Antioxidants as antidepressants: fact or fiction?

Scapagnini G, Davinelli S, Drago F, De Lorenzo A, Oriani G.

Source
Department of Medicine and Health Sciences, University of Molise, Campobasso, Italy.
g.scapagnini@gmail.com

Abstract
Depression is a medical condition with a complex biological pattern of aetiology, involving genetic and epigenetic factors, along with different environmental stressors. Recent evidence suggests that oxidative stress processes might play a relevant role in the pathogenic mechanism(s) underlying many major psychiatric disorders, including depression. Reactive oxygen and nitrogen species have been shown to modulate levels and activity of noradrenaline (norepinephrine), serotonin, dopamine and glutamate, the principal neurotransmitters involved in the neurobiology of depression. Major depression has been associated with lowered concentrations of several endogenous antioxidant compounds, such as vitamin E, zinc and coenzyme Q10, or enzymes, such as glutathione peroxidase, and with an impairment of the total antioxidant status. These observations introduce new potential targets for the development of therapeutic interventions based on antioxidant compounds. The present review focuses on the possible role of oxidative stress processes in the pathogenesis of depression. The therapeutic potential of antioxidant compounds as a co-adjuvant treatment to conventional antidepressants is discussed. For instance, N-acetyl-cysteine has been shown to have a significant benefit on depressive symptoms in a randomized placebo-controlled trial. Additionally, curcumin, the yellow pigment of curry, has been shown to strongly interfere with neuronal redox homeostasis in the CNS and to possess antidepressant activity in various animal models of depression, also thanks to its ability to inhibit monoamine oxidases. There is an urgent need to develop better tolerated and more effective treatments for depressive disorders and several antioxidant treatments appear promising and deserve further study.

Multiple aberrations in shared inflammatory and oxidative & nitrosative stress (IO&NS) pathways explain the co-association of depression and cardiovascular disorder (CVD), and the increased risk for CVD and due mortality in depressed patients.

Maes M, Ruckoanich P, Chang YS, Mahanonda N, Berk M.

Source
Maes Clinics @ TRIA, Bangkok, Thailand. dr.michaelmaes@hotmail.com

Abstract
There is evidence that there is a bidirectional relationship between major depression and cardiovascular disorder (CVD): depressed patients are a population at risk for increased cardiac morbidity and mortality, and depression is more frequent in patients who suffer from CVD. There is also evidence that inflammatory and oxidative and nitrosative stress (IO&NS) pathways underpin the common pathophysiology of both CVD and major depression. Activation of these pathways may increase risk for both disorders and contribute to shared risk. The shared IO&NS pathways that may contribute to CVD and depression comprise the following: increased levels of pro-inflammatory cytokines, like interleukin-1β (IL-1β), IL-2, IL-6, IL-8, IL-12, tumor necrosis factor-α, and interferon-γ; T cell activation; increased acute phase proteins, like C-reactive protein,
haptoglobin, fibrinogen and α1-antitrypsin; complement factors; increased LPS load through bacterial translocation and subsequent gut-derived inflammation; induction of indoleamine 2,3-dioxygenase with increased levels of tryptophan catabolites; decreased levels of antioxidants, like coenzyme Q10, zinc, vitamin E, glutathione and glutathione peroxidase; increased O&NS characterized by oxidative damage to low density lipoprotein (LDL) and phospholipid inositol, increased malondialdehyde, and damage to DNA and mitochondria; increased nitrosative stress; and decreased ω3 polyunsaturated fatty acids (PUFAs). The complex interplay between the abovementioned IO&NS pathways in depression results in pro-atherogenic effects and should be regarded as a risk factor to future clinical CVD and due mortality. We suggest that major depression should be added as a risk factor to the Charlson “comorbidity” index. It is advised that patients with (sub)chronic or recurrent major depression should routinely be assessed by serology tests to predict if they have an increased risk to cardiovascular disorders.


