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Research Article

Different Q10-Formulations Result in an Increase in the Fast Beta-Domain of the EEG

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Abstract

Objectives: Measuring the net effects of a Q10 substitution on the EEG and the d2 concentration test comparing three different formulations.

Methods: Three different Q10 formulation (Greenspeed@, Gerimed®, and Power Magic®Q10) were given to 15 human volunteers in a randomized, double-blind cross-over design while measuring the changes in EEG-power bands (alpha, beta, theta and delta) as well as evaluating the error rate in the concentration and attention d2-test before and 1 hour after ingestion

Results: Power spectra in the EEG demonstrated a highly significant increase in the beta-band (8-13 Hz; $p< 0.01$) after all three formulations, the largest being after intake of Greenspeed® and the lowest after intake of Power Magic®Q10. This closely correlated with a reduction in error rate using the d2-concentration test, where again Greenspeed® did show the most beneficial effect, PowerMagic® Q10 rated last, while Gerimed® took a middle position.

Conclusion: Correlation between power in the EEG beta-band and the incidence of error rate was high (spearmen rank correlation coefficient $r= -0.96$) suggesting that all three Q10 preparation, while differing in their degree of efficacy, were able to increase neuronal cell activity, an effect which resulted in an increase in alertness and focused attention. This very likely is mediated by the increase in ATP formation within the mitochondria of neuronal cells, where Q10 is a necessary constituent within the electronic transport chain.

Keywords: *Q10 Formulation; Central Nervous System; Electroencephalography; D2-Concentration Test; Mitochondria*

Introduction

Dietary supplements containing Q10 are constantly in the rise, as they present a necessary ingredient which activates the electrode transport chain (ETC) within the mitochondria a vital energy source of every cell. Especially in to-days world where nutrition mostly contains preprocessed carbohydrates, often with chemical additives just to soothe the palate, such as monosodium glutamate, artificial coloring for freshness and so-called low fat products, which however for the sake of tastiness contain high amount of sugar, eventually result in a lack of necessary micronutrients for the formation of the basic fuel for cellular activity, called ATP (adenosine triphosphate). Because of these changes endorsed by to-days food industry and further engraved by modern fast-food behaviorism, within the past 30 - 50 years most necessary basic nutritional elements to sufficiently synthesize Q10 are lacking. This eventually ends up in a marked deficit resulting

in a suboptimal Q10 levels, being underlined by the fact that mostly in every chronic ailment there is a significant deficit in Q10-levels. In this context, it is also noteworthy, that any patient taking a statin drug for high cholesterol levels, because of the blockade of the enzyme HMG-CoA reductase, this ultimately will end-up in a deficit of the coenzyme Q10, as both have an upstream common pathway, which is blocked by the statin drug resulting in a cholesterol-lowering effect but also in an insufficient manufacture of the vital coenzyme Q10 [1,2]. Because of such HMG CoA reductase inhibition, endogenous biosynthesis of the essential co-factor coenzyme Ql0, required for energy production, often is associated with impairment of organ function such as the myocardium, the liver, the brain, and/or the musculature. It therefore has become common practice that any patient on a cholesterol-lowering agent should at the same time be given a Q10 preparation, which will compensate for the coenzyme Q10 deficit.

While there is a myriad of Q10 preparations on the market there is no guarantee that this coenzyme Q10 when taken orally, eventually would pass the gut-blood barrier within the intestinal tract (the watery layer on top the enterocytes), a necessary prerequisite to get into the blood circulation. In addition, after getting into the blood circulation, however Q10 only becomes available for the cells, once it has passed the cellular barrier. This is a necessary as it feeds the electronic transport chain (ETC) of the mitochondria necessary for synthesis of adenosine triphosphate (ATP). We therefore set out to evaluate the efficacy of three different commonly used Q10 preparations having different additional additives for increase in efficacy and solubility. By measuring the changes within the electroencephalogram (EEG) after Q10 ingestion, it was postulated that EEG waves not only would reflect the passage of sufficient amounts of Q10 through the gut wall (i.e. bioavailability), but at the same time would also delineate the efficacy of the Q10 preparations on cerebral neuronal cell function. As nervous cells are in a constant need of energy and Q10 being their main driving force, any additional intake would upregulate ATP synthesis, an effect which ultimately would show up in a higher state of desynchronization of cortical waves accompanied by a higher state of mental concentration.

