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Opposite Roles of Co-enzyme Q10 and Formaldehyde in Neurodegenerative Diseases

Jinan Xu, MD[1,2,†], Xingjiang Jin, BA[2,†], Zuting Ye, BA[2], Dandan Wang, BA[2], Hang Zhao, MD[2], and Zhiqian Tong, PhD[1,2]

Abstract

Most of neurodegenerative diseases (NDD) have no cure. The common etiology of neurodegenerations is unclear. Air pollutant-gaseous formaldehyde is notoriously known to induce demyelination and cognitive impairments. Unexpectedly, an amount of formaldehyde has been detected in the brains. Multiple factors can induce the generation and accumulation of endogenous formaldehyde. Excessive formaldehyde can induce oxidative stress to generate H_2O_2; in turn, H_2O_2 promote formaldehyde production. Clinical investigations have shown that an abnormal high level of formaldehyde but low level of coenzyme Q10 (coQ10) was observed in patients with NDD. Further studies have proven that excessive formaldehyde directly inactivates coQ10, reduces the ATP generation, enhances oxidative stress, initiates inflammation storm, induces demyelination; subsequently, it results in neurodegeneration. Although the low water solubility of coQ10 limits its clinical application, nanomicellar water-soluble coQ10 exhibits positive therapeutical effects. Hence, nanopackage of coQ10 may be a promising strategy for treating NDD.

Keywords

neurodegenerative diseases, demyelination, endogenous formaldehyde, coenzyme Q10, inflammation storm

Introduction

Neurodegenerative diseases (NDD) are a diverse group of neurological diseases characterized by neuron loss, demyelination, and irreversibly functional decline.[1] Typical NDD includes Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophiclateral sclerosis (ALS), cerebellar atrophy (CA), etc.[2] Substantial evidences suggest that mitochondrion plays a critical role in aging-related neurodegeneration. Both mutations in mitochondrial DNA and oxidative stress indeed accelerate the ageing process, which is a confirmed risk factor for NDD.[2] With the increasing trend of population aging, more people are suffered from NDD every year, affecting their quality of life in the world.[3] Most of NDD have no cure. These diseases bring a heavy economic and social burden in the global. To explore the common etiology of neurodegeneration is urgently needed.

An kind of air pollutant, gaseous formaldehyde (FA), is notoriously known to induce cognitive impairments and demyelination in animals[4] and humans.[5] Unexpectedly, an amount of FA has been detected in the brains.[6,7] Multiple factors can induce the generation and accumulation of endogenous FA.[8] In AD, amyloid-beta (Aβ) induces FA accumulation by binding with formaldehyde dehydrogenase (FDH) and inactivating it.[9] Generally, FA induces oxidative stress, which generates hydrogen peroxide (H_2O_2);[10] in turn, H_2O_2 enhances FA production and accumulation.[11] More worse, excessive FA directly inactivates mitochondrial coQ10, reduces the ATP generation,[12-14] enhances oxidative stress, initiates inflammation storm (ie release of IL-1, IL-6, TNF-α,

[1]Institute of Ningbo, Wenzhou Medical University, Wenzhou, China
[2]Key Laboratory of Alzheimer's Disease of Zhejiang Province, Institute of Aging, Oujiang Laboratory, School of Mental Health, Wenzhou Medical University, Wenzhou, China

[†]These authors have contributed equally to this work.

Corresponding Author:
Zhiqian Tong, Key Laboratory of Alzheimer's Disease of Zhejiang Province, Institute of Aging, Oujiang Laboratory, School of Mental Health, Wenzhou Medical University, Wenzhou, 325035, China.
Email: tzqbeida@ccmu.edu.cn

etc.),[10,15] induces demyelination of neurons.[16] Above data suggest that excessive FA is a critical endogenous factor for triggering NDD occurrence.