Coenzyme Q10 deficiency in mitochondrial DNA depletion syndromes.


Collaborators (17)


Source

Clinical Chemistry, Pathology and Neurology Departments, Hospital Sant Joan de Déu, Barcelona, Spain; Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III, Spain.

Abstract

We evaluated coenzyme Q10 (CoQ) levels in patients studied under suspicion of mitochondrial DNA depletion syndromes (MDS) (n=39). CoQ levels were quantified by HPLC, and the percentage of mtDNA depletion by quantitative real-time PCR. A high percentage of MDS patients presented with CoQ deficiency as compared to other mitochondrial patients (Mann-Whitney-U test: p=0.001). Our findings suggest that MDS are frequently associated with CoQ deficiency, as a possible secondary consequence of disease pathophysiology. Assessment of muscle CoQ status seems advisable in MDS patients since the possibility of CoQ supplementation may then be considered as a candidate therapy.


Coenzyme Q deficiency in muscle.

Trevisson E, DiMauro S, Navas P, Salviati L.

Source

Clinical Genetics Unit, Department of Pediatrics, University of Padova, Italy.

Abstract

PURPOSE OF REVIEW:

Coenzyme Q (CoQ) is a vital component of the mitochondrial respiratory chain. A number of patients with CoQ deficiency presented with different clinical phenotypes, often affecting skeletal muscle, and responded
well to CoQ supplementation. We discuss recent advances in this field with special attention to muscle involvement.

**RECENT FINDINGS:**

The identification of genetic defects causing CoQ deficiency has allowed to distinguish primary forms, due to mutations in biosynthetic genes, from secondary defects caused either by mutations in genes unrelated to CoQ biosynthesis or by nongenetic factors. To date, none of the patients with genetically proven primary deficiency presented with an exclusively (or prominently) myopathic phenotype. Most patients with myopathy were found to harbor other genetic defects (mutations in electron-transferring-flavoprotein dehydrogenase or mitochondrial DNA). The majority of patients with CoQ deficiency still lack a genetic diagnosis. The pathogenesis of CoQ deficiency cannot be attributed solely to the bioenergetic defect, suggesting that other roles of CoQ, including its antioxidant properties or its role in pyrimidine metabolism, may also play crucial roles.

**Coenzyme Q and mitochondrial disease.**

Quinzii CM, Hirano M.

Source

Department of Neurology, Columbia University Medical Center, 630 West 168th Street, New York, NY 10032, USA.

Abstract

Coenzyme Q(10) (CoQ(10)) is an essential electron carrier in the mitochondrial respiratory chain and an important antioxidant. Deficiency of CoQ(10) is a clinically and molecularly heterogeneous syndrome, which, to date, has been found to be autosomal recessive in inheritance and generally responsive to CoQ(10) supplementation. CoQ(10) deficiency has been associated with five major clinical phenotypes: (1) encephalomyopathy, (2) severe infantile multisystemic disease, (3) cerebellar ataxia, (4) isolated myopathy, and (5) nephrotic syndrome. In a few patients, pathogenic mutations have been identified in genes involved in the biosynthesis of CoQ(10) (primary CoQ(10) deficiencies) or in genes not directly related to CoQ(10) biosynthesis (secondary CoQ(10) deficiencies). Respiratory chain defects, ROS production, and apoptosis contribute to the pathogenesis of primary CoQ(10) deficiencies. In vitro and in vivo studies are necessary to further understand the pathogenesis of the disease and to develop more effective therapies.

**Primary and secondary CoQ(10) deficiencies in humans.**

Quinzii CM, Hirano M.

Source

Department of Neurology, Columbia University Medical Center, New York, USA.