Materials and Methods

Following explanations about the nature of the study as it would request a three-time ingestion of different types of a Q10 formulation of supplements with no side-effects, 15 volunteers agreed to participate (11 men and 4 women with a mean age 49 ±15 SD, with a mean height of 171± 9.6 cm, and a mean weight of 68 ± 13 kg). Volunteers were not taking any kind of medication, they did not consume alcohol on a regular basis, ate a normal diet and did not use any drugs for recreational purposes. For continuous and computerized on-line recording of EEG-waves, volunteers were attached to two Ag/AgCl scalp stick-on electrodes at the fronto-parietal position Fp1-A1according to the 10/20 system [3], contralateral to their strong arm with a grounding electrode positioned at FPz at the medium forehead [4]. Hooked-up to a preamplifier data were fed into a portable computerized EEG machine (Lifescan®, Diatek company, San Diego, USA), which by means of aperiodic analysis, referring to zero-line crossing [5], computed the power of all electroencephalographic waves within the typical EEG spectra alpha (8 - 13 Hz), beta (13 - 30 Hz), theta (3 - 8 Hz) and delta (0.5 - 3 Hz) over a time epoch of 60 secs [6].

For comparison purposes volunteers took three different Q10 formulation at three different occasions in a double-blind, cross-over design with a necessary time interval of 2 weeks for washout. Each of the preparations, in addition to Q10 contained different ingredients most of which were meant for increase in solubulisation and emulsification purposes consenting pharmacy standards. All three preparations were checked for any kind of contamination residues such as heavy metal, pesticides, herbicides or fungicides succumbing to strict regulatory rules of the European Food Safety commission. Independent test in laboratories for the stable concentrations of the ingredient were being conducted in order to guarantee safety and purity. The suppliers are internationally qualified and certified according to the ISO 2200 Norm in Good-Management Practice (GMP), as gene modified raw material was considered unsuitable for the production of any of these supplements containing Q10. Whenever possible the raw martial was of herbal or pure mineral origin. The three following Q10 supplements were used for the study containing different adjuncts mainly for the purpose of solubulisation:

1. **Greenspeed®** (from SoluSwiss LLC, Davos-Platz/Switzerland) an oral solution, where the recommended 25 ml contained the following ingredients and dosages: ubiquinone or Q10 50 mg, Siberian ginseng extract 300 mg, Vit B3 (nicotinamide) 48 mg, Vit B2 4.2 mg, Vit E 25 mg, Vit C 160 mg as an antioxidant and the sugar monosaccharide ribose in a dose of 1000 mg. For better reabsorption of Q10 silymarine 5 mg, curcumin 5 mg, while the flavonoid quercetine 2 mg was used for antioxidative purposes and chrysine 5mg was added because of its anti-inflammatory properties. In addition to these additives gum Arabic was used for emulsifying purposes.

2. **Gerimed®** (from Adena Pharma, Burgwedel/Germany) a sublingual formulation, where the recommended 12 gtt contained coenzyme Q10 in a dose of 30 mg, emulsified into glycerin, water, while red palm seed- and coconut oil which were added for solubulisation purposes, together with the emulsifier soy lecithin in a non-GMO preparation.

3. **Power Magic®Q10** (from LoLaFe company, Niendorf-Holstein/Germany) taken as an oral solution, where the recommended 25 ml contained the following ingredients and dosages: ubiquinone or Q10 in a dose of 240 mg, NADH (or Q1) 4,2 mg, Vit E 160 mg, Vit B12 33 µg, ribose 1000 mg, plus evening primrose oil for solubulisation and glycerin plus diacetyl tartaric acid esters of mono- and diglycerides of fatty acids for emulsifying purposes.

Determination of efficacy of Q10 on neuronal cells by use of different power spectra within the electroencephalogram

Following application of the electrodes and after adaptation to a quiet surrounding, artifact-free electroencephalographic waves as derived from the subject, were fed into the EEG-computer while power was computed and matched to their appropriate power spectra alpha, beta, theta and delta over a time period of 60 secs. Following one hour after ingestion, data (μV^2) in the different power spectra of the electroencephalogram (delta, that, alpha and beta) were computed and later printed out by a built-in printer for statistical analysis.

