Neurobiology and Quantified E.E.G. of Coenzyme Q10

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Abstract

Brain oxidative stress may be involved in a number of diseases and aging. Coenzyme Q10 is the only known lipid soluble endogenous antioxidant that animal cells can synthesize "de novo" and for which there exist enzymatic mechanisms that can regenerate the antioxidant from its oxidized form resulting from its inhibitory effect of lipid peroxidation. Synthetic CoQ10 given to patients with benign essential hypertension has a neuropsychopharmacological effect similar to a "cognitive enhancer" (bioequivalency concept) documented by Quantified Pharmaco EEG™ (QPEEG). This neuropsychopharmacological effect may play an important future role in treating or preventing cerebral oxidative damage in vascular and other conditions such as those observed in benign essential hypertension and other pathological brain conditions as well as in physiologic aging.

Introduction

Oxidative damage to the brain may be involved in aging, hypertension, stroke, Parkinson's disease, Alzheimer's disease, states of compromised cerebral blood flow, ionizing radiation, heavy metal intoxication, Down's syndrome, Huntington's disease, and other neuropsychiatric illnesses.[7]

In 1955 Festenstein et al In Morton's laboratory in Liverpool observed a new compound in pig intestine, rat liver and kidney. From its chromatographic behavior, UV and IR spectra, they proposed a steroid structure, however based on its ability to be reduced and oxidized in the presence of mitochondria, succinate and cyanide, Crane et al in 1957 proposed a quinoid molecular structure as 2,3-dimethoxy 5-methyl 6 methylprenyl benzoquinone.

CoQ10 biosynthesis involves a series of steps. The first one is the synthesis of the ring from aromatic amino acids (tyrosine and phenylalanine) supplied by the diet. The other one is the synthesis of the isoprenoid side chain, followed by prenylation of the ring with the aid of 4-hydroxybenzoate prenyltransferase. After the ring has been prenylated, there occurs a sequence of reactions involving the modifications of the ring, such as decarboxylation, hydroxylations, and methylations.

CoQ10 in the reduced form, in reconstituted membranes, in the absence of alphatocopherol, inhibited lipid peroxidation which is a conclusive evidence for its role of antioxidant in biological membranes.

Multiple experimental and clinical studies have shown the antioxidant properties of CoQ10 but its potential action over human brain function have not been reported\published.[8,9]

Neurotoxicity of MPTP (1-Methyl-4-phenyl-1,2,5,6,-tetrahydropyridine), produces Parkinson's in humans and experimental animals. MPTP and Its metabolites inhibits mitochondrial respiratory chain resulting in ATP depletion in vivo which leads to secondary excitotoxicity and free radical generation, and various degrees of striatal dopamine depletion is observed. CoQ10 seems to have a protective role as documented by Shulz et al.[24]

CoQ10 features a high degree of hydrophobicity and its widespread occurrence in biological membranes and in low density lipoprotein, suggest and important role in cellular defense against oxidative

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damage, and in addition participates in electron transport at the mitochondrial level linked to ATP synthesis as mentioned before.[10,11,12]

CoQ10 acts primarily by preventing the formation of lipid peroxy radicals (LOO•) , where vitamin E is generally believed to exert its effect mainly by quenching these radicals.[13]

In addition CoQ10 may act by eliminating LOO• directly or through the regeneration of vit. E from alpha-tocopheroxyl radical in accordance with conclusion of L. Packer and associates, a process that otherwise may rely on access to water-soluble antioxidants such as ascorbate.[14]

In recent years it has been demonstrated that CoQ10 in animal cells occurs in several locations in addition to the inner membrane of mitochondria, including the Golgi apparatus, endoplasmic reticulum, lysosomes, peroxisomes, and plasma membranes. There is evidence that CoQ10 is synthesized in the endoplasmic reticulum from which it is transported via the Golgi apparatus to its various cellular destinations. It is also discharged across the plasma membrane to the bile and to the blood, where it is bound to plasma lipoprotein.

Observations were made by Kalen et al in human tissues, showed a maximal level of CoQ10 in most organs at the age of 20 years followed by decline.

CoQ10 Levels decrease with aging but also lowering of tissue concentration has been observed in a number of pathological conditios such as cardiomyopathies and degenerative muscle disease, however in dementia only post-morten data is available.

