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RESEARCH ARTICLE

NUTRITIONAL PSYCHIATRY: COENZYME Q10 IN THE BRAIN - HEART AXIS

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ABSTRACT

Nutritional psychiatry is a new area of research that seeks the relationship of nutrients in the brain axis and associated comorbidities. At the moment, there is an increasing discussion on the brain and heart axis seeking the understanding of the activity in reducing oxidative stress and mitochondrial respiratory chain, among the nutrients investigated is coenzyme Q10 (CoQ10). This important nutrient, which has a number of already established functions, has benefits in the treatment of psychiatric and heart disorders, it is believed to be the result of its antioxidant property and production of mitochondrial energy. However, there is a scarcity of studies on CoQ10 in the line of nutritional psychiatry, including there is still no consensus on the appropriate dosage or therapeutic plasmatic level of this nutrient. And this information is necessary both for the treatment of mitochondrial diseases and psychiatric and heart disorders. Therefore, this study seeks to describe the current knowledge about CoQ10 in the axis of nutritional psychiatry in the disordens brain and heart.

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INTRODUCTION

Nutritional psychiatry is a new area for the study of the correlation of mental disorders, metabolic and nutritional abnormalities in chronic diseases. The term "Nutritional Psychiatry" emerged in 2013 after a consensus statement that advocated as a new field of research focused on developing comprehensive, cohesive and scientifically rigorous evidence to support a shift in thinking around the role of diet and nutrition in health. Since then, interaction between cardiologist-nutritionist-psychiatrist-neuroscientist has been recommended for investigation of disorders involved in the brain and heart axis (1-3). So far, some studies on the brain and heart axis show a growing discussion about nutrients, mainly seeking the understanding of the activity in reducing oxidative stress and mitochondrial respiratory chain, among them: coenzyme Q10 (CoQ10) (4-6).

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CoQ10 is a liposoluble provitamin synthesized endogenously, with antioxidant property and potential in the treatment of neuropsychiatric and heart diseases (7-9). Recent studies suggest the role of oxidation of CoQ10 in the pathogenesis of Parkinson's disease, depression, chronic fatigue, heart failure and coronary disease. This is due to its ability to enhance the mitochondrial electron transport chain, reduce the production of oxidative stress and eliminate free radicals to protect mitochondrial and lipid membranes from oxidative stress (10-12). However, treatment protocols for patients with brain and heart axis disorders have not yet been standardized and results vary between studies (11). Although it is not the focus of nutritional psychiatry to support the use of nutritional supplements the researcher Jacka *et al*., 2017 (13) have been speculating the use of these supplements and the relationship with the increase in psychopharmacological efficacy in various ways, perhaps directly altering the activity of neurotransmitters or indirectly reducing inflammation, known to contribute to the development of diseases in the axis of neuropsychiatry and associated chronic diseases. Certainly, this new area of nutritional psychiatry will allow us to broaden our look under the design of future research that evaluates the intervention in mental health facing a multi and interdisciplinary approach.

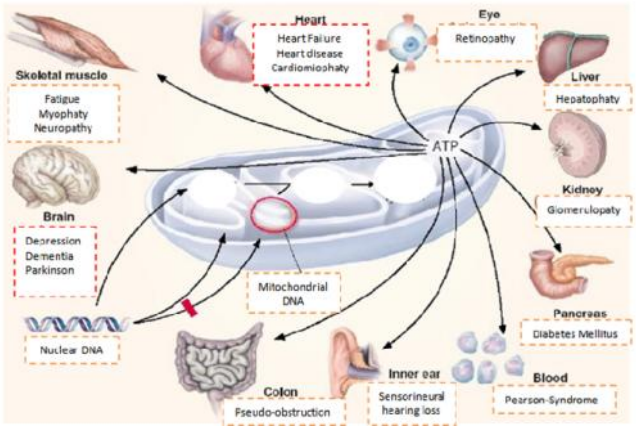

Figure 1: Mitochondrial DNA diseases and associated comorbidities. Adapted Jonhs D.R., 1995

Therefore, this review study aims to describe the current knowledge about CoQ10 in disorders related to the brain and heart axis.

