Review

CoQ10 and Mitochondrial Dysfunction in Alzheimer's Disease

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CoQ_{10} and Mitochondrial Dysfunction in Alzheimer's Disease

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Abstract: Progress in understanding the pathogenesis and treatment of Alzheimer's disease (AD) is based on the recognition of the primary causes of the disease, which can be deduced from the knowledge of risk factors and biomarkers measurable in the early stages of the disease. Insights into risk factors and the time course of biomarker abnormalities point to a role for mitochondrial dysfunction and oxidative stress in the onset and development of AD. Coenzyme Q_{10} (CoQ_{10}) is a lipid antioxidant and electron transporter in the mitochondrial electron transport system. The availability and activity of CoQ_{10} is crucial for proper mitochondrial function and cellular bioenergetics. Based on the mitochondrial hypothesis of AD and the hypothesis of oxidative stress, the regulation of the efficiency of the oxidative phosphorylation system by means of CoQ_{10} can be considered promising in restoring the mitochondrial function impaired in AD, or in preventing the onset of mitochondrial dysfunction and the development of amyloid and tau pathology in AD.

Keywords: Alzheimer's disease; coenzyme Q_{10}; mitochondrial dysfunction; oxidative stress; drug

1. Introduction

Neurodegeneration and aging of the brain are influenced by genetic and epigenetic factors, external and internal environment, lifestyle, trauma and diseases. Impaired synaptic and structural neuroplasticity in aging is associated with pathophysiological, functional, and morphological changes in the brain that may serve as biomarkers of brain aging and neurodegeneration. Pathophysiological biomarkers of brain aging include factors that are linked to the mitochondrial dysfunction [1]. Due to the key role of mitochondria in bioenergetics, oxidative stress, metabolism, neuroinflammation, neuroplasticity, and apoptosis [2–4], attention has long been paid to mitochondrial dysfunction in aging and age-related neurodegenerative diseases such as Alzheimer's disease (AD) [5–7].

In general, mitochondrial dysfunction is associated with reduced ATP production, increased production of reactive oxygen species (ROS), release of proapoptotic factors, and disturbed calcium homeostasis. The reduced production of ATP is mainly caused by the impaired function of the oxidative phosphorylation system (OXPHOS), which includes a series of redox reactions ending in oxygen, during which the mitochondrial electron transport system (ETS) transfers electrons between the complexes of the respiratory chain with the formation of the proton motive force, but also of superoxide [8]. The essential carrier of electrons from complex I or from complex II to complex III is coenzyme Q (CoQ), especially CoQ_{10} in humans. The availability and activity of CoQ_{10} and the Q-cycle play a significant role in the effectiveness of the OXPHOS system. In addition, CoQ_{10} functions as a lipid antioxidant and a necessary factor for controlling protein uncoupling and opening mitochondrial permeability transition pores (mPTPs).

CoQ_{10} is endogenously synthesized in every cell; it is also partially absorbed through food, which can affect its availability and activity. Supplementation of CoQ_{10} and its analogs is tested in the treatment of diseases related to oxidative stress and disruption of cellular energy, including

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neurodegenerative diseases [9]. This review summarizes findings on the role of oxidative stress and mitochondrial dysfunction in the pathophysiology of AD, with a focus on the role of CoQ_{10}.

2. Alzheimer's disease

AD is a degenerative disease characterized by amyloid beta (Aβ) and tau protein pathology, where increased formation of neurotoxic Aβ oligomers and plaques and tau hyperphosphorylation (leading to microtubule disruption and the formation of neurotoxic tau oligomers and neurofibrillary tangles (NFTs)) are associated with progressive neuronal loss, a decline in cognitive functions and the development of dementia [10]. Mitochondrial dysfunction, neuroinflammation, oxidative stress, disruption of neurotransmission, metabolic disorders, accumulation of transition metals, vascular damage, and chronic hypoperfusion of brain tissue are also involved in the pathogenesis of AD, which is captured in various interconnected biological hypotheses of AD (Figure 1) [11].