Their data indicate an intricate interplay among the three major biosynthetic products of mevalonate metabolism, i.e. , CoQ10, dolichol, and cholesterol. Parallel to the decrease in CoQ10 upon aging there is a drastic increase of in dolichol.

Brain tissue is quite vulnerable to oxidative stress due to its high consumption of oxygen (20% of the oxygen inhaled), its richness in lipids and its low content of catalase and glutathione. In hypertension produced by arterial vasoconstriction, free radicals are generated by a ischemia and reperfussion like phenomenum. Low plasma levels of CoQ10 have been found in a number of pathological conditions and in hypertension as compared with age matched normal controls.[15] In neuron's mitochondria where neurotransmitters synthesis takes place, CoQ10 availability seems quite important in synaptic efficacy.[21,22,23]

Upon administration of clofibrate or di(2-ethylhexyl)phthalate (DEHP) to rats, an increased synthesis of CoQ10 in liver was found, which is quite interesting, since suitable models for studying CoQ10 synthesis are limited. The response was an increased level of CoQ10 in liver, muscle, blood and heart, but not in brain.[20]

CoQ10 increases the hypotensive effects of enalapril and nitrendipina.[28]

In experimental animals middle cerebral artery occlusions of increasing duration followed by reperfussion are associated with progressive reductions in forebrain ascorbate [1] alpha-tocopherol,[2] CoQ10,[3] and glutathione levels,[4] confirming free radical mediated injury. Presumably the reduction

Table 1. Distribution of CoQ10 in Subcellular Fraction from Rat Liver.

	Organ age group				
	1-3 days	0.7-2 years	19-21 years	39-43 years	77-81 years
Heart	36.7	78.5	110.0	75.0	47.2
Kidney	17.4	53.4	98.0	71.1	64.0
Liver	12.9	45.1	61.2	58.3	50.8

Table 2. High Concentration of CO Q10 in Cellular Energy Formation Organelles.

Fraction	CoQ10 in micro/milligram protein
Homogenate	0.79
Golgi vesicle	2.62
Lysosomes	1.86
Mitochondria	1.40
Inner mitochondrial membrane	1.86
Plasma membrane	0.74
Cytosol	0.02

in levels of these antioxidants represents an attempt to quench free radical peroxidation of membranes lipid components, particularly mitochondrial membranes.

The free radical mediated cerebral lipid peroxidation induced by ischemia has been proposed to inhibit synthesis of prostacyclin.[5] This observation led to the proposal that free-radical lipid peroxidation amplifies and accelerates cerebral tissue damage by inhibiting prostacyclin synthesis and thereby result in initiation of intravascular coagulation.[6]

Finally, the cerebral effect of experimentally generated O2• derived free radicals have been investigated by infusion of xanthine oxidase and hypoxantine into the caudate putamen.[7]

Infusion of this O2• radical generating system into the brain is associated with changes of permeability of the blood brain barrier, cellular injury and edema, thus O2• derived free radicals are capable of producing significant cerebral injury.

Exogenous synthetic CoQ10 supplementation prevents plasma reduction induced by HMG-CoA reductase inhibitors.[25]

Selenium deficiency may be related to a decreased CoQ10 levels. The effect of long term (18 months) selenium deficiency on the liver CoQ10 in the rat were 40-67% of the levels in selenium adequate animals.[26]

The present study was designed to asses the neuropharmacological effect of CoQ10 given orally by using QPEEG™ based on its antioxidant capacity.

Materials and Methods

Patients (40) with benign essential hypertension, age range 40 to 55, equal

Table 3. A comparison of CoQ10 concentration. Brain tissue is comparably low in CoQ10 concentration and most importantly has a low redox state.

Distribution and redox state of CoQ10 in human tissues

Tissue	Amount (micro/gm)	Redox state (% reduced)
Hear	114.0	61
Kidney	66.5	75
Liver	54.9	95
Muscle	39.7	65
Pancreas	32.7	00
Thyroid	24.7	70
Brain	13.4	23
Lung	7.9	**25**

number of male - female, medicated only with betablockers. Excluded from the study were patients with history of hypertensive crisis, presence of any other medical conditions and hypertension treatment needing the use of diuretics.