Abstract
CoQ(10) deficiencies are clinically and genetically heterogeneous. This syndrome has been associated with five major clinical phenotypes: (1) encephalomyopathy, (2) severe infantile multisystemic disease, (3) cerebellar ataxia, (4) isolated myopathy, and (5) nephrotic syndrome. In a few patients, pathogenic mutations have been identified in genes involved in the biosynthesis of CoQ(10) (primary CoQ(10) deficiencies) or in genes not directly related to CoQ(10) biosynthesis (secondary CoQ(10) deficiencies). Respiratory chain defects, ROS production, and apoptosis variably contribute to the pathogenesis of primary CoQ(10) deficiencies.


**Human CoQ10 deficiencies.**

Quinzii CM, López LC, Naini A, DiMauro S, Hirano M.

**Source**

Department of Neurology, Columbia University Medical Center, New York, NY 10032, USA.

**Abstract**

Coenzyme Q10 (CoQ10 or ubiquinone) is a lipid-soluble component of virtually all cell membranes and has multiple metabolic functions. A major function of CoQ10 is to transport electrons from complexes I and II to complex III in the respiratory chain which resides in the mitochondrial inner membrane. Deficiencies of CoQ10 (MIM 607426) have been associated with four major clinical phenotypes: 1) encephalomyopathy characterized by a triad of recurrent myoglobinuria, brain involvement, and ragged-red fibers; 2) infantile multisystemic disease typically with prominent nephropathy and encephalopathy; 3) cerebellar ataxia with marked cerebellar atrophy; and 4) pure myopathy. Primary CoQ10 deficiencies due to mutations in ubiquinone biosynthetic genes (COQ2, PDSS1, PDSS2, and ADCK3 [CABC1]) have been identified in patients with the infantile multisystemic and cerebellar ataxic phenotypes. In contrast, secondary CoQ10 deficiencies, due to mutations in genes not directly related to ubiquinone biosynthesis (APTX, ETFDH, and BRAF), have been identified in patients with cerebellar ataxia, pure myopathy, and cardiofaciocutaneous syndrome. In many patients with CoQ10 deficiencies, the causative molecular genetic defects remain unknown; therefore, it is likely that mutations in additional genes will be identified as causes of CoQ10 deficiencies.


**CoQ10 deficiency diseases in adults.**

Quinzii CM, Hirano M, DiMauro S.

**Source**

Department of Neurology, Columbia University Medical Center, P&S 4-420, 630 West 168th street, New York, NY 10032, USA.

**Abstract**

Deficiency of Coenzyme Q10 (CoQ10) in muscle has been associated with a spectrum of diseases including infantile-onset multi-systemic diseases, encephalomyopathies with recurrent myoglobinuria,
Cerebellar ataxia, and pure myopathy. CoQ10 deficiency predominantly affects children, but patients have presented with adult-onset cerebellar ataxia or myopathy. Mutations in the CoQ10 biosynthetic genes, COQ2 and PDSS2, have been identified in children with the infantile form of CoQ10 deficiency; however, the molecular genetic bases of adult-onset CoQ10 deficiency remains undefined.


**Cardiofaciocutaneous (CFC) syndrome associated with muscular coenzyme Q10 deficiency.**

Aeby A, Sznajer Y, Cavé H, Rebuffat E, Van Coster R, Rigal O, Van Bogaert P.

**Source**

Department of Pediatric Neurology, Erasme Hospital, Free University of Brussels (ULB), 808 route de Lennik, 1070, Brussels, Belgium. alec.aeby@ulb.ac.be