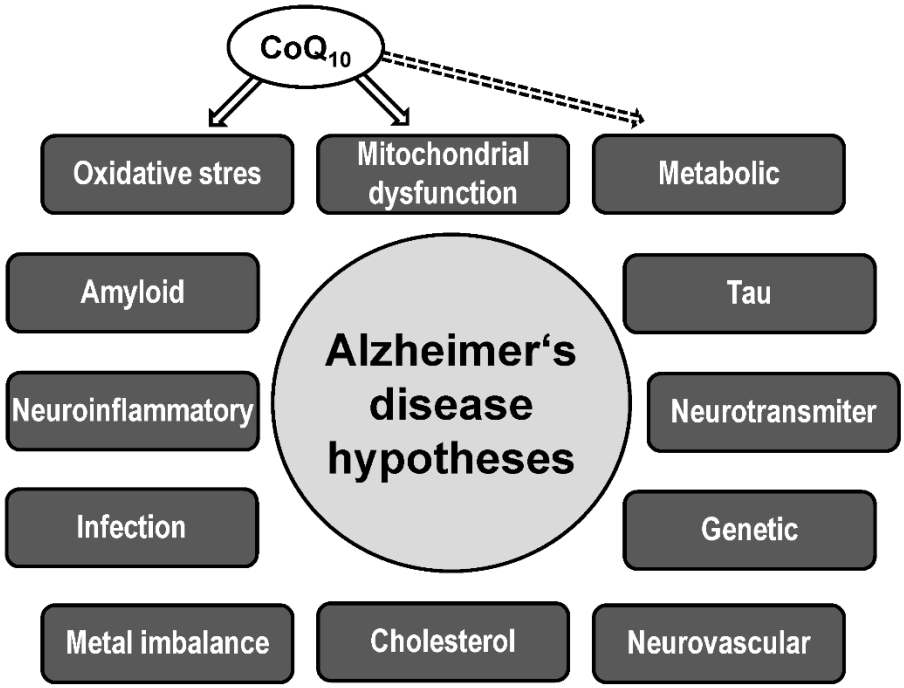

Figure 1. Biological hypotheses of Alzheimer's disease.

Aβ pathology and tauopathy are mainly involved in the etiology of AD [12,13]. The direct cause of brain cell damage and neuroplasticity in AD is primarily the effects of free radicals and apoptotic processes. The targets of new potential AD drugs are mainly processes related to Aβ and P-tau neurotoxicity, mitochondrial dysfunction, oxidative stress, metabolic disorders, and neuroinflammation.

The main pathophysiological feature of AD is impaired proteostasis of pathways involved in the synthesis, folding, post-translational modifications, aggregation, targeting, and degradation of Aβ and tau protein in the brain. Mitochondria, mitochondria-associated membranes (MAM), and endoplasmic reticulum (ER), which are connected to the ubiquitin proteasome system, autophagy system, ROS production, regulation of free cytosolic calcium, and apoptosis, are significantly involved in these processes.

2.1. Risk factors

The main risk factor for the sporadic form of AD is age. Aging is a complex event, for the explanation of which suitable biomarkers are sought at the molecular, cellular and physiological levels, which cause or accompany aging [3]. In general, age-related neurodegeneration is influenced by environmental factors (age, diet, exercise, lifestyle, and cognitive reserve), metabolic and oxidative

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stress, mitochondrial dysfunction, genetics and epigenetics, cerebrovascular dysfunction, blood-brain barrier dysfunction, neurotoxicity, and neuroinflammation [14]. The essence of the aging hypothesis, as well as the hypothesis of neurodegenerative diseases, is a gradual increase in cellular dysfunctions caused by the accumulation of protein, lipid, and nucleic acid dysfunctions.

The biology of aging and neurodegeneration is associated with metabolic and oxidative stress, inflammation, DNA mutations and related processes [15]. Biomarkers of aging include genomic instability, telomere attrition, epigenetic changes, loss of proteostasis, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis [16].

The exact cause of AD onset remains controversial. Progress is expected from longitudinal studies allowing the identification of risk factors and early biomarkers of AD detectable in peripheral blood long before the onset of clinical symptoms of the disease [17]. Occurrence of the APOE ε4 allele is a major genetic risk factor for late-onset sporadic AD [18,19], as ApoE4 increases the neurotoxicity of Aβ and tau, which have a role in AD pathology [20]. Epigenetic changes, including changes in mtDNA, have been shown to be important in the pathogenesis of AD [21]. The autosomal dominant (familial) form of AD, which is defined as pathologically confirmed dominantly inherited AD, occurs in less than 1% of all cases [22]. However, all forms of AD are thought to share similar pathophysiological processes.