Quantified EEG (QEEG™) and Dynamic Brain Mapping™ was performed by using a Brain Function Monitoring unit #308 made by H.Z.I. Research Center, New York Medical College, with 10-20 system montages of the American E.E.G. Society, with homolateral ear electrode as reference, before and 1 hour after 100 mg. CoQ10 (synthetic) given orally. Digital mathematical analysis of the four frequency bands primary and first derivative cortical spontaneous bioelectrical activity recorded in the entire E.E.G. for 5 minutes in epochs of 5 seconds each.[17]

ANOVA of E.E.G. alpha frequencies (8-12 Hz) and alpha relative power, determined that increments of less than 30% between baseline and 1 hour post CQ10 100mg. orally must be considered a placebo effect, therefore statistical significant changes are those above 30% of alpha activity, have a bioequivalent pattern of a cognitive activator (moderate psychostimulant) according with H.Z.I. database and the International Pharmaco EEG Society. It is important to mention that with this non-invasive method, biodisponibility of the administered substance is determined in situ, and in a non-invasive fashion, by changes of brain cortical activity as it is shown in QEEG,™ therefore such substance must have been absorbed, metabolized, and eventually crossed the blood brain barrier.[18,27]

Quantified electrophysiology (electroencephalography and evoked potentials) refers to the computer-based acquisition, display, storage, and analysis of EEG Dynamic Brain Mapping™ and Topological Brain Mapping™ are brain function images either of frequency or time domain (power) analysis.[19] Submitted data is the average of the entire population tested.

Results

Table 1 shows QEEG™ data percentages of frequencies of baseline and 1 hour post CoQ10 100mg. Increments of alpha activity, are statistically significant (42%) in T values (T value= % Diffential Map (Post-Pre) of Post Map. It is important to see that this augmented alpha activity (cognitive enhancement) correlates with diminished slow activity delta and theta which is usually observed in patients with moderate to advanced cerebrovascular disease.

Figure 1(page 6) shows the transaxial view of alpha activity only, of the entire recording , (frequency domain map, real and interpolated electrodes). Decreased activity in frontal lobes, above pre Rp, and increased , below 1 hour post CoQ10. **Figure 2** (page 7) shows the right lateral views, and the absolute highest map of all frequency bands (dominant activity). Note that theta activity in the frontal lobe is replaced by alpha activity in the post CoQ10 image.

Figure 3 and **figure 4** (page 8) show QEEG profiles of all EEG frequency bands of test population before and after a 100 mg dose of CoQ10. The QEEG data of CoQ10 reveals a mirror-like effect of both profiles and a bioequivalent effect (a similarity to the QEEG profile of psychostimulants). Co Q10 dosing results in subjects exhibiting a slow activity Delta Theta and extremely fast Beta activity.

Figure 4 plots the Test Dose Response™ 1 Hour Mean plot and the highest similarity coefficient value for each of the recorded time periods. The grey extensions to the X and Y axis shows the classification of the Test Dose drug where Black (center) represents no classification or a placebo effect.

Conclusions

Synthetic CoQ10 given orally to patients with benign essential hypertension have a bioequivalent effect of a moderate

Table 1. shows QEEG Data Percentages of Frequencies of Baseline and 1 Hour Post CoQ10 100mg.

	PRE (before Rp/)				POST (after Rp/)			
	Delta	Theta	Alpha	Beta	Delta	Theta	Alpha	Beta
Montage R-82a								
F3	9.7	32.0	26.1	32.1	4.2	18.3	34.9	47.5
F4	7.9	29.5	27.6	34.8	5.7	17.7	35.4	45.6
C3	10.0	30.2	29.1	30.5	1.1	18.0	45.5	35.1
C4	10.6	30.1	26.2	32.8	0.9	16.0	42.3	40.5
P3	11.8	30.3	32.3	25.4	1.0	13.0	51.9	33.8
P4	6.6	27.3	35.9	29.9	0.9	11.0	52.0	34.2
01	6.1	25.1	39.4	29.2	1.2	13.0	53.5	32.0
02	9.2	26.0	36.2	20.3	2.0	17.0	45.0	34.2
Montage R-82b								
F7	4.3	28.9	27.6	38.9	6.4	21.2	37.5	34.6
F8	3.5	27.1	24.6	44.3	3.3	35.3	31.4	29.9
T3	3.7	27.3	29.7	39.1	2.1	15.3	46.2	36.1
T4	8.3	11.0	23.0	65.5	2.2	15.3	37.9	44.4
T5	2.2	28.4	36.5	32.7	1.6	16.6	49.0	32.5
T6	1.4	33.2	35.6	29.6	2.2	15.2	48.8	33.4
01	4.8	26.1	40.0	28.8	1.0	13.0	60.4	25.2
02	2.1	26.0	41.7	29.9	1.3	16.4	53.1	28.8