COENZIMA Q10: CoQ10, also called Ubidecarenone, is a benzoquinone present in virtually all cells of the body, except the red blood cells, and participates in the production processes of adenosine triphosphate (ATP). As it is essential in this process, organs with higher energetic demand such as the heart, brain, kidneys and liver, present higher concentrations of CoQ10 (13-15) (Figure 1). CoQ10 has two forms: ubiquinol and ubiquinone, however, the most efficient antioxidant form is attributed to ubiquinol, due to its ability to increase plasma levels and cross the blood-brain barrier. Other functions of CoQ10 include membrane stabilization and modulation of gene expression (14- 15). The view of all these functions, a deficiency in CoQ10 status could possibly contribute to the pathophysiology of neuropsychiatric and heart diseases, causing a failure in mitochondrial energetic metabolism and compromising cellular antioxidant capacity. A CoQ10 deficiency may also result from a genetic defect by biosynthesis, known as primary deficiency, or as a result of a mutation in a gene not directly involved in the biosynthesis of CoQ10, known as secondary deficiency (16-18).

The cause of secondary CoQ10 deficiency seems to be more common than primary deficiencies, which is associated with respiratory mitochondrial chain dysfunction (21-23). The decrease in plasma CoQ10 levels may reflect a greater utilization or need for the defective tissue of the respiratory mitochondrial chain, as well as liver failure, since this is the main site of synthesis for circulatory CoQ10. However, research in this area is gradually uncovering potential facts based on their specific nutritional deficiencies, brain conditions and genetic profiles, seeking to understand the basic factors that may influence the metabolism of CoQ10 (24-26).

Recent studies show that CoQ10 deficiency could possibly contribute to the pathophysiology of brain and heart disease, causing a failure in mitochondrial metabolism, and the potential repercussions of this CoQ10 depletion include associations with Parkinson's disease, depression, chronic fatigue syndrome, coronary artery disease and heart failure (26-28). Some studies in Parkinson's disease have begun to suggest that in the early stages of the disease, daily intake of certain doses of CoQ10 may help slow the degenerative process. The results showed that groups given 1200mg of CoQ10 daily showed an improvement in mental and motor function and in the ability to perform daily activities (such as dressing and eating) 44% higher compared to the group treated with placebo (29). Regarding the use of CoQ10 as a supplement for patients who suffered a heart attack showed a decrease in cases of other related problems, angina, arrhythmia and even other subsequent infarctions compared to patients who took placebo instead of CoQ10 after suffering the attack (30). Some evidence showed that the administration of CoQ10 improved the health condition in the treatment of hypertension compared to those who took only placebo (31, 33).

BIODIPONIBILITY: CoQ10 is synthesized from tyrosine, while another part is synthesized from acetyl-CoA via mevalonate, the same route used in the first steps of cholesterol biosynthesis. CoQ10 can be obtained from diet or food supplements, but is also produced endogenously. Meat, poultry and fish are the most concentrated sources of CoQ10, and daily intake of these foods provides between 2 to 20 mg, which does not significantly increase the levels of CoQ10 in blood and tissues. Small amounts are found in cereals, soybeans, nuts and vegetables, particularly spinach and broccoli (34,35). The absorption of CoQ10 from the diet (or supplements) occurs in the small intestine and is influenced by the presence of food and beverages. It is better absorbed in the presence of foods rich in lipids. After absorption, CoQ10 is transported to the liver where it is transported by lipoproteins and concentrated in the tissues (36-37). The concentration of CoQ10 in human tissues reaches its peak at age 20, decreasing with age, which increases the need for its supplementation, since the lack of CoQ10 can cause damage to the brain, other organs and mitochondria in the body (37- 38). To improve the absorption of CoQ10, the use of gel and oil-based formulations of CoQ10 has been recommended in preference to tablets in the treatment of patients with mitochondrial diseases. Recently, reported that liquid emulsion improved the bioavailability of CoQ10 over solid formulations (39). After oral supplementation of CoQ10 it takes approximately 6 hours to reach its maximum plasma concentration.