The central nervous system (CNS) is the main pathological sites of NDD, and urine is anatomically distant from CNS compared to other biological fluids, such as: cerebrospinal fluid (CSF) and plasma; therefore, the components in urine are not often considered to be a suitable biomarker for NDD. However, recent studies have indicated that urinary components may act as a source of NDD biomarkers if suitable markers are predetermined in urine and other samples of metabolic and proteomics approaches. A series of studies in recent years suggest the potential of urine as a source of NDD biomarkers.[17-22] Clinical investigations have demonstrated that patients with AD or PD[14,23,24] were often associated with an abnormal high level of endogenous FA but low level of coenzyme Q10 (coQ10, a powerful endogenous antioxidant).[25,26] Urinary FA levels are positively correlated with severe degree of AD,[23] and potentially act as a marker for predicting treatment efficacy.[27]

Active compounds produced by the metabolism of the body provide a promising target to be evaluated as a potential therapy for various pathological conditions in NDD.[27] Among them, endogenous coQ10 is a key cofactor involved in mitochondrial oxidative phosphorylation and an effective endogenous antioxidant.[28] It has been found to exert neuroprotective effects against oxidative stress-induced damage and mitochondrial respiratory chain dysfunction in a variety of NDD.[29] This review provides evidence that coQ10 may be a potential drug target and/or biomarker in NDD.

Role of Endogenous Formaldehyde in Neurodegenerative Diseases

Formaldehyde and Alzheimer's disease. Extensive evidence indicates that endogenous FA is mainly involved in the "one-carbon cycle" mediated by the 5,10-methylene tetrahydrofolate reductase (MTHFR),[30] which participates in some physiological and pathological functions. For example, low levels of active FA act as a memory-related molecule to regulate learning and memory.[31] However, it at high concentrations acts as a protein degenerative agent to induce NDD, such as AD and ALS.[12-14] It has been proven that multiple factors, such as: age,[32-34] stress,[35] stroke,[36] diabetes,[37] virus infected,[38-42] clinical operation,[43] and some diets (deep-sea fish polluted with methyl mercury[44,45]), can result in FA accumulation.[8]

Epidemiological investigations have shown that increasing age is the most critical risk factor for AD, with most cases in 65 years of age and older.[46] Disruption of FA metabolism during ageing lead to FA accumulation by increasing the activity of semicarbazide-sensitive amine oxidase (SSAO, a FA-generating enzyme) but decreasing the activity of FDH (a FA-degrading enzyme); especially, age-related FA induces tau hyperphosphorylation to form neurofibrillary tangels (NFTs) [47,48] and inhibits N-methyl-D-asparate currents (NMDA-currents), thereby impairing cognitive functions.[49] In addition, mitochondrial damage has been found in sporadic and/or hereditary dementia patients,[50] and the polymorphism of mitochondrial aldehyde dehydrogenase 2 (ALDH2) is an important risk factor for late-onset AD in the Chinese population.[51] These findings suggest that ALDH2 mutation-associated FA overload accelerates cognitive impairments in AD.[31] In a survey of 604 healthy older adults, the levels of age-associated FA in the urine were negatively correlated with cognitive ability.[23] In a double blind study, urinary FA levels were substantially elevated in 91 patients with dementia and slightly elevated in 50 patients with mild cognitive impairment (MCI).[7] The levels of urinary FA were negatively related to the scores of simple mental state examination (MMSE, $Rs = -.441$, $P < .0001$).[7] Age-related FA is considered to be a direct trigger of sporadic dementia in the elderly.[49]

Recent studies have revealed that amyloid-beta (Aβ) not only induces FA production through oxidative demethylation of serine residues *in vitro*, but also inhibits FA degradation, leading to FA accumulation by reducing the activity of FDH. In turn, FA promotes Aβ aggregation, exerts neurotoxicity, and causes cognitive deficits in early-onset familial and late-onset AD. Hence, there is a vicious cycle between FA accumulation and Aβ assembly, which plays an important role in the deterioration of AD.[12] To make matters worse, FA induces Aβ deposition in the extracellular space (ECS) of brain, thereby blocking the influx of drugs (dissolved in the interstitial fluid) into damaged neurons in the deep cortex.[52] Thus, excessive FA is a trigger for Aβ oligomerization intracellularly and fibrillation extracellularly in AD.

