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Tau Protein: Target of Coenzyme Q10 as a Protective Effect Against Alzheimer's

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Abstract:
Alzheimer's disease (AD) is the most common cause of dementia in elderly humans. The functional loss and abnormal aggregation of the Tau protein within the cytoplasmic space of the neurons of the cerebral cortex are factors that have been closely associated with neuronal death and the establishment of this neurodegenerative process. Tau suffers from certain abnormal post-translational modifications such as hyperphosphorylation and proteolytic cuts that lead to its functional alteration, changes in its subcellular location, aggregation and toxicity. On the other hand we have Coenzyme Q10 that contributes to generating cellular energy in the mitochondria. As we age, CoQ10 production declines and we are faced with an "energy crisis." CoQ10 deficiency in cells causes accelerated aging. The objective of this study is to identify the interaction between tau protein and CoQ10 as the latter is associated as a protective factor against degenerative diseases including Alzheimer's.

Key words: Tau protein, coenzyme Q10, Alzheimer's disease, protective factors.

Introduction

Alzheimer's disease (AD) is associated with the most common cause of dementia, a term associated with the loss of cognitive abilities and memory, with 60-80% of cases worldwide presenting this disease. Currently, more than 50 million people live with dementia and this number doubles every 20 years (Alzheimer's Disease International) (Figure 1).

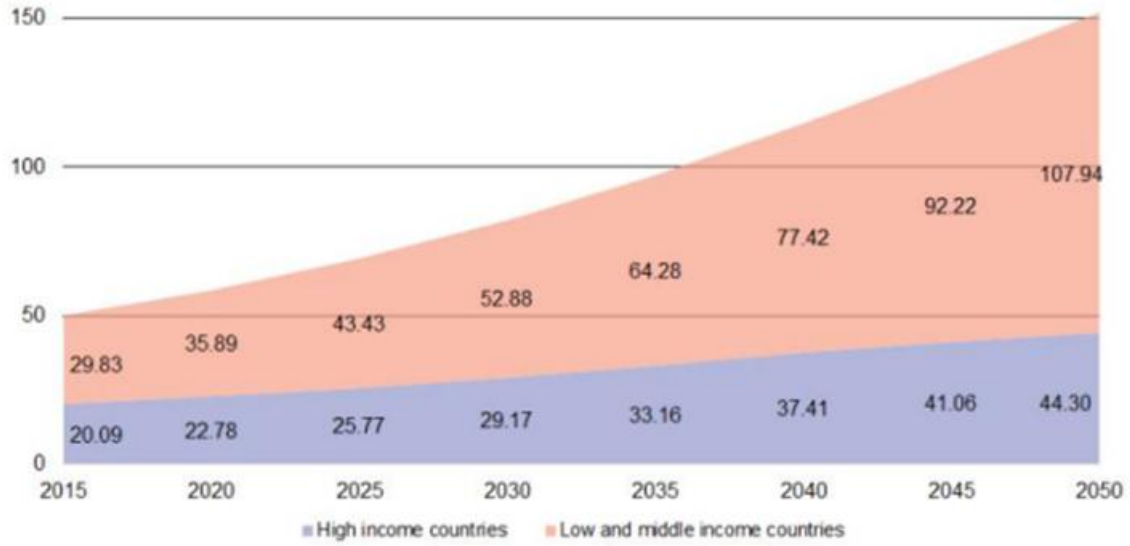

Figure 1. People with dementia. Projection of the number of people (millions) who will develop dementia by comparing the level of economic income (Alzheimer's disease international).

At the anatomical level, AD-type dementia is due to the selective death of certain neuronal populations in the hippocampus, entorhinal cortex, amygdala, and cerebral cortex. In neurons affected by Alzheimer's disease, there is an abnormal autoaggregation of Tau protein, forming abnormal intracellular polymers called paired helical filaments (FHAs). The detailed and precise ultrastructure of these filaments is still subject to analysis; however, Tau autoaggregation is known to be initiated by abnormal binding of its carboxy-terminal repeat domains, which is specifically mediated by the presence of certain hexapeptide sequences. [1] (Figure 2)

