ORIGINAL ARTICLE

Lower plasma Coenzyme Q10 in depression: a marker for treatment resistance and chronic fatigue in depression and a risk factor to cardiovascular disorder in that illness

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Abstract

INTRODUCTION: There is now evidence that major depression is accompanied by an induction of inflammatory and oxidative and nitrosative stress (IO&NS) pathways and by a lowered antioxidant status. Coenzyme Q10 (CoQ10) is a strong antioxidant that has anti-inflammatory effects.

METHODS: This paper examines the plasma concentrations of CoQ10 in 35 depressed patients and 22 normal volunteers and the relationships between plasma CoQ10 and treatment resistant depression (TRD), the severity of illness as measured by means of the Hamilton Depression Rating Scale (HDRS) and the presence of chronic fatigue syndrome (CFS).

RESULTS: We found that plasma CoQ10 was significantly (p=0.0002) lower in depressed patients than in normal controls. 51.4% of the depressed patients had plasma CoQ10 values that were lower than the lowest plasma CoQ10 value detected in the controls. Plasma CoQ10 was significantly lower in patients with TRD and with CFS than in the other depressed patients. There were no significant correlations between plasma CoQ10 and the HDRS.

DISCUSSION: The results show that lower CoQ10 plays a role in the pathophysiology of depression and in particular in TRD and CFS accompanying depression. It is suggested that depressed patients may benefit from CoQ10 supplementation.

The findings that lower CoQ10 is a risk factor to coronary artery disease and chronic heart failure (CHF) and mortality due to CHF suggest that low CoQ10 is another factor explaining the risk to cardiovascular disorder in depression. Since statins significantly lower plasma CoQ10, depressed patients and in particular those with TRD and CFS represent populations at risk to statin treatment.

INTRODUCTION

There is now evidence that major depression is accompanied by an induction of inflammatory and oxidative and nitrosative stress (IO&NS) pathways, which cause depressive symptomatology. This theory was called the monocyte-T-lymphocyte, cytokine or inflammatory hypothesis of depression (Maes, 1993; 1995; 1999; 2008; Schiepers *et al.* 2005). The first papers which showed that T cell and monocytic activation are new pathways in depression were published in 1990 and 1991 (Maes *et al.* 1990; 1991). Since then many consistent reports have been published on increased levels of proinflammatory cytokines, e.g. interleukin-1 (IL-1), IL-2, IL-6, IL-8, IL-12, interferon-γ (IFNγ) and tumor necrosis factor-α (TNFα), and acute phase proteins (Schiepers *et al.* 2005). Also translational research shows that inflammatory processes and neural-immune interactions in the brain are new pathways in depression (Maes *et al.* 2009b; Goshen *et al.* 2008). In animal models, the increased production of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNFα, and consequent brain neuroinflammation may induce depressive symptoms, such as anorexia, soporific effects, reduction of locomotor activity and exploration, anhedonia and cognitive disturbances (Maes *et al.* 2009b; Goshen *et al.* 2008; Anisman *et al.* 2005; Qin *et al.* 2007). In humans, cytokine-based immunotherapy may induce depression through cytokine-induced changes in the metabolism of serotonin (Maes *et al.* 2001; Bonaccorso *et al.* 2002; Wichers *et al.* 2005; Forlenza and Miller, 2006).