Formaldehyde and Parkinson's Disease

PD is characterized by loss of substantial nigra neurons, resulting in striatum dopamine deficiency.[53] The aggregation of α-synuclein and mitochondrial dysfunction appear to be synergistic features of PD, and mitochondrial dysfunction is associated with α-synuclein aggregation in the degenerating neurons in PD.[54] It is well known that α-synuclein can induce oxidative stress and reactive oxygen species (ROS) generation,[55,56] which is accompanied by H_2O_2 production;[12,57,58] in turn, H_2O_2 promotes FA generation and accumulation rapidly (Figure 1).[59]

The typical pathological features of PD include abnormal accumulation of α-synuclein, deregulation of metal ion metabolism, oxidative stress, mitochondrial dysfunction, and neurotransmitter defects in the striatum and substantia nigra.[53,60,61] The FA-degrading enzyme- ALDH2 has been found to be decline in both activity and expression in PD patients,[62] and FA can have spontaneous chemical reaction with dopamine *in vitro*,[63] suggesting that excessive FA may be the direct reason of dopamine deficiency in the striatum and substantia nigra. Previous study revealed that FA-crosslinked α-synuclein oligomers can serve as important calibrators to

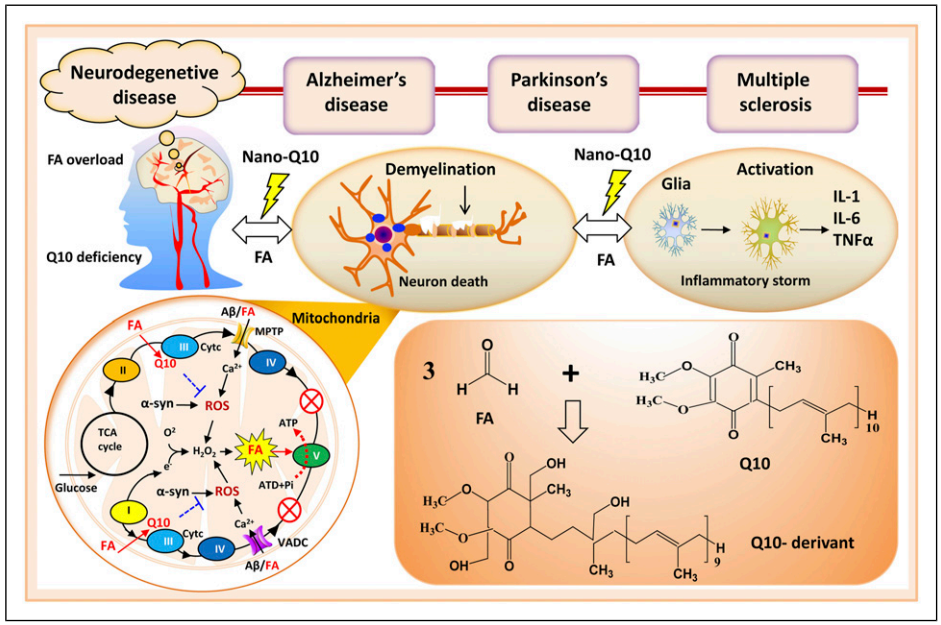

Figure 1. Roles of formaldehyde and coenzyme Q10 in the etiology of neurodegenetive disease. Abbreviation: ATP, adenosine triphosphate; Aβ, amyloid-beta; Cyt-c, cytochrome C; FA, formaldehyde; IL-1, interleukin-1; IL-6, interleukin-6; Q10, coenzyme Q10; Nano-Q10, nano-packaged coenzyme Q10; ROS, reactive oxygen species; α-syn, α-synuclein; TCA, tricarboxylic acid cycle; TNF-α, tumor necrosis factor-α; VDAC: voltage-dependent anion selective channel.

facilitate comparative and normalized α-synuclein biomarker studies.[60]

In addition, FA-crosslinked α-synuclein oligomers can be used as important calibrators to facilitate comparative and normalized α-synuclein biomarker studies.[60] Brain cells of patients with PD exhibit dysglycemia,[64] and excess FA promotes hyperglycemia and cognitive impairment through interaction with insulin,[65] suggesting that FA may be involved in dysglycemia in PD patients. Hypermethylation may be associated with the pathogenesis of some PD cases, some genes in PD patients have higher levels of methylation-active.[66] Excessive protein carboxy-methylation, increasing FA may cause neurotoxic effects through the potent metabolite FA to play a critical role in the sadenosyl-methionine (SAM)-induced PD-like neuronal damage and aging.[61]