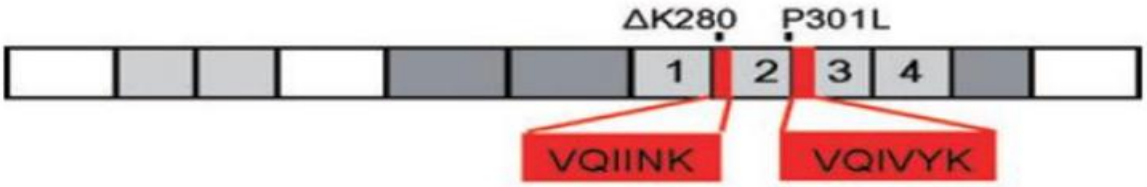

Figure 2. Scheme of the Tau molecule. Repeated domains of the Tau molecule are indicated by numbers, and red highlights the presence of hexapeptide motifs that are critical for the association and self-aggregation of Tau in the form of FHAs (Mandelkow, 2007).

On the other hand, when FHAs accumulate in large quantities in the cytoplasm, they form massive aggregates, forming neurofibrillary tangles (MNFs). These are characteristic fibrillary brain lesions of AD and are recognized microscopically as flame-shaped structures by histological and immunostaining techniques. [two]

Based on the number of MNFs in the brain parenchyma, the neuropathological evolution of AD was established as a confirmatory postmortem diagnostic criterion of having suffered from AD in life. Depending on their location and number in the aforementioned subregions, the neuropathological progression of the disease was correlated with the clinical symptoms of the patient before his death. [23]

In this way, the neuropathological diagnosis is known as "Braak stages", divided into 6 stages: I and II of incipient AD, are stages similar to normal aging with a limited number of MNF in the entorhinal cortex. III and IV, MNFs appear in the hippocampus and this correlates with the appearance of early and intermediate clinical symptoms of AD. V and VI, the MNF reaches the cerebral neocortex and severe dementia occurs. [4]

Thus, multiple methods have been used for the early detection and prevention of AD. Thus, in recent years, antioxidants have been suggested as possibly useful agents to prevent and treat AD, since they have in turn been associated with a reduced and detrimental activity for reactive oxygen species (ROS).[5] Coenzyme Q10 (CoQ10), also known as ubiquinone and ubidecarenone, is an endogenously synthesized provitamin involved in a variety of cellular processes, most notably the electron transport chain of mitochondrial and adenosine triphosphate

(ATP) synthesis. Therefore, CoQ10 has been used as a dietary supplement or medicine for more than 30 years. [6]

Thus, the bioavailability of CoQ10 supplements in humans seems to depend on the constituent excipients of the formulations, in addition to the physiological characteristics of the individuals. This becomes essential, since the benefits of the good physiological responses of CoQ10 depend on its bioavailability, in addition to its uptake by tissues, liver, adipose tissue and circulating cells. [7]

However, CoQ10 levels will be decreased with advancing age, and this decrease may contribute in part to some of the manifestations of aging. Other studies have shown CoQ10 to have neuroprotective action in AD by protecting against oxidative damage and attenuating mitochondrial dysfunction. There are also reports of still exploratory results in relation to AD, where some of these previous studies demonstrate potential effects of CoQ10 in said neuropathology. [8.9]

Based on this, the objective of the literature review study was developed with the aim of evaluating the neuroprotective effects of CoQ10 and its interaction with the TAU protein in AD.

Methodology

Qualitative research was carried out to design a literature review study, elaborated according to the use of keywords in the resources of the available scientific database, to obtain the results and, subsequently, the proposed design of the study. Therefore, the following nomenclatures were obtained, registered in the Descriptors of Health Sciences (DeCS) to obtain the studies. The descriptors selected for filtering were: Alzheimer's disease, TAU protein, Coenzyme Q10, Neuroprotection. Then, "and" between words was used as a search strategy to filter the studies in the databases, following the following methodological model: Alzheimer's Disease and Tau Protein, Coenzyme Q10 and Alzheimer's Disease, TAU Protein and Coenzyme Q10. The literature search was carried out in the period of October and December 2021, delving into various search engines and databases in order to obtain information and review previous studies on the exposed topic. In order to achieve the objective of the study

Results

Tau Protein and its Role in Alzheimer's Disease

The Tau protein, which belongs to the MAPs (microtubule-associated proteins) family, is encoded in humans by a 16-exon gene (MAPT) located on chromosome 17q21. Due to the alternative splicing of exons 2, 3 and 10, 6 mature isoforms of the protein are produced in the CNS (figure 3). [10] Exons 2 and 3 code for two amino-terminal inserts, while exon 10 codes for a microtubule-binding repeat domain. Under normal conditions, the protein is located in the axons of neurons bound to microtubules to provide stability to these support structures. [11]