Mean of % in all leads before Rp/	Mean of % in all leads after CQ10
Alpha 31.9	45.4
Beta 34.5	34.8
Theta 27.4	17.1
Delta 5.9	2.3

Montages= topographic setting of scalp electrodes.
Increments of alpha activity, are statistically significant (42%) in T values (Tvalue= %Diffential Map (Post-Pre) of Post Map .

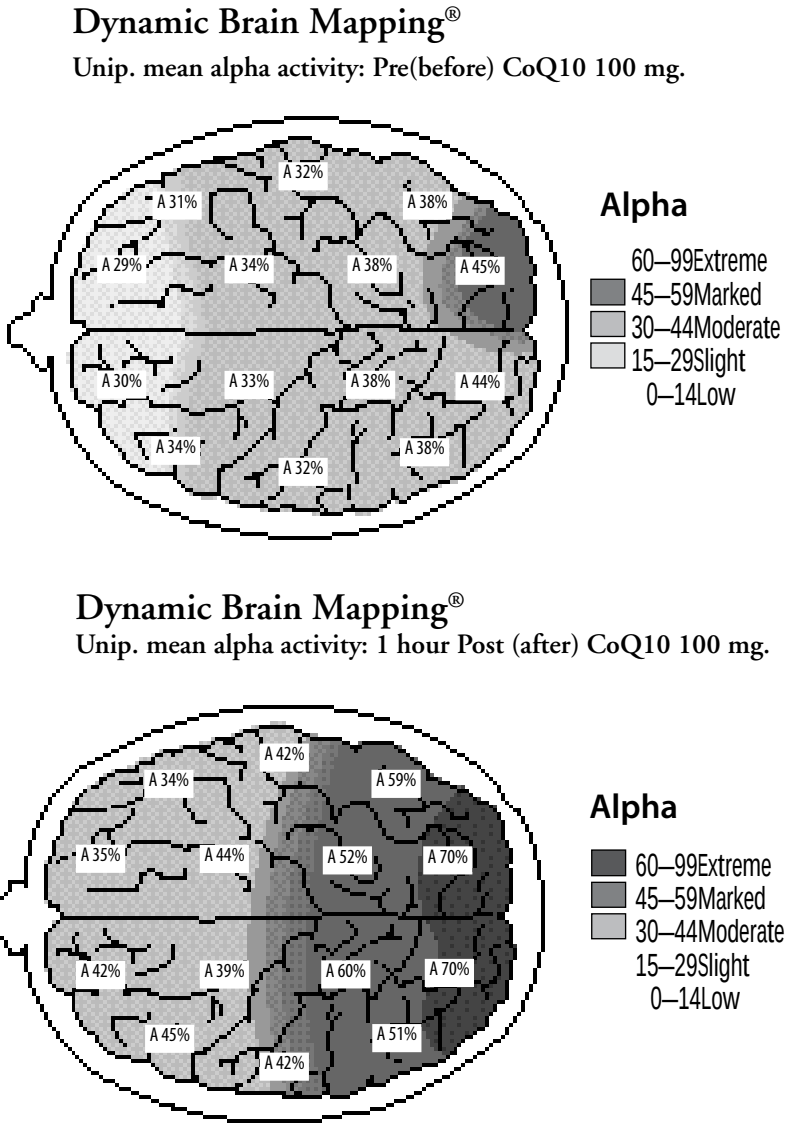
psychostimulant known as a cognitive activator/enhancer.

Benign hypertension is probably the most simple and common example of brain oxidative stress and is usually associated with low plasma levels of CoQ10 when compared to normal matched controls, provided a model for antioxidant replacement therapy, orthomolecular medicine, and its potential efficacy.