Determining the efficacy of Q10 on mental capacity by using the d2-concentration and attention test

In addition, subjects in a double-blind fashion and shortly after the EEG-session had to undergo a concentration and attention test (d2-test), which is described in detail elsewhere [7]. In short, the test consisted in stroking off the selective letter "d" with two bars on the right-hand side of randomly assigned 21 targets in 14 long rows of letters of the alphabet resulting in a detail-discrimination within a specific time period of 3 min. Thereafter hits, misses and mistakes were calculated and computed as per cent of what should have been done correctly.

Statistical Analysis

All statistical analysis was performed using the Prism 5 software for Mac OS X (Graph Pad Software Inc. San Diego, USA). In order to demonstrate any possible statistical difference within the power of the various power bands of the EEG, the one-way analysis of variance using Newman Keul`s multiple comparison test was used for each power band with Bonferroni`s multiple comparison correction. For computation of statistical significance in the concentration and attention test, results of the Q10 formulation (verum) were compared with the control phase using the ANOVA Newman Keul`s multiple comparison test.

The number of subjects necessary to demonstrate statistical significance was calculated presuming a 70% incidence of difference in EEG power as demonstrated elsewhere [8]. The results were taken in order to calculate the number of individuals necessary to demonstrate significant difference in EEG activity in subjects with and without the nutraceutical drink. Power analysis assumed an at least 30% increase in the activity within the fast EEG beta- and alpha-domain following consumption of the energy drink. With a value of $\alpha = 0.05$ and $\beta = 0.90$ it was computed that at least 12 subjects were required in order to demonstrate significance. To minimize the effect of data loss a total of 15 volunteers were enrolled. Group differences were computed for statistical difference using the Newman Keul`s multiple comparison test or the paired t-test when indicated, whichever was applicable.

Under the assumption of a non-parametric distribution, computation of a correlation between the numbers of error rates in the d2 test and their corresponding power in the EEG-beta domain, the Spearman correlation test was used. All statistical tests were two-sided and were considered as significant at the $p < 0.05$ level.

Results

EEG-power spectra are a reliable indicator as they reflect the firing rate of cortical cells which depend on the synthesis of their burning fuel within the cells, i.e. the formation of new ATP. A typical representative example of the EEG with the distribution of power within the different power spectra in the control situation is depicted in Figure 1.

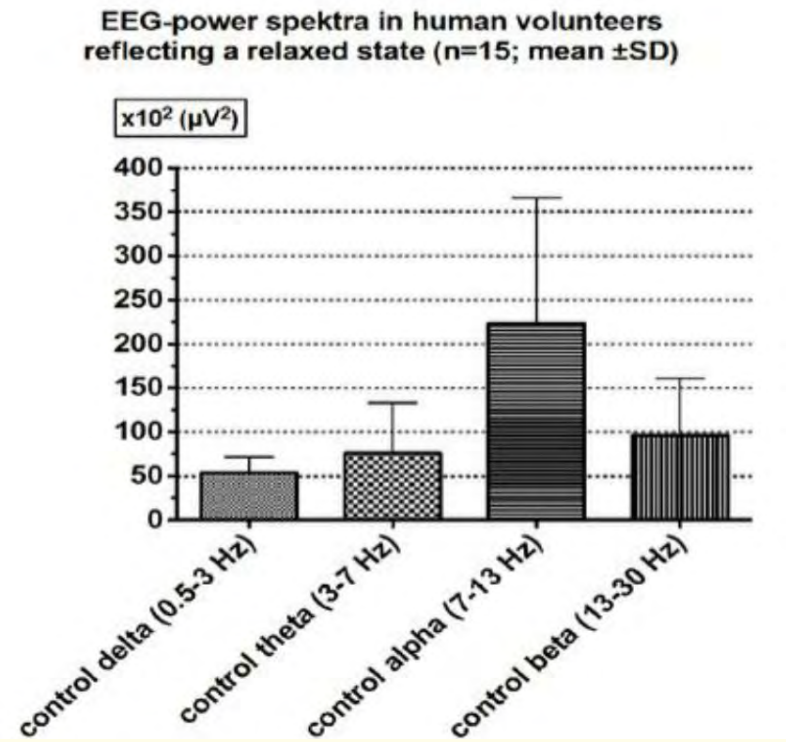

Figure 1: *Representative example of the distribution of power in the different alpha-, beta-, theta- and delta-band of the electroencephalogram in a control and relaxed state.*