The main risk factor for the most common sporadic form of AD is age. Therefore, progress in understanding the pathophysiology of AD is largely linked to progress in understanding the mechanisms of aging-related neurodegeneration. Other risk factors for AD are female gender [23,24], other genetic and epigenetic variations [18,25], brain injury [26] and internal and external environmental factors and stressors [27,28], including low levels of education [29], lifestyle [30], infection [31], cardiovascular disease [32] and metabolic dysregulation [33] such as type 2 diabetes mellitus (T2DM) [34]. The most significant environmental risk factors for the development of AD are late-life depression and T2DM [28].

2.2. Biomarkers

Validated biochemical biomarkers of AD are low concentrations of Aβ42 in CSF, which reflect Aβ deposition in the brain, and increased tau in CSF, which is a marker of neuronal degeneration or damage. Tau biomarkers include both total tau (T-tau) and phosphorylated tau (P-tau) [35]. Currently, Alzheimer's disease biomarkers are mainly sought and studied (i) neuroimaging (focused on structural and functional changes, decreased connectivity, hypometabolism, and pathological aggregates of Aβ and tau [36–39], (ii) proteomic and metabolomic [40], and (iii) oxidative stress [41], mitochondrial [42,43], and neuroinflammatory [44].

The time course of measurable pathophysiological biomarkers in relation to the clinical course of AD can be used as a basis for the development of new drugs in AD targeting pathophysiological processes in the early stages of the disease. A hypothetical time course of biomarker abnormalities and pathological changes in AD is proposed based on longitudinal measurement of Aβ and P-tau in CSF or in brain by PET, measurement of neurodegeneration by FDG-PET (hypometabolism) and MRI (hippocampal atrophy), and synaptic dysfunction by FDG -PET and fMRI, neuroinflammatory changes, and mitochondrial dysfunction [17,22,37,45,46]. According to this model, the onset of AD (even decades before the recognition of clinical symptoms of the disease) is associated with age-related mitochondrial dysfunction and the neurotoxicity of Aβ oligomers, while neurodegeneration and progression of AD is more associated with the neurotoxicity of P-tau oligomers and NFTs.

2.3. Mitochondrial hypothesis

The mitochondrial cascade hypothesis of AD posits that mitochondrial dysfunction determines the initiation and development of this disease. According to this hypothesis, primary changes in mitochondrial function may induce a cascade of processes that lead to AD-specific neuropathological changes. Aβ and tau pathology/neurotoxicity may also be potentiated by interaction with

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mitochondrial proteins and membranes. According to the original mitochondrial cascade hypothesis [47], the basic level of mitochondrial function is genetically determined, and the decline of mitochondrial function is determined by aging processes, genetic factors, and environmental influences. If the decline in mitochondrial function exceeds a certain threshold, then the histological and pathophysiological changes specific to AD are triggered.

According to the mitochondrial cascade hypothesis, AD neuropathology arises secondary to mitochondrial dysfunction when the age-associated decline in mitochondrial function reaches a point where compensatory mechanisms are no longer effective [17,48,49]. The primary cause of the disease may not only be mitochondrial dysfunction, amyloidopathy or tauopathy, but also changes in the activity of factors that can cause them and which are localized in mitochondria, such as ApoE4 [50], glycogen synthase kinase 3 [51,52], and monoamine oxidase [53]. It appears that AD may have multiple initiating pathological factors that interact with each other.

Amyloid and tau pathology are considered to be specific for AD, but due to the mutual interactions and feedback effects of the aforementioned processes, it is not yet clear what triggers AD. According to the integrative amyloid-tau-mitochondrial hypothesis [17], the interaction of risk factors and biomarkers and their mutual synergy rather than the primary effects of one particular factor are decisive for the development of AD.

Mitochondrial-associated endoplasmic reticulum (ER) membranes (MAMs) play a key role in maintaining calcium homeostasis, phospholipid and cholesterol metabolism, import of lipids from the ER into mitochondria, initiation of autophagy, mitochondrial fission, and apoptosis. Thus, MAMs have a role in the development of neurodegenerative diseases such as AD [54–57]. According to the MAM hypothesis, AD is mainly a communication disorder between ER and mitochondria [58].