Further research seems quite important if we think in terms of the abundance of cerebrovascular disease morbidity/mortality nowadays which is frequently preceded by a history of hypertension. Should enzyme CoQ10 be given to all patients with any form of hypertension and other vascular diseases to prevent brain oxidative damage ?

It has been shown that post-mortem exams of brain tissue with cerebrovascular disease have a low amount of magnesium (Mg), ascorbate, alpha-tocopherol,

Figure 1.Transaxial views of alpha activity only, of the entire recording , (frequency domain map, real and interpolated electrodes). Decreased activity in frontal lobes, above pre Rp\, and increased , below 1 hr. post CoQ10 100mg.



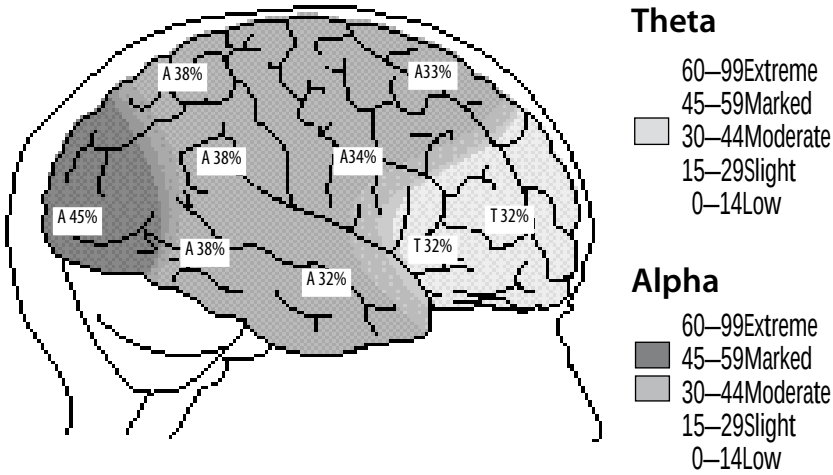
CoQ10 , and increased calcium..[16] Should CoQ10 be administered with these other elements ?

This study shows statistical significant changes in brain function after the administration of CoQ10, it does not show the effect of its continuos or prolonged use, however based on the changes observed a valid therapeutic predictability is achieved. Chronic administration of CoQ10 in a

Figure 2. Right Lateral Views. Absolute highest map of all frequency bands (dominant activity). Observe Theta activity in frontal lobe above image, replaced by alpha post CoQ10 100mg below.

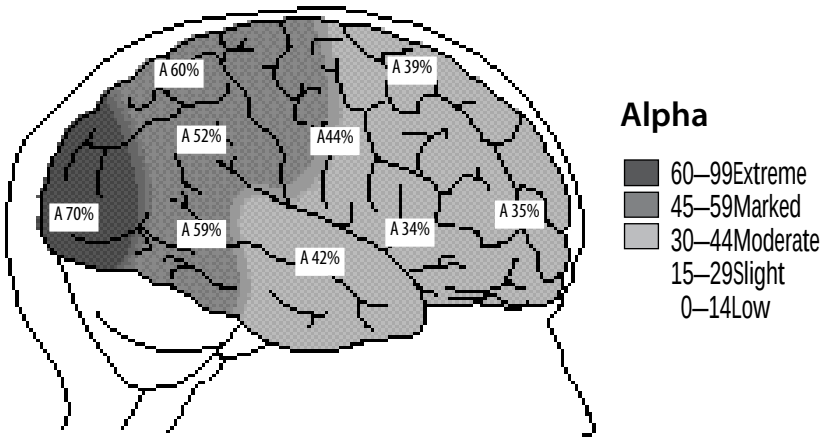
Dynamic Brain Mapping®

Unip. mean abs highest (before) CoQ10 100 mg.



Dynamic Brain Mapping®

Unip. mean abs highest 1 hour post (after) CoQ10 100 mg.



given population most likely will confirm these findings.

Cognition deficit is involved in physiologic and pathologic aging, in most neuropsychiatric illnesses, as well as many medical diseases such as those conditioned by nutritional errors and/or ecological factors, which may accelerate normal aging and may lead to dementia.