There, a characteristic high power in the alpha domain (8 - 13 Hz) is visualized, which reflects a relaxed and sedated state commonly ascribed to a reduced state of vigilance [9,10]. One hour after intake of any of the Q10 nutraceutical drinks and compared to control, subjects all demonstrated a significant increase ($p < 0.01$, and $p < 0.005$ respectively) in activity within the fast beta-band (13 - 30 Hz) being a sign of an increase in vigilance and sustained attention [11]. At the same time, however, there was little but no significant change in the delta-, and the theta-band, while power in the alpha-band (8 - 13 Hz) did show a significant decline after intake of two solutions with the exception of Power Magic®Q10 intake, which was characterized by a significant increase in the alpha-domain (table 1). These trends although seen after each of the Q10 empowered drinks was not uniform, in as much that the Greenspeed® solution resulted in the highest increase in activity in the beta-band followed by the Gerimed® and thereafter by the Magic Power®Q10 formulation (table 1). There was

no significant difference of increase of power the beta-band between Greenspeed® and the Gerimed®, both of which however demonstrated a much higher and significant increase ($p < 0.05$) when compared to the Magic Power® Q10 solution.

Control/Q10 - preparation	Delta-band 0.5 - 3 Hz	Theta-band 3 - 8 Hz	Alpha-band 8 - 13 Hz	Beta-band 13 - 30 Hz
Control	54 ± 18 CI 50 - 57	76 ± 58 CI 65 - 86	223 ± 143 CI 196 - 249	97 ± 64 CI 85 - 108
Greenspeed®	59 ± 11 CI 55 - 63	83 ± 46 CI 46 - 69	190 ± 65** CI 158 - 205	198 ± 207*** CI 196 - 230
Gerimed®	44 ± 10 CI 40 - 48	82 ± 58 CI 58 - 108	142 ± 54*** CI 120 - 164	203 ± 111*** CI 157 - 249
Magicpower® Q10	44 ± 8.3 CI 42 - 47	125 ± 43* CI 58 - 84	225 ± 96* CI 196 - 255	124 ± 49** CI 109 - 139

Table 1: *Relative amounts of power in different EEG - domain (Grand mean ± standard deviation and their respective confidence intervals) following different Q10 formulations, after 1 hour of intake (n=15; significance level *p < 0.05; **p < 0.01 or ***p < 0.005).*

Such changes in EEG activity and their differences in regard to the amount of increase in power within the fast beta-domain was also reflected in the attention and concentration test (d2-test). Here especially Greenspeed® induced a highly significant decline in error rate one hour after intake, which is closely followed by the Gerimed® preparation, while the Magic Power®Q10 solution rated third in regard to its effectiveness in diminishing error rate (Figure 2). Also, the correlation coefficient between the number of errors in the concentration and attention d2-test and the corresponding power within the beta-domain (17 - 30 Hz) was high with an R2-value of -0.88 demonstrating high significance with a p-value of 0.001. This greatly reflects the notion that any increase in beta activity within the cerebral cortex is reflected with an increase in attention and vigilance, data which underline an old but still valid presumption [11].