The mitochondrial hypothesis of AD is supported by the observation that aging (as the most important risk factor for AD) affects the function of mitochondria in brain cells, and thus the generation of ATP, calcium homeostasis, and the regulation of gene expression [1,6]. Changes with age occur in the gene expression of mitochondrial proteins, the morphology of mitochondria and their fission and fusion [59], oxidative damage of mtDNA [60], the function of the OXPHOS system [61], depolarization of the inner membrane and opening of mPTPs [62]; cellular NAD+ levels and the NAD:NADH ratio also decrease [63].

Mitochondrial dysfunction in AD includes bioenergetic impairment, increased ROS production, impaired mitochondrial dynamics and trafficking, and DNA mutations [64,65]. Mitochondrial abnormalities, including impaired function of mitochondrial ETS complexes and ATP production, have been described in AD [66]. One possibility to regulate the processes associated with neurodegeneration in AD is the regulation of the OXPHOS system through the availability and activity of CoQ_{10} using metabolic modulators, drugs, diet, and exercise [67,68].

Disruption of synaptic plasticity is one of the first steps in the neurodegeneration process associated with aging and the development of neurodegenerative diseases such as AD. Early deficits in synaptic mitochondria in AD include increased Aβ accumulation, mitochondrial dysfunction, increased mPTP, decreased mitochondrial respiration, and decreased complex IV activity [69]. At the same time, Aβ and tau pathologies are in a reciprocal relationship with mitochondrial dysfunction and oxidative stress in AD [17,70–72]. In a mouse model of AD, disruption of mitochondrial bioenergetics has been shown to precede the development of AD pathology [73]. Aβ accumulates in mitochondria and reduces the enzymatic activity of complex II and IV, reduces mitochondrial respiration, and impairs mitochondrial dynamics [74–76]. Damage to mitochondrial bioenergetics in AD was demonstrated both by measurements in the brains of AD transgenic mice and by PET neuroimaging in human AD brains [65]. Aβ and tau appear to act synergistically to damage the OXPHOS system, with tau damaging complex I and Aβ damaging complex IV [77].

2.4. Oxidative stress hypothesis

According to the free radical theory of aging [78–80], aging and age-related diseases are associated with overproduction of ROS, primarily from mitochondria, and subsequent damage to

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cellular proteins, lipids, and nucleic acids. Although oxidative stress is accepted as a key modulator of the biological processes of aging and neurodegeneration [81], useful endogenous mechanisms regulated by ROS [82] must also be taken into account in therapeutic interventions and attention must also be paid to the role of other manifestations of mitochondrial dysfunction, such as impaired bioenergetics, inflammation, mtDNA mutation, impaired mitophagy and retrograde signaling from mitochondria to the nucleus [83–86].

According to the oxidative stress hypothesis, the cause of the development of AD is oxidative stress, where damage to brain cells by ROS contributes to neurodegeneration and cognitive decline. At the same time, mitochondrial dysfunction, but also Aβ and P-tau can contribute to the increased production of RONS [87]. ROS can trigger an inflammatory response and, conversely, inflammation induces oxidative stress [88]. Damage to synapses and brain cells due to oxidative stress may be both a consequence and a cause of Aβ and tau neurotoxicity in AD [89]. Mitochondrial dysfunction is also involved in the development of oxidative stress, so administration of CoQ_{10} as an antioxidant and/or regulators of CoQ_{10} activity in oxidative phosphorylation could be effective in AD therapy.