In spite of the fact that was discovered

Figure 3. Neurophysiological (QEEG) profiles of all E.E.G. frequency bands of tested population before (thin lines) and after Co Q10 100 mg (thick lines)

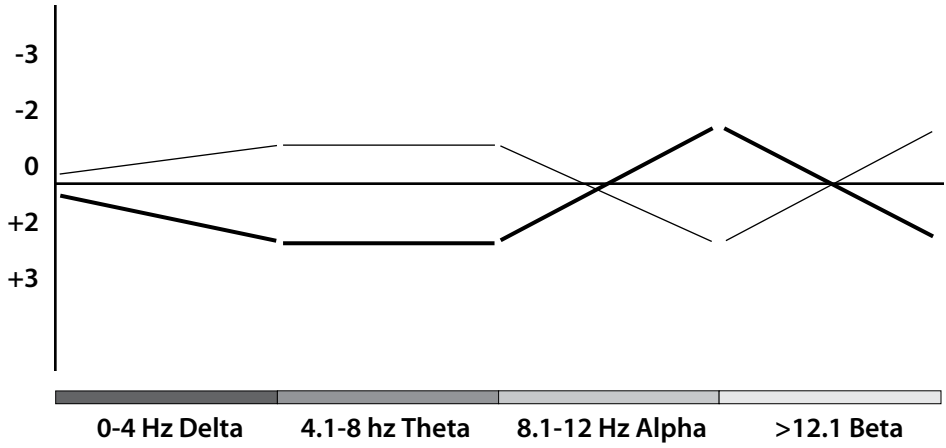
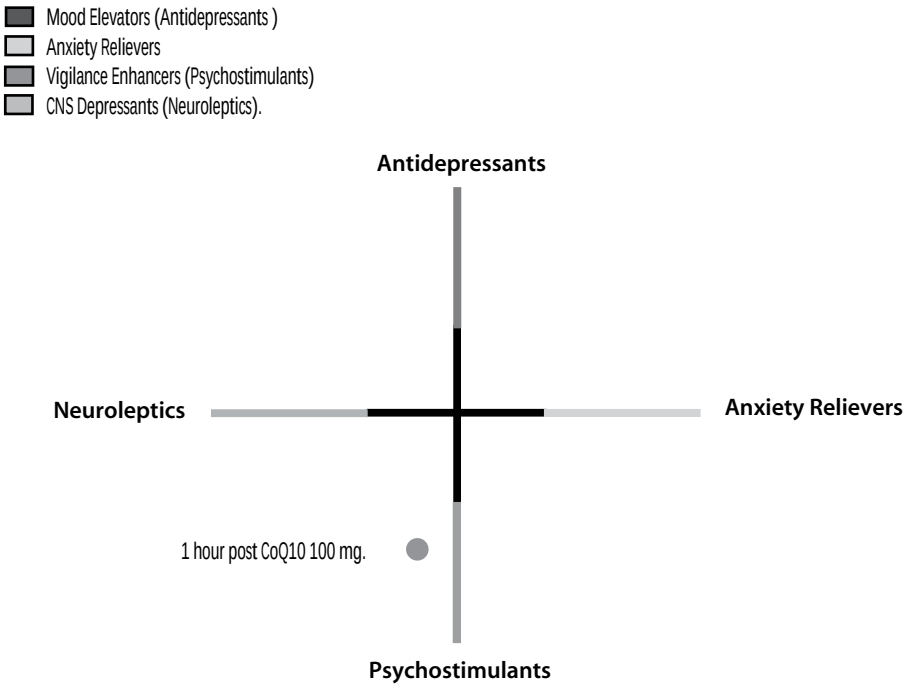


Figure 4. Testdose Response™ 1 hour mean plot. Plots the highest similarity coefficient value for each of the recorded time periods. The grey extensions to the X and Y axis shows the classification of the Test Dose Drug where Black (center) no classification or placebo effect.



40 years ago, our basic knowledge about this lipid is limited. Interest has increased recently about our only endogenous lipid-soluble antioxidant which plays an important role in the mitochondria respiratory chain as well as in most membranes.

Further research will be needed in order to establish Normal Age Related Plasma levels of CoQ10 which may be indicative of oxidative stress sustaining capacity.

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