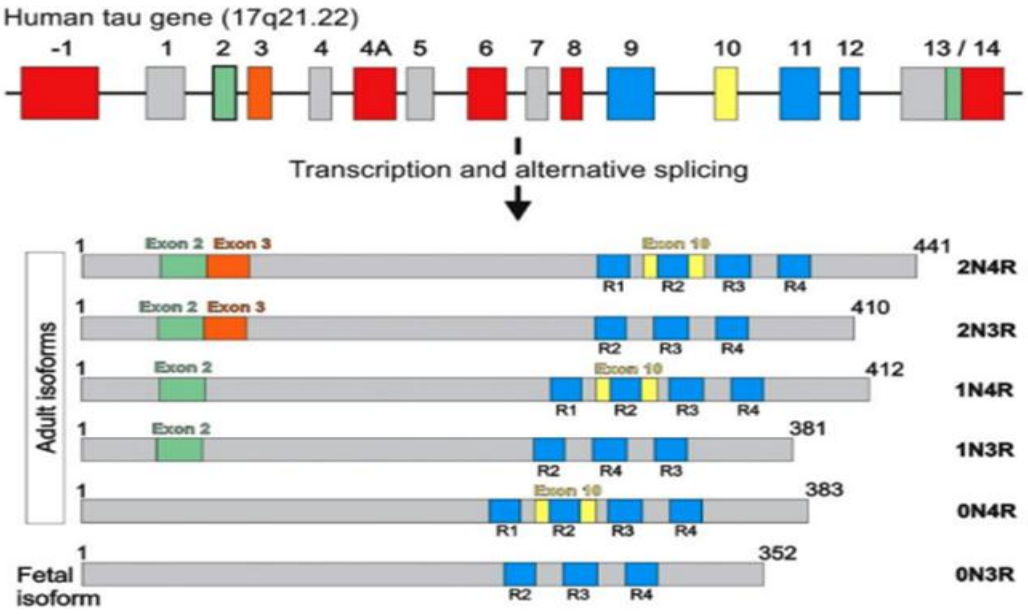

Figure 3. Tau gene. The 6 different Tau isoforms are found in the adult CNS, while in the fetal stage, only the smallest isoform is present due to the loss of exons 2, 3 and 10 (Pîrşcoveanu, 2017).

Although the mechanism by which Tau ceases to be a functional protein and ends up abnormally self-assembling is not known, it has been proposed that there are various post-translational modifications that convert this protein into a non-functional entity that loses its ability to associate with the microtubules of the cells. axons. [12] Phosphorylation of Serine, Threonine, and Tyrosine residues negatively regulates Tau binding to microtubules, allowing a dynamic mechanism for the assembly and remodeling of these subcellular elements. A high number of Tau phosphorylatable residues have been identified in AD, which, when processed by various kinases, not only produces a loss of affinity for microtubules, but also this protein tends to redistribute itself to the neuronal soma and it is there that it aggregates in the form of FHAs and MNFs that trigger the pathophysiology of AD. [13]

Coenzyme Q10

CoQ10 (2,3-dimethoxy-5-methylbenzoquinone) is a fat-soluble quinone ring attached to 10 isoprene pendant units. Its discovery was made by Dr. Leonard Mervyn, who was working with Lambert Healthcare for the first time in humans in 1955, while studying biochemical changes in kidney pathology. His work was finally published in 1958, in The biochemical journal. [14] Also named ubiquinone because of its ubiquitous presence, it plays an important role in the last part of the cellular energy generation cycle (called the electron transport chain) where most of the ATP for cells is produced. [fifteen]

In this way, the studies carried out in the last 60 years have shown its antioxidant function, by blocking the peroxidation of proteins, lipids and eliminating free radicals. It is very clear that oxidative stress can result in serious molecular damage, affecting DNA and proteins, producing cellular aging. In this way, it has been shown that the expression of Coenzyme Q10 in various tissues allows its action to reduce premature cellular aging and therefore the neurodegenerative process. [16]