Inflammatory responses are known to be accompanied by an induction of oxidative and nitrosative stress (O&NS) pathways. Likewise, depression is accompanied by indicants of oxidative stress, such as increased levels of malondialdehyde (MDA), a byproduct of polyunsaturated fatty acid peroxidation and arachidonic acid; 8-hydroxy-2-deoxyguanosine, indicating oxidative damage to DNA by oxygen radicals; and IgM responses against phosphatidyl inositol (Forlenza and Miller, 2006; Sarandol *et al.* 2007; Maes *et al.* 2007c). Other findings in depression point toward nitrosative stress, e.g. increased IgM responses against NO-bovine serum albumin (Maes *et al.* 2008). Moreover, depression in characterized by a significantly reduced antioxidant status, as indicated by lowered blood levels of antioxidants, such as serum zinc, vitamin E and C, tryptophan and tyrosine, glutathione peroxidase, and albumin (Maes and Meltzer, 1995; van Hunsel *et al.* 1996; Maes *et al.* 1994; 1997b; 2000; Ozcan *et al.* 2004; Khanzode *et al.* 2003). In animals models of stress-induced depression reduced concentrations of brain glutathione, another antioxidant, are observed (Pal and Dandiya, 1994; Gutteridge and Halliwell, 1994).

There is ample evidence that depression is associated with neurodegeneration and a reduced neurogenesis in the brain (Maes *et al.* 2009b; Campbell and MacQueen, 2006; Stockmeier *et al.* 2004; Koo and Duman, 2008) and that both factors are caused by neuroinflammatory processes (Maes *et al.* 2009b). Different neurotoxic mechanisms that are induced or altered by IO&NS pathways may be involved, e.g. neurotoxic cytokines; O&NS pathways; glucocorticoids; neurotoxic TRYCATs (tryptophan catabolites), which production is enhanced by inflammation; and lowered ω3 polyunsaturated fatty acids (Maes *et al.* 2009b). Recently, these new pathways in depression have been described in the inflammatory & neurodegenerative (I&ND) hypothesis of depression (Maes *et al.* 2009b).

Up to 15% of the depressed patients suffer from treatment resistant depression (TRD). There is now evidence that IO&NS and I&ND pathways are involved in TRD (Maes *et al.* 2009b) as evidenced by for example an increased $CD4^+/CD8^+$ T cell ratio; serum IL-6 and production of IL-6 and TNFα; and significantly lower serum zinc (Maes *et al.* 1997b; Kubera *et al.* 1999; Maes *et al.* 1997a; O'Brien *et al.* 2007).

Another factor that may participate in the IO&NS and I&ND pathways in depression is a deficiency of plasma coenzyme Q10 (CoQ10). CoQ10 is a strong anti-oxidant that confers resistance to mitochondrial damage by O&NS and an anti-inflammatory agent that decreases the production of, for example, TNFα (Chaturvedi and Beal, 2008; Schmelzer *et al.* 2007a; 2007b; 2008). Moreover, CoQ10 has neuroprotective properties, protecting neurons and brain cells against central neurotoxic damages (Chaturvedi and Beal, 2008; Young *et al.* 2007; Li *et al.* 2005; Matthews *et al.* 1998). Recently, we found that plasma CoQ10 is significantly reduced in patients with myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS), another illness characterized by induction of the IO&NS pathways (Maes *et al.* 2009a; 2007a; 2007b). However, to the best of our knowledge, no research has examined plasma CoQ10 in depression, TRD and CFS in depression.

The present study has been carried out in order to examine whether major depression is accompanied by lowered plasma CoQ10 and to examine the relationships between lower CoQ10 and TRD, chronicity of depression, depressive symptomatology and CFS in depression.

SUBJECTS AND METHODS

Subjects

Fifty-seven subjects participated in the present study, i.e. 22 healthy volunteers and 35 major depressed patients. The latter were admitted to the Maes Clinics, Antwerp, Belgium. The patients were classified as major depression according to DSM-IV-TR criteria (APA, 2000), using a semistructured interview. Severity of depression was measured with the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). The presence of the symptoms of ME/CFS was assessed by means of the Center for Disease Control and Prevention (CDC) criteria (Fukuda *et al.* 1994). The CDC criteria rule out

to make the ME/CFS diagnosis when melancholia is present. Nevertheless, we employed the CDC criteria to delineate the presence of the CFS according to the following criteria:

a) the patient has to suffer from severe chronic fatigue for at least six months; and
b) at least four of the following symptoms should be present: substantial impairment in short-term memory or concentration; sore throat; muscle pain; multi-joint pain without selling or redness; headache of new type; unrefreshing sleep; and post exertion malaise lasting more than 24 hours.