**Abstract**

The cardiofaciocutaneous (CFC) syndrome is characterized by congenital heart defect, developmental delay, peculiar facial appearance with bitemporal constriction, prominent forehead, downslanting palpebral fissures, curly sparse hair and abnormalities of the skin. CFC syndrome phenotypically overlaps with Noonan and Costello syndromes. Mutations of several genes (PTPN11, HRAS, KRAS, BRAF, MEK1 and MEK2), involved in the mitogen-activated protein kinase (MAPK) pathway, have been identified in CFC-Costello-Noonan patients. Coenzyme Q10 (CoQ10), a lipophilic molecule present in all cell membranes, functions as an electron carrier in the mitochondrial respiratory chain, where it transports electrons from complexes I and II to complex III. CoQ10 deficiency is a rare treatable mitochondrial disorder with various neurological (cerebellar ataxia, myopathy, epilepsy, mental retardation) and extraneurological (cardiomyopathy, nephropathy) signs that are responsive to CoQ10 supplementation. We report the case of a 4-year-old girl who presented a CFC syndrome, confirmed by the presence of a pathogenic R257Q BRAF gene mutation, together with a muscular CoQ10 deficiency. Her psychomotor development was severely impaired, hindered by muscular hypotonia and ataxia, both improving remarkably after CoQ10 treatment. This case suggests that there is a functional connection between the MAPK pathway and the mitochondria. This could be through the phosphorylation of a nuclear receptor essential for CoQ10 biosynthesis. Another hypothesis is that K-Ras, one of the proteins composing the MAPK pathway, might be recruited into the mitochondria to promote apoptosis. This case highlights that CoQ10 might contribute to the pathogenesis of CFC syndrome.


**Coenzyme Q10 deficiencies in neuromuscular diseases.**

Artuch R, Salviati L, Jackson S, Hirano M, Navas P.

**Source**

Biochemistry Department, Hospital Sant Joan de Déu, Barcelona, Spain.

**Abstract**

Coenzyme Q (CoQ) is an essential component of the respiratory chain but also participates in other mitochondrial functions such as regulation of the transition pore and uncoupling proteins. Furthermore, this compound is a specific substrate for enzymes of the fatty acids beta-oxidation pathway and pyrimidine nucleotide biosynthesis. Furthermore, CoQ is an antioxidant that acts in all cellular membranes and lipoproteins. A complex of at least ten nuclear (COQ) genes encoded
proteins synthesizes CoQ but its regulation is unknown. Since 1989, a growing number of patients with multisystemic mitochondrial disorders and neuromuscular disorders showing deficiencies of CoQ have been identified. CoQ deficiency caused by mutation(s) in any of the COQ genes is designated primary deficiency. Other patients have displayed other genetic defects independent on the CoQ biosynthesis pathway, and are considered to have secondary deficiencies. This review updates the clinical and molecular aspects of both types of CoQ deficiencies and proposes new approaches to understanding their molecular bases.

Coenzyme Q--biosynthesis and functions.
Bentinger M, Tekle M, Dallner G.

The antioxidant role of coenzyme Q.
Bentinger M, Brismar K, Dallner G.

Antioxidant and prooxidant properties of mitochondrial Coenzyme Q.
Abstract

Coenzyme Q is both an essential electron carrier and an important antioxidant in the mitochondrial inner membrane. The reduced form, ubiquinol, decreases lipid peroxidation directly by acting as a chain breaking antioxidant and indirectly by recycling Vitamin E. The ubiquinone formed in preventing oxidative damage is reduced back to ubiquinol by the respiratory chain. As well as preventing lipid peroxidation, Coenzyme Q reacts with other reactive oxygen species, contributing to its effectiveness as an antioxidant. There is growing interest in using Coenzyme Q and related compounds therapeutically because mitochondrial oxidative damage contributes to degenerative diseases. Paradoxically, Coenzyme Q is also involved in superoxide production by the respiratory chain. To help understand how Coenzyme Q contributes to both mitochondrial oxidative damage and antioxidant defences, we have reviewed its antioxidant and prooxidant properties.

Dhanasekaran M, Ren J.