The oxidative stress hypothesis is based on the observation that oxidative stress, i.e. an imbalance between the production and elimination of ROS, occurs in neurodegeneration associated with AD and with aging. Increased ROS production and/or reduced antioxidant defenses lead to the accumulation of dysfunctional proteins, lipids and nucleic acids (including mtDNA) and impaired mitophagy. In neurons, superoxide is mainly produced in the mitochondrial matrix during electron transfer in ETS (mainly generated by the mitochondrial complexes I and III). Superoxide is converted directly in the matrix by superoxide dismutase to less reactive hydrogen peroxide, which, however, passes through membranes and can be converted to a very reactive hydroxyl radical in the cytosol [8]. Mitochondrial dysfunction can lead to increased oxidative and nitrosative stress, as impaired electron transfer in the mitochondrial ETS leads to increased production of ROS and the formation of reactive hydroxyl radicals, and impaired transport of calcium ions into the mitochondrial matrix induces increased production of nitric oxide (NO) and the formation of reactive peroxynitrite. These radicals can initiate increased peroxidation of membrane lipids in AD [90]. Lipophilic antioxidants such as CoQ_{10} have a protective effect on the peroxidation of membrane lipids.

Damage to synapses and brain cells due to oxidative stress may be both a consequence and a cause of Aβ and tau neurotoxicity in AD [89]. Mitochondrial dysfunction is also involved in the development of oxidative stress, so administration of CoQ_{10} and/or regulation of CoQ_{10} activity in the ETS is being tested in AD therapy. Administration of CoQ_{10} as an antioxidant had no significant effect on biomarkers associated with amyloid and tau pathology in AD measured in CSF (Aβ42, tau, and P-tau), nor on cognitive function [91]. Also, administration of CoQ_{10} did not have a significant therapeutic effect in other neurodegenerative diseases such as Parkinson's disease and Huntington's disease [92].

3. Coenzyme Q_{10}

Coenzyme Q_{10} (CoQ_{10}, ubiquinone, 2,3 dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone) is the most common form of coenzyme Q in humans [93]; it is found in all cell membranes, where it acts as an electron carrier and antioxidant. CoQ_{10} occurs in three redox forms, as oxidized form (ubiquinone, $C_{59}H_{90}O_4$), reduced form (ubiquinol, $C_{59}H_{92}O_4$), and semi-oxidized form (semiquinone, $C_{59}H_{91}O_4^{\bullet}$; under physiological conditions it occurs as an ion $C_{59}H_{90}O_4^{-\bullet}$) (Figure 2).

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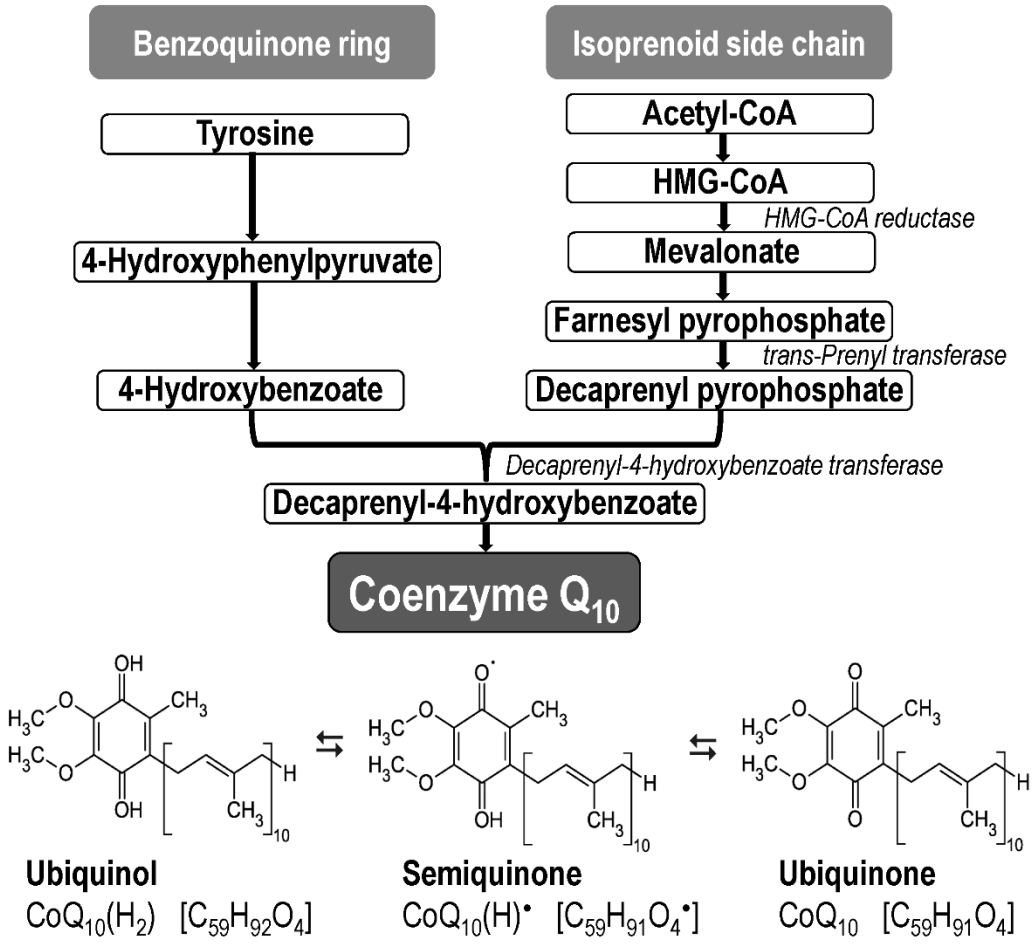