The severity of CFS was scored by means of the Fibromyalgia and CFS Rating Scale (FF scale) (Zachrisson *et al.* 2002). The FF scale measures 12 symptoms which are characteristic for fibromyalgia and CFS, i.e. pain, muscular tension, fatigue, concentration difficulties, failing memory, irritability, sadness, sleep disturbances, autonomic disturbances, irritable bowel, headache, and subjective experience of infection. Staging of treatment resistance was based on prior treatment responsivity according to the criteria of Thase and Rush (1995). We classified the patients as suffering from TRD when they fulfilled the following criteria:

a) nonresponse to two adequate trials with antidepressant agents from different classes, e.g. tricyclics (TCSs) or selective serotonin reuptake inhibitors (SSRIs);
b) the previous stage (stage a) plus a failure to respond to one augmentation therapy;
c) the previous stage plus failure to respond to two augmentation strategies; and
d) the previous stage plus a nonresponse to electroconvulsive treatment.

Nineteen of the depressed patients included in this study fulfilled the abovementioned criteria for TRD. The others (n=16) had never had a single adequate trial with antidepressants or showed a nonresponse to one adequate trial. Of those patients 15 were treated successfully in the Maes Clinics and therefore were classified as non-TRD patients. One patient who previously did not respond to one trial with SSRIs did not respond to our treatment and therefore was classified as a patient with TRD. Consequently, in total 20 patients were classified as suffering from TRD and 15 were classified as non-TRD.

We have excluded all subjects with life-time diagnoses of psychiatric DSM IV-R disorders other than major depression, e.g. psychotic, substance use and organic mental disorders. Patients with substance abuse (last 6 months prior to the studies) were excluded to participate in this study. We also omitted subjects with other medical illnesses, e.g. endocrine (e.g. Cushing, thyroid disease), metabolic (e.g. diabetes type 1 or type 2), immune, like autoimmune and inflammatory bowel disorders) and cardio-vascular (e.g. hypertension, arteriosclerosis) disorders. Moreover, we have excluded subjects with abnormal blood tests, such as alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatinine, and thyroid stimulating hormone (TSH). Subjects who had suffered from infections during the last two months prior to the study were excluded. We have excluded depressed patients who were treated with anti-psychotic drugs, anticonvulsants or mood stabilizers the year prior to the studies. All subjects were free of drugs known to affect immune or endocrine functions. None had been taking statins or beta-blockers and supplements with CoQ10. The normal volunteers were free of any medication for at least 1 month prior to blood sampling; no one had ever been taking psychotropic drugs or was a regular drinker. Patients and controls gave written informed consent after the study protocol was fully explained; the study has been approved by the local ethical committee.

Methods

Plasma for the assay of CoQ10 was sampled in the morning hours after an overnight fast. CoQ10 was determined using a HPLC method manufactured by Chromsystems Diagnostics (Munich, Germany). This reagent kit allows the reliable chromatographic determination of CoQ10 in an isocratic HPLC run using UV detection (275 nm). CoQ10 is released by precipitating the proteins and then concentrated using solid phase extraction. Inclusion of an internal standard minimizes any analytical variation. We followed the instructions as provided by Chromsystems Diagnostics. The Intra-assay coefficient of variation (CV) was < 5%, and the inter-assay CV < 6%.

Statistics

Differences between group means were checked by analysis of variance (ANOVA) or covariance (ANCOVA). The independence of classification systems was ascertained by means of analysis of contingence tables (χ^2-test) and Fisher's exact probability test. The diagnostic performance of plasma CoQ10 for depression and TRD was checked by means of ROC (receiver operating characteristics) analysis with computation of the area under the ROC curve, sensitivity, specificity and predictive value of a positive test result (PV+) and with kappa statistics (Zweig and Campbell, 1993). Relationships between variables were ascertained by means of Pearson's product-moment correlation coefficients, regression analyses and multiple regression analyses with an p–to-enter of p=0.05. In order to check the symptomatic profiles of diagnostic groups we employed stepwise linear discriminant analysis (LDA) with an F-to-enter of p=0.05. The significance was set at α=0.05 (two tailed).