Abstract

Coenzyme Q (ubiquinone, 2-methyl-5,6-dimethoxy-1,4-benzoquinone), soluble natural fat quinine, is crucial to optimal biological function. The coenzyme Q molecule has amphipathic (biphasic) properties due to the hydrophilic benzoquinone ring and the lipophilic poly isoprenoid side-chain. The nomenclature of coenzyme Q-n is based on the amount of isoprenoid units attached to 6-position on the benzoquinone ring. It was demonstrated that coenzyme Q, in addition to its role in electron transport and proton transfer in mitochondrial and bacterial respiration, acts in its reduced form (ubiquinol) as an antioxidant. Coenzyme Q-10 functions as a lipid antioxidant regulating membrane fluidity, recycling radical forms of vitamin C and E, and protecting membrane phospholipids against peroxidation. The antioxidant property, high degree of hydrophobicity and universal occurrence in biological system, suggest an important role for ubiquinone and ubiquinol in cellular defense against oxidative damage. Coenzyme Q-10 is a ubiquitous and endogenous lipid-soluble antioxidant found in all organisms. Neurodegenerative disorders, cancer, cardiovascular diseases and diabetes mellitus and especially aging and Alzheimer's disease exhibit altered levels of ubiquinone or ubiquinol, indicating their likely crucial role in the pathogenesis and cellular mechanisms of these ailments. This review is geared to discuss the biological effect of coenzyme Q with an emphasis on its impact in initiation, progression, treatment and prevention of neurodegenerative, cardiovascular and carcinogenic diseases.
Abstract

Coenzyme Q(10) (ubiquinone), which serves as the electron acceptor for complexes I and II of the mitochondrial electron transport chain and also acts as an antioxidant, has the potential to be a beneficial agent in neurodegenerative diseases in which there is impaired mitochondrial function and/or excessive oxidative damage. Substantial data have accumulated to implicate these processes in the pathogenesis in certain neurodegenerative disorders, including Parkinson's disease, Huntington's disease and Friedreich's ataxia. Although no study to date has unequivocally demonstrated that coenzyme Q(10) can slow the progression of a neurodegenerative disease, recent clinical trials in these three disorders suggest that supplemental coenzyme Q(10) can slow the functional decline in these disorders, particularly Parkinson's disease.


Coenzyme Q10 administration and its potential for treatment of neurodegenerative diseases.
Beal MF.

Source
Neurochemistry Laboratory, Massachusetts General Hospital, Boston 02114, USA.

Abstract

Coenzyme Q10 (CoQ10) is an essential cofactor of the electron transport chain as well as an important antioxidant. Previous studies have suggested that it may exert therapeutic effects in patients with known mitochondrial disorders. We investigated whether it can exert neuroprotective effects in a variety of animal models. We have demonstrated that CoQ10 can protect against striatal lesions produced by both malonate and 3-nitropropionic acid. It also protects against MPTP toxicity in mice. It extended survival in a transgenic mouse model of amyotrophic lateral sclerosis. We demonstrated that oral administration can increase plasma levels in patients with Parkinson's disease. Oral administration of CoQ10 significantly decreased elevated lactate levels in patients with Huntington's disease. These studies therefore raise the prospect that administration of CoQ10 may be useful for the treatment of neurodegenerative diseases.


Coenzyme Q10: a review of its promise as a neuroprotectant.
Young AJ, Johnson S, Steffens DC, Doraiswamy PM.

Source
Duke University Medical Center, Durham, NC 27703, USA. young109@mc.duke.edu

Abstract

Coenzyme Q10 (CoQ10) is a powerful antioxidant that buffers the potential adverse consequences of free radicals produced during oxidative phosphorylation in the inner mitochondrial membrane. Oxidative stress, resulting in glutathione loss and oxidative DNA and protein damage, has been implicated in many neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and Huntington's disease. Experimental studies in animal models suggest that CoQ10 may protect against neuronal damage that is produced by ischemia, atherosclerosis and toxic injury. Though most have tended to be pilot studies, there are published preliminary clinical trials showing that CoQ10 may offer promise in many brain disorders. For example, a 16-month randomized, placebo-controlled pilot trial in 80 subjects with mild Parkinson's disease
found significant benefits for oral CoQ10 1,200 mg/day to slow functional deterioration. However, to date, there are no published clinical trials of CoQ10 in Alzheimer's disease. Available data suggests that oral CoQ10 seems to be relatively safe and tolerated across the range of 300-2,400 mg/day. Randomized controlled trials are warranted to confirm CoQ10's safety and promise as a clinically effective neuroprotectant.