Figure 2. Basic steps in coenzyme Q_{10} biosynthesis and three redox isoforms. HMG-CoA – β-Hydroxy β-methylglutaryl-coenzyme A.

The main cellular functions of CoQ_{10} include (i) electron transport in the mitochondrial electron transfer system (ETS) with a key role in the formation of ATP, (ii) antioxidant action including protection against lipid peroxidation, participation in the reduction/recycling of other antioxidant molecules (α-tocopherol and ascorbate), and stabilization of the plasma membrane and cell redox balance (iii) apoptosis and modulation of mPTPs, (iv) signaling modulation of gene expression, including anti-inflammatory effects, (v) maintenance of proton gradient on the lysosomal membrane, and (vi) activation of mitochondrial uncoupling proteins [94–97].

Coenzyme Q_{10} (ubiquinone, CoQ_{10}) is present in mitochondria as part of the electron transport chain. CoQ_{10} is a lipophilic molecule located in cell membranes, mainly in the inner mitochondrial membrane (IMM); is crucial for electron transfer between complex I or II and complex III of the respiratory chain [98] and also from other dehydrogenases [9,99,100] localized on the outer or inner surface of the IMM. Furthermore, CoQ_{10} is an important factor in the activation of protein uncoupling, controls the mPTP, participates in the transport of electrons in plasma membranes and lysosomes, affects the structure and fluidity of membranes and acts as an endogenous lipid antioxidant [9,101]. Moreover, CoQ_{10} and its redox state could indirectly modulate a number of mitochondrial and non-mitochondrial metabolic pathways, such as sulfide metabolism, one-carbon metabolism, glutathione, and ferroptosis; it can therefore be included in the pathophysiology of some metabolic diseases [100].

In addition to the main role in electron transport in the mitochondrial ETS, CoQ_{10} has other mitochondrial functions, mainly as a cofactor in the activation of uncoupling [102] and in the control of the mPTP [103]. CoQ_{10} is also involved in the function of redox systems in various membranes, the structure and fluidity of membranes [104], gene expression, cell growth, differentiation, and apoptosis [105]. The reduced form of $CoQ_{10}(H2)$ (ubiquinol) acts as an antioxidant and scavenger of

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free radicals, thereby preventing oxidative damage to lipids, proteins and nucleic acids. On the other hand, CoQ_{10} can also have a pro-oxidant role, as it can participate in the formation of superoxide and hydrogen peroxide [106].

The internal synthesis of CoQ_{10} starts from the amino acid tyrosine (benzoquinone ring) and from the mevalonate pathway (isoprenoid side chain) (Figure 2) [107,108]. Current knowledge about CoQ_{10} biosynthesis is described in detail in a series of reviews [109–111]. A collection of enzymes that produces CoQ_{10} (termed as complex Q) is localized in the inner mitochondrial membrane and in the endoplasmic reticulum [94,95].