RESULTS

Figure 1 shows the plasma CoQ10 values in depressed patients and normal controls. ANOVA showed that plasma CoQ10 was significantly lower in the major depressed patients than in the normal volunteers (F=23.6, df=1/55, p=0.00006). Covarying for age and sex in an ANCOVA did not change these results (F=20.7, df=1/53, p=0.0001). Neither gender (F=0.11, p=0.7) nor age (F=0.00, p=0.9) were significant in this analysis. There were no significant differences in age (F=1.3, df=1/55, p=0.2) between normal controls (mean age ±SD = 45.4 ±10.1 years) and major depressed patients (mean age = 42.1 ±10.5 years). There was no significant difference (χ^2 =1.6, df=1, p=0.0.2) in the gender distribution between normal controls (5 male/17 female) and major depressed patients (15 male/20 female patients). The lower plasma CoQ10 showed a significant diagnostic performance for major depression: the area under the ROC curve was AUC=81.7%; at a cut-off point of CoQ10 < 490 μg/L (that is the lowest CoQ10 value established in the normal controls) we found a sensitivity = 51.4%, specificity = 100.0%, and PV+ = 100% (κ=0.45, t=4.02, p=0.0004).

Depressed patients with TRD (mean CoQ10=420.0 ± 107.0 μg/L, n=15) had significantly (F=15.3, df=1/33, p=0.0007) lower plasma CoQ10 than patients without TRD (mean CoQ10=581.7 ± 125.8 μg/L, n=20). There were no significant differences in age (F=0.0, df=1/33, p=0.98) between depressed patients with (mean age=42.1 ±10.3 years) and without (mean age=42.1 ±11.1 years) TRD. There was no significant difference (χ^2 =0.5, df=1, p=0.5) in the male/female ratio between TRD (8 male/7 female) and non-TRD (7 male/13 female) patients. Lower plasma CoQ10 showed a significant diagnostic performance for TRD versus non-TRD: the area under the ROC curve was AUC=83.5%; at a cut-off point of CoQ10 < 415 μg/L we found: sensitivity=60.0%, specificity=95.0%, and PV+=90% (κ=0.57, t=3.98, p=0.0006).

Depressed patients with CFS (mean CoQ10=445.8 ±123.6 μg/L, n=17) had significantly (F=8.7, df=1/33, p=0.006) lower plasma CoQ10 than patients without CFS (mean CoQ10=575.3 ±131.2 μg/L, n=18). There was no significant difference (χ^2 =0.3, df=1, p=0.6) in the male/female ratio between those with (6 male/11 female) and without (9 male/9 female) CFS. Those with CFS (mean age=45.9 ±10.5 years) were somewhat (F=4.9 df=1/33, p=0.03) older than those without (mean age=38.4 ±9.3 years). Covarying for age (and gender) in an ANCOVA did not change the significant differences in CoQ10 between both groups (F=8.2, df=1/31, p=0.007), while age was not significant in this analysis (F=0.00, p=0.9). The number of patients with CFS was not significantly different between patients with (10/5) and without (7/13) TRD. The presence of CFS (F=4.3, df=1/31, p=0.04) and TRD (F=10.3, df=1/31, p=0.003) independently from each other predicted low CoQ10 values (F=7.1, df=3/31, p=0.001; results of a factorial design ANOVA with TRD and CFS as treatments; the interaction pattern was non-significant: F=0.0, df=1/31, p=0.8).