Various studies have shown that in AD many molecules are involved in its pathophysiology, whether they are proteins, vitamins, substrates, enzymes acting as triggers of the disease or regulatory factors that prevent or avoid cell damage, as is the case of Coenzyme Q10 that its concentration is increased in the brain, which has been interpreted as a possible protective response against oxidative stress, and plasma levels have been found to be normal. [17]

Neuroprotection Given by the Tau Protein and the Participation of Coenzyme Q10

Thus, in neurological degeneration in AD, we will find the tau protein abnormally phosphorylated in the region rich in prolines in the amino acids Ser and Thr,50 these phosphorylation sites can be detected with highly specific antibodies such as: AT100 (Ser212 and Ser214), AT8 (Ser202/Thr205), PHF-1 (Ser396/Ser404) and TG3 (Thr231/Ser235) among others. Figure 4. [18]

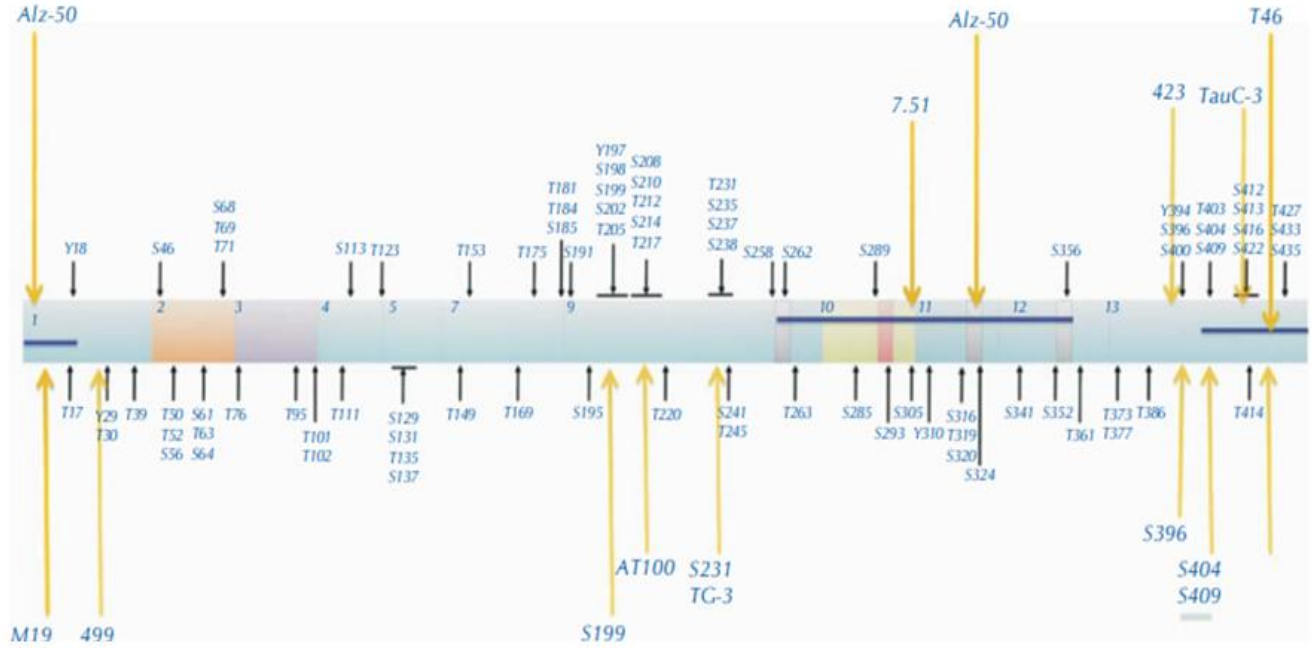

Figure 4. Tau protein phosphorylation sites. Tau protein has 85 possible phosphorylation (black): 45 serines, 35 threonines and five tyrosines. In AD, 30 sites have been identified where we find highly phosphorylated tau protein (red). In green, the phosphorylated forms found in normal adult brains are observed, and in blue, the phosphorylations of tau protein is identified in normal and AD cases. Also shown are some antibody recognition sites directed against tau protein (yellow arrows)

Increased tau protein phosphorylation in AD is associated with a defense mechanism to combat oxidative stress. It has already been mentioned that, in AD, in neurons with fibrillar degeneration, MTs will be depolymerized, however, in studies carried out in MNFs, MTs without alterations were evidenced. This finding allowed the hypothesis that a fraction of the phosphorylated tau protein was still associated with MTs [19].

