination)], these results should be considered preliminary until confirmed by a larger phase III study.

It is important to clarify how the exogenous CoQ_{10} works in the brain to reduce the dopaminergic neurodegeneration. Previous *in vitro* studies have demonstrated that CoQ_{10} can reduce the death of dopaminergic cells induced by rotenone (23) and H_2O_2 (24). These studies indicate that CoQ10 offers neuroprotection at the mitochondrial level in the apoptotic pathway against mitochondrial dysfunction and oxidative stress. Although CoQ_{10} attenuated the toxin-induced reduction of dopamine content and tyrosine hydroxylase-immunoreactive

neurons in the striatum of the MPTP mouse model, it is still unknown how this nutrition affects the mitochondrial function (25). Horvath *et al*. (26) reported that the mechanism of the neuroprotective effect of CoQ_{10} in a primate PD model was through activation of uncoupling protein 2 (UCP2), which regulates mitochondrial inner membrane potential, ATP levels and local thermogenesis. Interestingly, lack of UCP2 increased the sensitivity of dopamine neurons to MPTP, whereas UCP2 overexpression decreased MPTP-induced nigral dopamine cell loss in mice (27). The authors suggested the critical importance of UCP2 in normal nigral dopamine cell metabolism and offer a novel therapeutic target, UCP2, for the prevention/treatment of PD.

From a scientific point of view, we would like to know if CoQ_{10} improves mitochondrial function to protect dopaminergic neurons from *in vivo* MPTP neurotoxicity. To demonstrate their neuroprotective effects, we now focus on whether brain mitochondrial function under pathological conditions and normal aging can be improved by nutritional supplements and natural products.

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