In the depressed patients, there were no significant correlations between plasma CoQ10 and age (r=0.13, p=0.6), gender (point biserial correlation: r=-0.08, p=0.6), the HDRS score (r=0.13, p=0.5) and the total FF scale score (r=0.19, p=0.3). In the depressed subgroup

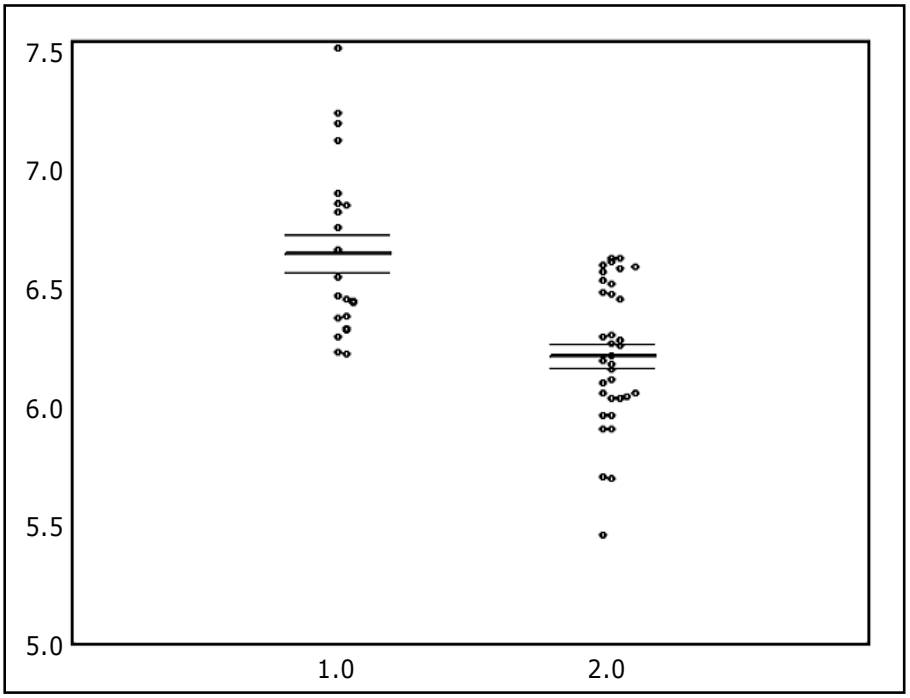

Figure 1. Scatter plot of the measurements of Co-enzyme Q10 (in transformation and in μg/L) in 33 major depressed patients and 22 normal volunteers (NV).

we were unable to detect any differences in plasma CoQ10 between subjects who suffered from a chronic major depression for more than 2 years and those who did not. There was no significant correlation between plasma CoQ10 and the number of depressive episodes. Part of the depressed patients took antidepressants by the time of blood samplings (n=15), while the others were unmedicated. There were no significant differences in plasma CoQ10 between depressed patients who were taking antidepressants (mean CoQ10=547.7 ±116.0 μg/L, n=15) and those without (mean CoQ10=485.9 ±156.9 μg/L, n=20). In depressed patients no significant relationships could be detected between plasma CoQ10 and any of the 12 FF scale items, either by stepwise multiple regression analysis of plasma CoQ10 on the 12 FF items or by stepwise LDA with as groups the depressed patients divided into groups with lower (<490 μg/L) versus higher (>490 μg/L) CoQ10 values.

DISCUSSION

This is a first study which shows that major depression is accompanied by a CoQ10 deficiency and that lower plasma CoQ10 is significantly related to treatment resistance and the presence of CFS in depression.

The first major finding of this study is that depression is characterized by a low CoQ10 syndrome: up to 51.4% of the depressed patients showed plasma CoQ10 values that were lower than 490 μg/L, i.e. the lowest CoQ10 value established in the normal volunteers. In the next paragraphs we discuss that lower CoQ10 plays a role in the IO&NS and I&ND pathways in depression.