Formaldehyde and Multiple Sclerosis

In the brains of patients with NDD, such as: AD or MS, the expression of SSAO (a FA-producing enzyme) is raised, and serum FA levels are also elevated.[14,67] Some human subjects who had suffered from methanol poisoning often exhibited the symptoms of MS (such as: demyelination and cognitive decline), which may be the effects of the oxidation of methanol to FA and subsequent protein modifications leading to immune responses.[67] Gaseous FA exposures are considered to be a possible risk factor for the development of ALS.[68] In fact, hypoxia can promote a massive accumulation of endogenous FA in the brains.[69] Consistently, hypoxia-like tissue damage in the type III of MS lesions may be caused by mitochondrial damage,[70] because FA exerts potent cytotoxicity, at least in part, by inducing oxidative stress, mitochondrial dysfunction, and ultimately apoptosis.[71] Hence, FA-induced mitochondrial damage contributes to the occurrence of MS.

Role of Endogenous Coenzyme Q10 in Neurodegenerative Diseases

CoQ10 (also named ubiquinone 50) composed by a quinone ring, that forms the head, and a hydrofobic tail, which contains 10 isoprenoid units, is a lipophilic, redox active molecule located in all cellular membranes. It can be found in all the tissues, but the highest concentrations of it are detected in heart, brain, kidney and liver. CoQ10 is naturally present in the vegetables. CoQ10 can accept 1 or 2 electrons both to be transferred into the respiratory chain, from complex I and II to complex III for ATP production. It is a powerful antioxidant that protects cell from ROS-induced damage in 2 ways: directly reacting with ROS and regenerating α-tocopherol and ascorbate. The reduced form, ubiquinol, is a powerful antioxidant that prevents oxidative damage by free radicals, including oxidation of lipids within the mitochondrial membrane. Hence, coQ10 strongly support the function of mitochondria.[72] Previous study quantified plasma COQ10 by ultra-performance liquid-chromatography-mass spectrometry (UPLC-MS) and recruited 40 patients with multiple system atrophy (MSA), 30 patients with Parkinson's disease (PD), and 30 healthy participants.[73] Plasma CoQ10 levels were significantly altered in MSA, PD

and control groups (P = 0.001). The cut-off point for differentiation between MSA patients and controls was maximal at 1710 ng/mL, with a sensitivity of 40 % and specificity of 97.5 % for the receiver operating characteristic curve (ROC curve).[73] Using the d6-CoQ10 internal standard, a sensitive liquid chromatography/tandem mass spectrometry (LC/MS/MS) method can be developed to accurately determine total CoQ10 levels.[73] Clinical applications of CoQ10 determination in cerebrospinal fluid (CSF) include identifying patients with CoQ10 deficiency in the brains and monitoring CoQ10 levels in the CSF after supplementation of it.[74]

CoQ10 and Alzheimer's Disease

Substantial evidence has supported the viewpoint that the critical role of oxidative stress and deficits in energy metabolism in the pathogenesis of various NDD.[28] Oxidative stress has been found to promote Aβ deposition in AD.[75] Notably, coQ10, an essential cofactor involved in mitochondrial oxidative phosphorylation, is also a potent antioxidant. Mitochondrial dysfunction has been considered to link with pathological changes in AD.[76] Its defects mainly occur in the complexes I, IV, and V of the electron transport chain, resulting in the production of free radicals.[77] Endogenous coQ10 is part of the electron transport chain,[78] suggesting that coQ10-related mitochondrial dysfunction contributes to the occurrence of AD.

In AD patients, the concentrations of coQ10 and FA varied inversely, suggesting that there is a spontaneous chemical reaction between these two compounds.[79,80] As an endogenous antioxidant, coQ10 has been found to decrease aldehyde levels,[57] and is an endogenous FA scavenger.[12] Using gas chromatography-tandem mass spectrometry (GC-MS/MS), it has been found that one molecule coQ10 have chemical reaction with three molecules of FA (Figure 1).[81] In addition, FA works with Aβ synergistically to inhibit cytochrome c oxidase (CcOX) activity and to reduce coQ10 levels, thereby decreasing adenosine triphosphate (ATP) production, and inducing neuronal death irreversibly.[12] Above data also indicate that the reaction between FA and coQ10 may be the fundamental reason of coQ10 deficiency in NDD.