A second peak of Plasma CoQ10 being observed about 24 hours, which has been attributed to enterohepatic recycling as well as redistribution to the circulation. The circulatory half-life of CoQ10 was reported to be approximately 36 hours, requiring a 2-week period of treatment interruption before returning to its baseline level after 4 weeks of supplementation. Currently, there is much discussion whether ubiquinol formulations have a better gastrointestinal tract absorption than CoQ10. It is estimated that the gastrointestinal (GI) absorption of ubiquinol is 3 to 4 times higher than that of CoQ10 (37- 40). It has been reported that the absorption deficiency of CoQ10 decreases as the dosage increases with a GI blocking absorption above 2,400 mg, and split doses have been recommended instead of a single dose, in conjunction with dietary fat and grapefruit juice consumption have also been reported to improve absorption of CoQ10 (34, 40-42). Contrast, high doses of vitamin E together with CoQ10 may prevent the absorption of CoQ10, resulting in lower plasma quinone levels, possibly as a result of competition during the GI absorption process (43). Clinical monitoring of CoQ10 levels is usually based on plasma levels with an established reference range ranging from 0.5 to 1.7 μM. Plasma CoQ10 level may be influenced by diet and circulatory lipoprotein status, may be useful in identifying evidence of cellular CoQ10 deficiency and increased tissue utilization and demand (44 -

46). However, in view of the questionable reliability of CoQ10 status in plasma, it is suggested as the most appropriate substitute for determining endogenous CoQ10 status, the "gold standard" of evaluation in skeletal muscle. In addition, it may be more appropriate to monitor the spinal fluid CoQ10 in patients with neuropsychiatric disease (47). Normally, doses in the range of 5 to 30 mg/kg/d have been administered to patients with documented low levels of tissue CoQ10, as well as to those with primary CoQ10 deficiency (49-51). Currently, there is no consensus on the dosage of CoQ10 or the plasma level that may be effective in the treatment of patients with mitochondrial, neuropsychiatric and heart disorders. Supplementation with CoQ10 is safe and well tolerated, exhibiting an excellent safety profile with doses up to 2,400 mg/d (49-50). Current evidence has shown that treatment with CoQ10 improves quality of life in patients with neuropsychiatric disorders and may play a role in slowing the progression of these disorders, including some studies have shown that CoQ10 has antidepressant effects (49-51). Treatment with CoQ10 significantly reduces fatigue and improves ergonomic performance during exercise and, therefore, may have the potential to alleviate the exercise intolerance and exhaustion demonstrated by people with myalgic encepholamyletis / chronic fatigue syndrome, fibromyalgia. The evidence base for the efficacy of CoQ10 treatment can be explained through its ability to mitigate oxidative stress and protect mitochondria (29-30). Parkinson's disease, a plasma CoQ10 level of 4.6 µmol / L was reported as the most effective to slow functional decline in patients. An in vitro study using human fibroblasts deficient in CoQ10 showed evidence of an improvement in bioenergetic status/normalization of cellular antioxidant status after 7 days of treatment with 5 µM of CoQ10 (52-53). Current evidence indicates that CoQ10 may be an effective supplement in improving quality of life in cases of mitochondrial diseases (54). For patients with heart failure treated with statins, the CoQ10 group improved exercise capacity, decreased signs and symptoms of heart failure. Even without the use of a drug such as statin, CoQ10 with a dosage of 120 mg per day, decreased LDL cholesterol by 6.5% and reduced blood pressure (55).

Conclusion

It is believed that a CoQ10 has a beneficial effect by the antioxidant capacity at the cellular level, especially in the treatment of patients with neuropsychiatric and heart disorders, so there is still no consensus on the dosage or plasma level of CoQ10 to achieve some clinical benefit and/or whether this is influenced by the pathophysiology of mitochondrial, neuropsychiatric and heart diseases. It is understood that the determination of CoQ10 status in biological samples other than plasma/serum should be advised, so that we can better reflect on the cellular uptake of exogenous CoQ10 and its biological activity. In this sense, this study brings a current gap in knowledge about CoQ10, which allowed us to describe it in the axis of nutritional psychiatry, and suggests that future studies may be developed to discuss the therapeutic efficacy of supplementation with CoQ10 in the axis of brain and heart disorders.

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