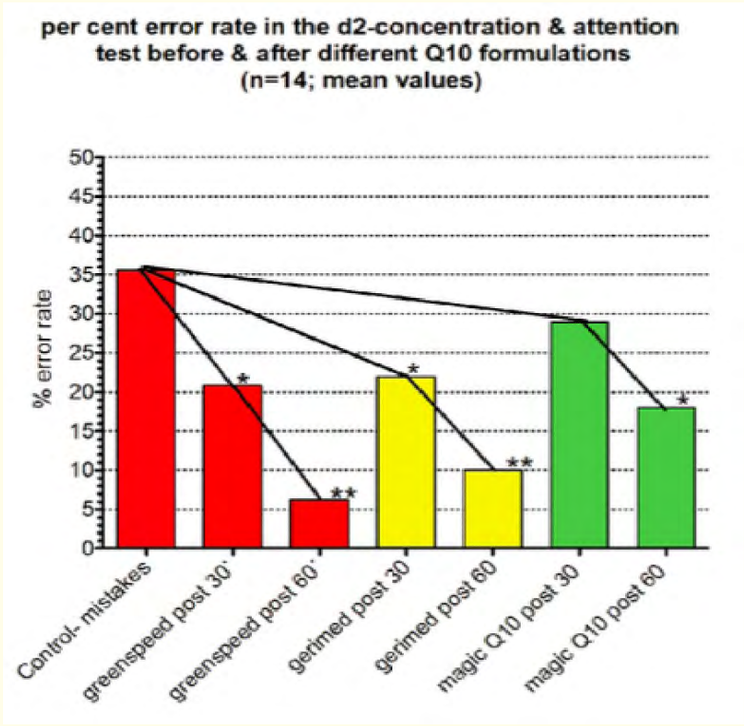

Figure 2: *Mean error rate in percent of subjects being exposed to the d2-concentration and attention test before and after intake of different Q10 formulations (n = 15; significance level *p < 0.05; **p < 0.001)*

Discussion

Coenzyme Q10 (CoQ10) is a naturally occurring oil-soluble, vitamin-like substance, which is essential for optimum health and longevity. Also, known as ubiquinone, CoQ10 is found in virtually every cell in the body, primarily in cellular mitochondria, being a vital

component of the electron transport chain (ETC) within mitochondria, which generates 95 percent of the body's energy via synthesis of adenosine triphosphate (ATP). Organs with the highest energy requirements, such as the heart, the liver, the kidney and the brain, also have the highest concentrations of CoQ10. Therefore, adequate CoQ10 is deemed vital for mental health and flexibility. The advantageous use of CoQ10 for mental clarity is underlined by data from others who clearly demonstrated significant benefit in patients with Alzheimer,

From our data, it can be derived that all three Q10 solutions are characterized by an increase in the fast frequency beta-domain of the EEG, being the EEG band which mirrors focused attention, and a high state of vigilance [9]. Such increase in beta-activity is also reflected in the d2-concentration and attention test, where the Greenspeed® formulation was more effective than any of the two other formulations resulting in focused attention and a scoring being the lowest in error rate, while at the same time also having a faster onset of action. These data are underlined by the fact that the other two Q10 preparations and especially Magic Power®Q10, although having the highest content of Q10, did not score highest in regard to activity on cerebral nervous cell firing rate as well as an increase in concentration and focused attention. Such difference in efficacy of Greenspeed® when compared to Magic Power® Q10 needs some explanation and cannot solely be related to the monosaccharide ribose as both preparations contained similar concentrations both of which should have furnace the ATP formation. While ribose is an essential part within the ATP particle [15] and most likely results in an additional beneficial effect by increasing the ATP synthesis in mitochondria, it does not seem to effect functionality as demonstrated by our data. Therefore, other parameters may be related to differences in efficacy one of which are the additional constituents affecting reabsorption and the formation of ATP within the cells. Such an assumption is underlined by data of a separate study where the regeneration capacity of ATP within mitochondria of leukocytes was significant ($p < 0.01$) in a verum group containing the Greenspeed® formulation when compared to placebo [16]. Therefore, the observed significant higher trumpeting energy turnover within the EEG, which was not seen in the other two preparations, can be attributed to the higher rate of bioavailability of Q10. In addition, it should be noted that another component within the preparation of Greenspeed®, the ginseng extract with its active ingredients eleutheroside A and E, can be considered an enhancer as it most likely acts as a PGP-pump inhibitors resulting in a higher concentration of Q10 at the site of action within the cellular matrix. Such assumption is corroborated by other data demonstrating that eleutherococcus selectively inhibits p-glycoprotein drug efflux pump expression of the multidrug transporter P-glycoprotein (PGP) system, which is encoded by the mdr1 gene being an integrated part of pharmacokinetic interactions [17,18].