CoQ10 and Parkinson's Disease

Loss of the dopaminergic neurons in the striatum and substantia is considered to be a critical factor for promoting PD occurrence. Recent studies have found that nitration and nitrosylation of α-synuclein, is closely related to PD. It is a small protein made of 140 amino acids, mainly expressed in CNS, in neocortex, thalamus, hippocampus, substantia nigra and cerebellum. It is present in the membrane of mitochondria in normal dopaminergic neurons. However, under overexpression conditions, α-synuclein monomers are aggregated into oligomers, which cause toxicity in response to subtoxic concentrations of mitochondrial toxins. It is widely known that α-synuclein induces a strong oxidative stress to produce ROS (a main pathological moment in PD). ROS is a family of extremely reactive molecules which have an unpaired electron that reacts with other substances. The 3 main components of ROS are superoxide (O_2-), H_2O_2 and hydroxyl radical (·HO). H_2O_2 is considered to be a principal compound related to cytotoxicity in dopaminergicneurons.[82]

The levels of markers of oxidation are increased in substantia nigra samples of PD patient, making a relationship between this kind of damage and the onset of disease. CoQ10 levels were reported to be 33 % lower in the blood and platelet mitochondria of PD patients compared to age- and sex-matched controls.[83] Mitochondrial dysfunction is believed to be the root cause of the death of dopamine-producing neurons. Since coQ10 (an endogenous antioxidant for reducing ROS) is the integral component of mitochondria, its deficiency can increase the risk of dopaminergic-neuron death in the brain and can lead to the development of PD.[84]

CoQ10 and Multiple Sclerosis

A systematic review has indicated that MS patients, especially those with more severe condition, had lower levels of coQ10 in the blood but higher levels of oxidative stress, when compared with controls.[85] Since MS patients were often accompanied by endogenous coQ10 deficiency, oral supplementation of coQ10 may contribute to the treatment of MS. Especially, coQ10 can act as a powerful antioxidant and anti-inflammatory compound capable of crossing the blood-brain barrier when administered peripherally (eg, orally or intravenously).[85]

Excessive FA has been found in the blood of MS patients, and reduction of FA by glycine improves the pathological characteristics of MS.[86] Especially, FA can induce demyelination,[5] and inflammation storm (stimulate the release of IL-1, IL-6 and TNFα).[10,15] Notably, IL-1, IL-6 and TNFα have been found to promote the demyelination of neurons (Figure 1).[16] CoQ10 application has been found to prevent demyelination and increase re-myelination in a chronic cuprizone (CPZ) model of MS. It attenuates CPZ-induced stress oxidative and inhibits inflammatory biomarkers.[87] CoQ10-scavenged FA may be a critical reason for treating MS in this CPZ-model.[12] Similarly, in another autoimmune MS model of the experimental autoimmune encephalomyelitis (EAE), coQ10 can reduce the levels of IL-1, IL-6 and TNFα.[88] In a clinical study of 24 patients with relapsing-remitting MS, coQ10 markedly reduces inflammatory factors and decreases oxidative stress.[89,90]

CoQ10 for Treating Neurodegenerative Diseases

CoQ10 and Alzheimer's disease. The current findings indicate that coQ10 treatment provides neuroprotection through its antioxidant activity against the adverse effects of Aβ on hippocampus synaptic plasticity.[75] Given the potent

antioxidant propensity of coQ10, some investigations have been carried out to assess endogenous coQ10 status in AD patients.[91] Previous study showed that coQ10-treated mice have better cognitive performance in the Morris water maze test than wild-type mice, and coQ10 alleviates the pathological characters of AD.[92] Encouragingly, an enhanced water soluble nano-coQ10,[93] or a nano-packaged coQ10 with a diameter of 30 nm has been proven to directly degrade FA, reduce intracellular Aβ oligomers and extracellular senile plaques (SPs); subsequently, it rescues memory functions in APP/PS1 mice.[12] Scavenging FA with resveratrol also reduces the formation of SPs and improves cognitive behavior in transgenic AD mice.[49] Thus, coQ10 as an endogenous FA scavenger may be used to treat AD patients.