3.1. CoQ10 in OXPHOS system

High-energy electrons enter the mitochondrial ETS via complex I (from the reduced coenzyme nicotinamide adenine dinucleotide, NADH) or via complex II (from the reduced coenzyme flavin adenine dinucleotide, $FADH_2$). The product of redox reactions in the complex I is the transfer of 4 protons per 1 NADH molecule into the intermembrane space. Electrons are transferred from complex I or complex II to complex III (coenzyme Q : cytochrome c – oxidoreductase, sometimes called the cytochrome bc_1 complex) by ubiquinol (reduced $CoQ_{10}(H_2)$) and enter protonmotive Q-cycle of the complex III. In the Q-cycle mechanism, protons are translocated across the inner mitochondrial membrane (IMM) as a result of reoxidation of ubiquinol at Q_o-site at the outer side of the IMM and reduction of ubiquinone (CoQ_{10}) at Q_i-site at the matrix side of the IMM (Figure 3). Respiration subunits in the Q-cycle are cytochrome c_1, cytochrome b (with low (b_L) and a higher (b_H) potential hemes), and Rieske protein. The substrates of redox reactions catalyzed by complex III are ubiquinol and two molecules of ferricytochrome c, the products are ubiquinone, two molecules of ferrocytochrome c, and four protons (released into the intermembrane space and used by ATP synthase during ATP biosynthesis) [97,112–114]. Total mitochondrial ETS activity is most easily measured as the kinetics of mitochondrial oxygen consumption [115,116]. Note, that the Q_o-site of the complex III is an important site for generation of superoxide and thus has a role in oxidative damage during aging and neurodegeneration.

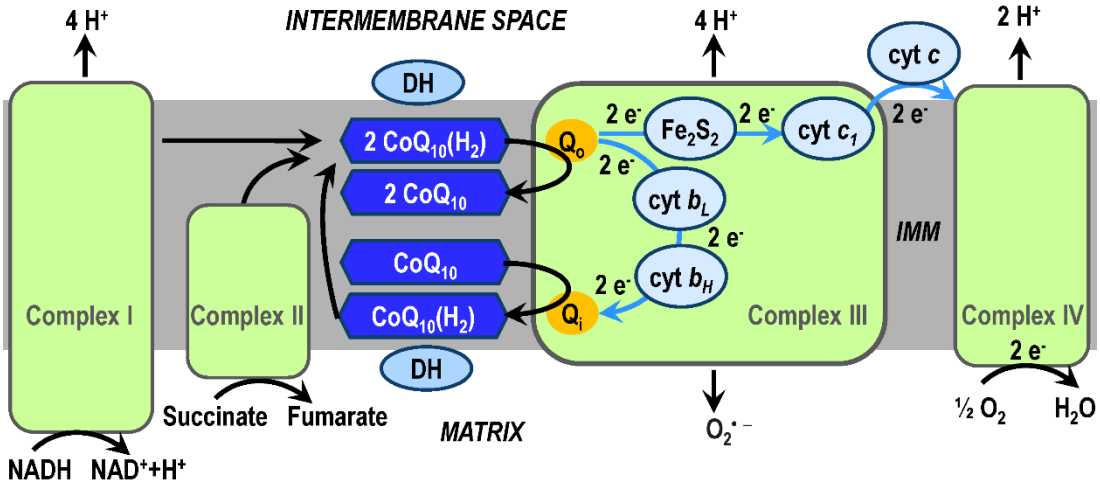

Figure 3. A simplified diagram of the mitochondrial electron transport system (ETS) with electron transfer in the Q-cycle of complex III. Electrons enter the ETS via complex I or via complex II and are transferred by coenzyme Q_{10} (CoQ_{10}) to complex III. CoQ_{10} can also transfer electrons from dehydrogenases (DH) located on the outer or inner surface of the inner mitochondrial membrane (IMM). In the Q_o-site complex III near the outer side of IMM, two electrons from one ubiquinol ($CoQ_{10}(H_2)$) and subsequently two more electrons from the second ubiquinol pass into two bifurcated transfer chains: (1) acceptor of two electrons is iron –sulfur cluster (Fe_2S_2 center) of the Rieske protein, which passes electrons via cytochrome c_1 (cyt c_1) to cytochrome c (cyt c) on the outer surface of the IMM. Cyt c transfers electrons to complex IV (cytochrome c oxidase), where oxygen is finally reduced

to water; (2) the acceptor of the second two electrons in the Q-cycle is cytochrome *b* containing low (cyt b_L) and a higher (cyt b_H) potential hemes; this chain supplies electrons to the Q_i-site at the matrix side of the IMM, where they reduce one ubiquinone (CoQ_{10}) to semiquinone and then to ubiquinol [113]. Complexes I and III (Q_o-site) are sources of superoxide ($O_2^{\bullet-}$).