Taken together natural antioxidants, and anti-inflammatory agents result in a higher rate of solubulisation which in combination with an inhibition of efflux out of cells leads into higher ATP formation within the neuronal tissue. This assumption is corroborated using the same formulation and was demonstrated elsewhere [16]. Such higher rate in the synthesis of ATP can be extrapolated from our data, affecting central nervous system activity, as being mirrored in a higher firing rate in the high-frequency beta EEG band (13 - 30 Hz), an effect ensuing in an increase of cognitive function and vigilance. In this context memory and performance are executive tasks, which can be measured in the d2-concentration and attention test. Both mental functions improved in a manner that focused attention augmented while at the same time the capability to concentrate and subconsciously suppressing any distraction enhanced. Since any kind of mental work puts additional demand for energy upon neuronal cells such requirement was made possible by supplementation with any one of the Q10 preparations, resulting in a surge of vigilance and an intensification in mental performance. The data of our study also underline the assumption that a higher state of vigilance and of undivided attention can be achieved with Q10, a model as originally proposed by Weeß and coworkers [19], where the process of mental promptness and of an adequate but also of a fast reaction results in an increase in concentration.

Why on the other hand a preparation with the highest Q10 content (i.e. Power Magic®Q10) did not result in similar optimal results as seen after Greenspeed®? The reasons for such a difference may be 2fold:

First and utmost of all it is necessary to know that Q10 is a lipophilic compound that dissolves easily in fat which, however, is very much reluctant to pass through the watery layer of the gut or the mucous membranes of the palate to get into the bloodstream. While reg-

ular Q10 is only able to penetrate the intestinal wall by 3% of its original content [20], all efforts by the various companies are undertaken to increase this influx [21]. In the case of Greenspeed® gum Arabic and various other additional components were used as to potentiate the influx and by increasing solubulisation resulting in a higher proportion of Q10 being reabsorbed.

Second, the natural compound ginseng, may have acted as a PGP-inhibitor and as a net result induced an increase in concentration of intracellular Q10 following intake of the Greenspeed® preparation. This potential advantage in generating higher intracellular levels is in contrast to MagicPower®Q10, and also to Gerimed® being underscored by the observed changes within central nervous system EEG activity. And in spite of the former using evening primrose oil to increase the rate of solubulisation together with glycerin and diacetyl tartaric acid esters of mono- and diglycerides of fatty acids for emulsifying purposes, these additional are however, not as effective like a PGP-inhibitor. This connotation is also underlined by data derived with the Gerimed® preparation, where for solubulisation purposes red palmseed- and coconut oil together with the emulsifier soy lecithin was used, demonstrating a lower efficacy and potency when compared to Greenspeed®. Because of such differences in the composition and in spite of its lower Q10-concentration, Greenspeed®, compared to the other two Q10-compositions, induced a much higher rate in EEG-changes, a finding which is underscored by the increase in focused attention as evaluated in the d2-test.

In conclusion, because of differences in the solubulisation technique as well as the difference of adjuncts in every one of the three preparations, especially the purported PGP-inhibitor ginseng, the major denominator in efficacy of a lipophilic agent such as Q10 is its rate of penetration through membranes and its accumulation at the site of action within the mitochondria. As such, additives seem to determine the rate of solubulisation followed by an enhancement of Q10 passing through the gut wall and/or the oral cavity, both of which normally present a barrier for any lipophilic agent as they consist of hydrophilic membranes. However, as the circulatory system is not the site of action, any data on plasma levels are not that useful to demonstrate efficacy. What is more important is the actual amount of Q10 reaching the inside of a cell, which in the Greenspeed formulation most likely was achieved by the PGP-inhibitor mediating the desired effects. In this respect Greenspeed® deemed superior in efficacy when compared with its two counterparts.

And lastly, it should be made clear that food sources alone may not be enough for those deficient in CoQ10. To put dietary CoQ10 intake into perspective, one pound of sardines, two pounds of beef, or two and one half pounds of peanuts, provide only 30 mg of CoQ10. Fortunately, no known toxicity or side effects have been observed in any supplemental CoQ10 which shows a moderate variability in its absorption, with some patients attaining good blood levels of CoQ10 on 100 mg per day while others require two or three times this amount to attain the same blood level. Supplementation with CoQ10 has been studied in amounts as high as 3600 mg per day with largely only gastrointestinal side effects observed. The observed safe level (OSL) risk assessment method indicated evidence of safety is strong at intakes of up to 1200 mg/day.

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