As people ageing, the ability of generating coQ10 is gradually declining, especially in people over the age of 50. Meanwhile, the capacity of reducing coQ10 synthesis reflects an increased risk of developing neurological diseases.[25] *In vitro* study using human venous endothelial cells (HVECs) suggest that coQ10 supplementation has a therapeutic potential in preventing the deleterious effects of Aβ deposition in the early asymptomatic stages of AD, which may slow the progression of neuropathology.[94] Pretreatment of HVECs with coQ10 prevents Aβ-induced cytotoxicity and oxidative damage by inhibiting Aβ trafficking and accumulation in the mitochondria.[94] Meanwhile, coQ10 supplementation has been found to dramatically reverse these consequences and increase serum total antioxidant capacity.[75]

CoQ10 and Parkinson's Diseases

Some preclinical studies of *in vitro* and *in vivo* models of PD have shown that coQ10 protects the nigrostriatal dopaminergic system.[95] Compare with age-/sex-matched controls, PD subjects had an abnormal lower levels of coQ10 in mitochondria.[96] Consistently, deficiency in the brain coQ10 has been observed in PD patients,[97] because coQ10 contents are decreased in the plasma and platelets in PD patients than healthy controls.[25,26] Hence, to a certain degree, supplementation of coQ10 could help to ameliorate in the symptom severity,[95] and to improve in color vision in PD patients.[98,98]

A Phase II clinical trial has shown that oral coQ10 prevents functional decline in patients with early PD. CoQ10 supplementation also has a significant mild symptomatic benefit on PD symptoms,[91] and markedly improved the performance Farnsworth–Munsell 100 Hue test (FMT).[99] Remarkably, there is not any assessment for the presence of underlying coQ10 deficiency in PD patients prior to initiation of coQ10 application before 2014.[100] This may also explain why the clinical efficacy of coQ10 has rarely been reported previously.[91]

CoQ10 and Multiple Sclerosis

Mitochondrial dysfunction and oxidative stress occur early in all major neurodegenerative diseases, oxidative stress is a driver of MS pathology.[101] There is convincing evidence that both of these two factors play a causal role in the pathogenesis of MS.[101] In neurological diseases, defeciency in coQ10 status have been reported, leading to disturbances in antioxidant status and mitochondrial dysfunction, often induces severe neuronal degeneration.[29,102,103] Elevated levels of serum FA in MS patients accumulate neurotoxicity,[104] and deplete endogenous Q10,[81] and result in neuronal damage, suggesting that Q10 can scavenge excessive FA in MS.

Some studies have found that there is a positive beneficial effect of coQ10 application on fatigue status in healthy, fibromyositis, statin-related fatigue, MS, and end-stage heart failure subjects.[85] A clinical investigation showed that application of 500 mg/day of coQ10 for three months can alleviate fatigue symptoms in MS patients (32 ± 7.65 years).[89] CoQ10 supplementation could improve the scavenging activity, reduced oxidative damage, and induce a shift towards a more anti-inflammatory milieu, in the peripheral blood of relapsing–remitting MS patients treated with 44 μg IFN-β1 and coQ10.[85] In addition, 12-weeks coQ10 supplementation in MS patients can reduce peripheral oxidative stress,[90] inhibit inflammation form,[89] and ameliorate fatigue and depressive symptoms.[105]

Summary and Outlook

The earliest of all references dates back to 1982 and the most recent to 2022. The early diagnosis, prognosis and monitoring of NDD are still far from meeting the requirements of precision medicine, and clinical treatments do not approach to the idea efficacy so far.[106] Since the common pathological areas of NDD are in the brains, the sampling the living tissue is often unrealizable or difficult for accurately diagnosing of NDD. Hence the development of reliable biomarkers for NDD diagnosis is urgently needed.[27] A large bodies of evidence have shown that there is a "preclinical" phase in patients with NDD, possibly starting several years before a subject's diagnosis. Although their behaviors seem to be normal, their brains have extensive pathological changes.[107,108] Recently, a non-invasive fluorescence spectrophotometry with ethyl cyanoacetate (FS-ECA) method has been developed to detect coQ10 in the urine samples of AD patients, and this method has the potential to replace HPLC to quantify blood coQ10 concentration (Figure 2).[24] These studies provide a good basis for rapidly detecting the biomarkers combined with urinary FA and coQ10 in NDD.