Nervenarzt. 2007 Dec;78(12):1378-82.

[Coenzyme Q10 in Parkinson's disease. Symptomatic or neuroprotective effects?].

[Article in German]
Storch A.

Source
Klinik und Poliklinik für Neurologie, Technische Universität Dresden, Fetscherstrasse 74, Dresden, Germany.
Alexander.Storch@neuro.med.tu-dresden.de

Abstract
Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive loss of dopaminergic neurons within the substantia nigra pars compacta. Experimental and clinical data point to a defect of the mitochondrial respiratory chain as a major pathogenetic factor in PD. Although the restoration of mitochondrial respiration and reduction of oxidative stress by coenzyme Q(10) (CoQ10) could induce neuroprotective effects against the dopaminergic cell death in PD, these effects of CoQ10 could also improve the dopaminergic dysfunction. Thus CoQ10 might theoretically exert both neuroprotective and symptomatic effects in PD. Current data from controlled clinical trials are not sufficient to answer conclusively whether CoQ10 is neuroprotective in PD. Moreover, several open and controlled pilot studies on symptomatic effects of CoQ10 revealed inconsistent results. A recent randomized, double-blind, placebo-controlled trial showed no symptomatic effects in PD. CoQ10 is well tolerated and safe as both monotherapy and add-on medication in PD patients. The present review discusses the current knowledge on neuroprotective and symptomatic actions of CoQ10 in PD.


Therapeutic role of coenzyme Q(10) in Parkinson's disease.

Shults CW.

Source
Department of Neurosciences, University of California San Diego, La Jolla, CA 92093, USA.
cshults@ucsd.edu

Abstract
Mitochondrial dysfunction has been well established to occur in Parkinson's disease (PD) and appears to play a role in the pathogenesis of the disorder. A key component of the mitochondrial electron transport chain (ETC) is coenzyme Q(10), which not only serves as the electron acceptor for complexes I and II of the ETC but is also an antioxidant. In addition to being crucial to the bioenergetics of the cell, mitochondria play a central role in apoptotic cell death through a number of mechanisms, and coenzyme Q(10) can affect certain of these processes. Levels of coenzyme Q(10) have been reported to be decreased in blood and platelet mitochondria from PD patients. A number of preclinical studies in in vitro and in vivo models of PD have demonstrated that coenzyme Q(10) can protect the nigrostriatal dopaminergic system. A phase II trial of coenzyme Q(10) in patients with early, untreated PD demonstrated a positive trend for coenzyme Q(10) to slow progressive disability that occurs in PD.
Mitochondria, oxidative damage, and inflammation in Parkinson's disease.

Beal MF.

Source

Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York Presbyterian Hospital, New York, New York 10021, USA. fbeal@med.cornell.edu

Abstract

The pathogenesis of Parkinson's disease (PD) remains obscure, but there is increasing evidence that impairment of mitochondrial function, oxidative damage, and inflammation are contributing factors. The present paper reviews the experimental and clinical evidence implicating these processes in PD. There is substantial evidence that there is a deficiency of complex I activity of the mitochondrial electron transport chain in PD. There is also evidence for increased numbers of activated microglia in both PD postmortem tissue as well as in animal models of PD. Impaired mitochondrial function and activated microglia may both contribute to oxidative damage in PD. A number of therapies targeting inflammation and mitochondrial dysfunction are efficacious in the MPTP model of PD. Of these, coenzyme Q(10) appears to be particularly promising based on the results of a recent phase 2 clinical trial in which it significantly slowed the progression of PD.