In addition to this, a study carried out by Binder, et al in 2003 in Chicago, identified that a truncation of the tau protein is associated with a decrease in FHAs. Said truncation was located at the Asp421 position of the carboxyl end of the molecule. In this tau cutting site, it is identified by molecules of the caspase family, mainly involved in caspase3, an enzyme involved in the apoptotic pathway, which is responsible for the truncation in Asp421. This data, per se, suggested that this carboxyl-terminal cleavage of tau could be caused by a response of the neuron to decrease or control the polymerization of tau protein in FHA. [twenty]

Some articles have documented that Coenzyme Q10 can intervene as a molecule that marks the cleavage sites of the TAU protein in order to carry out its truncation by means of the different antibodies involved in this mechanism. It has also been documented that it participates directly and indirectly by a mechanism not yet well established in its hyperphosphorylation, it has been demonstrated through clinical trials, finding phosphorylated tau species in the cytoplasm of neurons, however, these Studies showed that neurons with degeneration still behaved functionally. Taken together, these observations suggest that the accumulation of hyperphosphorylated tau protein in the cytoplasm is in a non-toxic state for the cell, thus becoming a protective factor when both molecules act together or separately. [21]

Discussion

Dr. Binder's group in Chicago in 2003, dedicated itself to investigating the pathological relationship between Tau and caspase activity, finding that Tau is a putative substrate for the action of these enzymes, as it has several canonical cut sites for these enzymes , particularly caspase. It was found in vitro that several caspases could cleave Tau at the aspartic acid-421 (D421) position, but the most efficient enzyme to do so was caspase-3 [22].

Other groups have used in vitro cell models, where they have expressed the intact Tau protein and its truncated variant at D421 in neuronal and non-neuronal cells (Fasulo et al., 2000). The results have been contradictory and at the beginning it was found that, when this truncated molecule was expressed in neurons, it was very toxic and produced neuronal death by apoptosis. These findings have been questioned by more groups, including ours, because in various in vitro cultured cell systems, the expression and toxicity of Tau truncated at D421 does not exactly lead to immediate death; rather, we have found that more subtle damage occurs. [23]

Regarding the effectiveness of its administration, in the study by Durán-Prado et al. (2014) 5 µM CoQ10 was administered to human umbilical vein endothelial cells (HUVEC) over a 24-hour period. The results showed that CoQ10 significantly inhibited mitochondrial Aβ peptide uptake and human endothelial cell trafficking, alleviating Aβ-induced oxidative damage, anti-necrotic and anti-apoptotic effect. [24]

Another study using low dose concentrations of (0, 0.01, 0.1, 1, 10, or 100 mM) for 48 hours in rat cortical neurons also demonstrated significant antioxidant action by inhibiting EO. CoQ10 reduced free radical levels in a dose-dependent manner. Meanwhile, CoQ10 treatment can increase the expression levels of p85aPI3K, phosphorylated Akt, phosphorylated glycogen synthase kinase-3β, and heat shock transcription factor, these proteins are involved in the survival process of neuronal cells. [25] In addition, there was a decrease in the levels of cytosolic cytochrome and cleaved caspase-3, which are associated with neuronal cell death. Associated with these results, the study suggests that the neuroprotective effects of CoQ10 on Aβ25-35 neurotoxicity are mediated by EO inhibition with PI3-K/Akt pathway activation (Choi et al., 2012)

Conclusion

According to the results obtained in the present work and the model presented, in the formation of FHAs, the phosphorylated species of the tau protein play a very important role in the initial neuroprotection to prevent the assembly of the molecule, which would end up with neuron cell death causing progressive dementia in Alzheimer's disease. That said, it is suggested that the MNFs, which are structurally densely hyperphosphorylated, could represent another mechanism to maintain and in a certain way protect the functionality of the neuron suffering from fibrillar degeneration. The interaction of CoQ10 in the metabolic processes of the TAU protein can attenuate the oxidative responses of β-amyloid aggregation in AD models showed significant results in the decrease of EO and ROS, thus avoiding the harmful effects of Aβ on synaptic plasticity, obtaining an antiapoptotic and antinecrotic effect. Although it is not clear if the interaction of both molecules increases the benefit significantly compared to when each one acts without the intervention of the other.

However, the results obtained to date are still preliminary, as there are still several gaps. Therefore, we suggest further long-term randomized controlled clinical trials.

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