It is widely known that mitochondria is the primary site of initiation and spread of disease processes.[109] Mitochondrial dysfunction-induced neuronal death is a joint pathway of all the NDD.[110,111] These deleterious aggregated proteins, such as: Aβ, α-synuclein, can result in oxidative stress, which produces a large amount of H_2O_2;[110] in turn, H_2O_2 induces the rapid production of FA.[11] Meanwhile, FA rapidly inactivates coQ10.[12] Hence, both excessive FA and coQ10 deficiency may be a principal reason for triggering mitochondrial degeneration and dysfunction. Research shows that the reaction

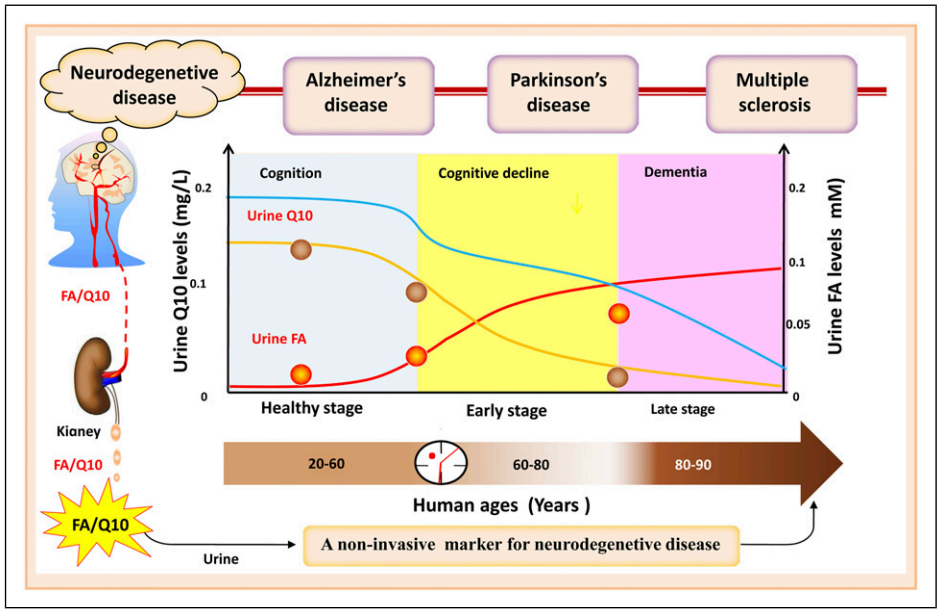

Figure 2. Levels of coenzyme Q10 and FA in the urine during human ageing. Red line: urine FA levels; Yellow line: urine Q10 levels; blue line: cognitive status. Abbreviation: FA, formaldehyde; Q10, coenzyme Q10.

ratio of FA and Q10 is about 3:1.[12] It is recommended that the Q10 concentration is about 0.17 mM when the FA pathological concentration is 0.5 mM. The daily supplemental Q10 content is about 364 mg for treating AD model mice. This concentration of Q10 was not over the doses (500 mg) presented in a previous study.[112]

Although natural coQ10 is low water soluble, a kind of enhanced water soluble nano-coQ10,[93] or the nano-packaged Q10 with a diameter of 30 nm can strengthen water solubility and alleviate the pathological characteristics and behaviors in AD model mice.[12] Gradually, some studies have introduced nano-packaged Q10 as a treatment, because nano-packaged Q10 has better water solubility and bioavailability compared to traditional Q10 drugs; the absorption rate of coenzyme-Q10 in solid lipid particles is approximately 3 times higher than that of direct oral coenzyme-Q10.[113] Also, the ability to penetrate the blood-brain barrier was enhanced. Substantial evidence suggests that nanoparticle-based drugs can penetrate into the cerebral cortex for treating brain disorders.[49] A previous study has shown that 30-nm packed Q10 penetrates both the BBB and extrcellular space (ECS), and can be devoured by the neurons in the deep layer of the cortex, which reduces Aβ- and tau-related pathological characteristics and improves cognitive behaviors in APP/PS1 mice.[12] In addition, nano-packaged Q10 also increases neuronal activity.

In a word, the detection of endogenous FA and coQ10 contents is helpful to monitor the process of NDD, and supplementation of nano-packaged coQ10 may contribute to the treatments of NDD.

Declaration of Conflicting Interests

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ORCID iDs

Jinan Xu https://orcid.org/0000-0003-3156-3028
Zhiqian Tong https://orcid.org/0000-0002-0511-0386

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