The findings of this study reinforce the existent literature which shows that depression is accompanied by a significantly decreased antioxidant status, as evidenced by lower serum zinc, vitamin E and C, glutathione peroxidase, tryptophan and tyrosine and albumin (see Introduction). It is safe to posit that the "low CoQ10 syndrome" in depression and the more general reduced antioxidative capacity in those patients may have impaired the anti-oxidative protection against the damaging effects IO&NS and, consequently, may be involved in the neurotoxic damage which occurs in depression (Maes *et al.* 2009b). It is now well established that CoQ10 has significant neuroprotectant properties, whereby this compound may protect neuronal cells against neuronal damages (Chaturvedi and Beal, 2008; Young *et al.* 2007; Li FC *et al.* 2005; Li G *et al.* 2005; Matthews *et al.* 1998; Kooncumchoo *et al.* 2006; Ishrat *et al.* 2006; Somayajulu *et al.* 2005). This explains why CoQ10 has the potential to be employed as a therapeutic intervention in neurodegenerative disorders (Somayajulu *et al.* 2005).

CoQ10 has also anti-inflammatory effects, e.g. by decreasing Nuclear Factor κB-gene expression and the production of pro-inflammatory cytokines, such as TNFα, and protecting against endoxin or LPS-induced inflammatory reactions (Schmelzer *et al.* 2007a; 2007b; 2008; Abd El-Gawad *et al.* 2001; Sugino *et al.* 1987). Thus, the deficiency of CoQ10 in depression may predispose toward greater inflammatory responses and a greater production of proinflammatory cytokines, such as TNFα, which eventually cause more damage and neurodegeneration (Maes *et al.* 2009b).

CoQ10 is also of paramount importance in the electron transport chain (ETC) within the mitochondria (Butler *et al.* 2003; Crane, 2001). On the inner membrane of the mitochondria, CoQ10 transfers electrons from complexes I and II to complex III which take part in the respiratory chain and the synthesis of ATP that powers the energy in our cells and our body (Butler *et al.* 2003; Crane, 2001; Dutton *et al.* 2000). CoQ10 and other mitochondrial constituents, such as lipoic acid, have protective properties against the generation and damaging effects of free radicals that are released during the abovementioned oxidative processes in the mitochondria (Chaturvedi and Beal, 2008; Liu, 2008). Thus, lowered plasma CoQ10 in depression may predispose towards a decreased mitochondrial respiratory chain and mitochondrial dysfunctions including damage to mitochondrial DNA. Mitochondrial disturbances including decreased gene expression and deletions of mitochondrial DNA were detected in major depression (Shao *et al.* 2008; Gardner *et al.* 2003; Suomalainen *et al.* 1992). In a rat model of depression, i.e. chronic mild stress, the mitochondrial complexes I, III and IV were inhibited in the cerebral cortex and cerebellum (Rezin *et al.* 2008).

The second major finding of this study is that patients with simultaneous CFS have significantly lower CoQ10 than patients without. Our results that CoQ10 is much lower in depressed patients with CFS is in agreement with those of another study showing that a low CoQ10 syndrome is a hallmark of genuine ME/CFS (Maes *et al.* 2009a). The findings are also in agreement with previous reports that statins may induce fatigue, myalgia and neurocognitive disorders, e.g. concentration and memory disturbances through a depletion of CoQ10 (Langsjoen *et al.* 2005; Passi *et al.* 2003). Indeed, statins inhibit the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor for cholesterol and the side chain of CoQ10 (Mabuchi *et al.* 2005; Chu *et al.* 2006). The results are also in agreement with those of other studies reporting that fatigue and exercise intolerance are common in illnesses characterized by low plasma CoQ10, such as autosomal recessive CoQ10 deficiency, mitochondrial disorders, Prader-Willi syndrome, Friedrich's ataxia, Steinert's myotonic dystrophy, cardiac and skeletal muscle dysfunctions, and cancers (Butler *et al.* 2003; Cooper *et al.* 2008; Siciliano *et al.* 2001; Rusciani *et al.* 2006; Palan *et al.* 2003). The fatigue in those patients is often treatable with CoQ10 supplementation (Cooper *et al.* 2008; Bonakdar and Guarneri, 2005; Singh *et al.* 2003).

A third major finding of this study is that lowered CoQ10 is a hallmark for TRD. Previously, it has been shown that another antioxidant confers resistance to

treatment resistance with antidepressants, i.e. lower serum zinc (Maes *et al.* 1997b). As described before, TRD is characterized by more severe disorders in different I&ND pathways, including increased TNFα production (Maes *et al.* 2009b). Thus, the lower CoQ10 syndrome in major depression may have lowered the protection against the neuroinflammatory and neurotoxic effects of IO&NS.

The low CoQ10 syndrome in major depression provides another explanation for the high comorbidity between cardiovascular disorders and depression, which has been detected in Caucasian and Asian populations (Huang *et al.* 2009). It is now well established that major depression is a significant risk factor to coronary artery disease (CAD) (Jakobsen *et al.* 2008) and that the comorbidity between depression and CAD results in an increased cardiovascular mortality (Somberg and Arora, 2008; Dickens *et al.* 2008). Also, primate data are consistent with the hypothesis that depression may cause coronary artery arteriosclerosis (Shively *et al.* 2009). CoQ10 is a protective factor preventing coronary artery disease (Yalcin *et al.* 2004). CoQ10 increases the resistance to the initiation of lipid peroxidation and has direct anti-atherogenic effect (Littarru and Tiano, 2007; Chapidze *et al.* 2005). There is now evidence that cardiac disorders, such as chronic heart failure (CHF), may be caused by a low CoQ10 syndrome and that low CoQ10 is an independent risk factor to mortality in CHF (Molyneux *et al.* 2008). Moreover, there are data that CoQ10 supplementation is of therapeutic value in congestive heart failure (Singh *et al.* 2007). CoQ10 may affect heart function through different mechanisms. A) low CoQ10 predisposes towards greater activity of the IO&NS pathways and therefore to increased inflammatory processes, including increased C-reactive protein and IL-6, and increased damage to membrane fatty acids by O&NS, including increased oxidized LDL cholesterol (Maes *et al.* 2009b), which are all known pathophysiological mechanisms in CAD. B) Direct effects of CoQ10 on the heart include enhancement of systolic function, left ventricular ejection fraction and myocardium contractility (Sander *et al.* 2006; Belardinelli, 2005) and improvement of the endothelium-dependent relaxation and endothelium-bound extracellular superoxide dismutase (Tiano *et al.* 2007).

As discussed before, statins may significantly lower plasma CoQ10 and induce symptoms that occur in CFS, such as myalgia, fatigue, neurocognitive symptoms and neuropathies (Langsjoen *et al.* 2005; Passi *et al.* 2003; Mabushi *et al.* 2005; Chu *et al.* 2006; Berthold *et al.* 2006). In rats, administration of simvastatin decreased CoQ10 levels in the heart and skeletal muscles (Kucharska *et al.* 2007). In HepG2 cells, simvastatin decreases mitochondrial CoQ10 and at higher doses increased cell death and damage to DNA caused by O&NS (Tavintharan *et al.* 2007). Littarru and Langsjoen (2007) state that in some conditions where depleted CoQ10 situations exist treatment with statins may seriously impair plasma and possible tissue levels of CoQ10, thus impairing skeletal muscle and myocardial bioenergetics. Since depression is accompanied by lower plasma CoQ10 and since very low CoQ10 values are observed in TRD and in depression with CFS, the latter represent populations at-risk to treatment with statins that would benefit from CoQ10 supplementation. Indeed, CoQ10 supplementation will reverse the depleted plasma CoQ10 concentrations (Mabushi *et al.* 2007; Keith *et al.* 2008) and statin-induced symptoms as well (Langsjoen *et al.* 2005; Caso *et al.* 2007).

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