The efficiency of the OXPHOS system, especially the transfer of electrons by means of CoQ_{10} and the Q-cycle, is influenced by the existence and organization of respiratory supercomplexes [117,118]. The most common supercomplexes (respirasomes) observed are complex I/III, complex I/III/IV, and complex III/IV. Supercomplex assembly is dynamic and their formation and stabilization depends on the lipid composition of the IMM, especially on the presence of cardiolipin [119]; the initiation of their formation can be associated with the membrane potential. The formation of supercomplexes can significantly increase the efficiency of the OXPHOS system by optimizing the utilization of ETS substrates, stabilizing complex I, and reducing the formation of ROS [120,121]. A constitutive part of respirasomes is CoQ_{10}, which exists in different CoQ_{10} pools in the IMM [122].

Dependence between respiratory complexes, supercomplex assembly dynamics, and the existence of CoQ_{10} pools in the effectiveness of the ETS system is intensively studied [123]. According to the classic fluid model, respiratory complexes I-IV are randomly distributed in the IMM and electron transfer between them is realized by electron carriers, CoQ_{10} located inside the IMM and cyt *c* located on the external surface of the IMM (Figure 3). The random collision model [124] assumed that mitochondrial electron transport is a process of random collisions based on the diffusion of individual components in the fluid IMM. The discovery of the existence of supercomplexes in the respiratory chain [125] and the recognition of their function [126] led to the modification of the fluid model to the plasticity model, which adds to the fluid model a new view of the structural and functional complexity in the transfer of electrons in the mitochondrial ETS as well as the function of the CoQ_{10} pool in the IMM [122,127,128].

The plasticity model assumes that respiratory complexes can function either individually or as components of supercomplexes. It has long been assumed that free CoQ_{10} resides in the IMM in a homogeneous pool [129]. With the discovery of respirasomes and their function, it is shown that there is a segmentation of CoQ_{10} molecules, into a pool attached by supercomplex I/III (CoQ_{NADH} pool) and into a pool available for complex II and other enzymes (CoQ_{FADH} pool) [120], while the two pools interact with each other. The majority of CoQ that receives electrons from $FADH_2$ and the majority of cyt *c* apparently remain unbound to supercomplexes.

3.2. CoQ10 in AD pathophysiology

CoQ_{10} is mainly formed endogenously, so the cause of a deficiency in CoQ_{10} can mainly be its impaired biosynthesis, increased degradation, or increased usage. In mitochondrial diseases, CoQ_{10} deficiency can be caused by mutations in genes responsible for CoQ_{10} biosynthesis, or secondarily by defects in other genes [130]. Endogenous metabolites, which are also involved in cholesterol production, may be involved in the regulation of CoQ_{10} biosynthesis [95]. By upregulating the synthesis of CoQ_{10}, not only its concentration but also its appropriate mitochondrial localization can be achieved. However, dietary intake can also contribute to CoQ_{10} availability, especially when its endogenous production is reduced with aging or with genetic mutations primarily or secondarily involved in CoQ_{10} biosynthesis.

Protective effects of CoQ_{10} against Aβ a neurotoxicity [131] and the observation that serum CoQ_{10} levels may be inversely associated with dementia risk [132] suggests that determination of serum CoQ_{10} levels could be useful for predicting the development of AD. Other studies, however, did not find significant differences in plasma CoQ_{10} concentrations in AD and controls. Although the results of some studies show that serum CoQ_{10} could be a predictor of dementia [132], CoQ_{10} deficiency has not been sufficiently demonstrated in peripheral blood [133]. But an association between clinical assessment of cognitive decline and plasma CoQ_{10} concentration was found, which may mean that even a small variation in CoQ_{10} availability or activity can trigger mitochondrial dysfunction.

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In permeabilized platelets from AD patients, reduced capacity of the electron transport system, altered activity of respiratory chain complexes (increased complex I activity and decreased complex IV activity) [43,134], and reduced plasma CoQ_{10} concentration were found, with complex IV activity being negatively correlated and respiratory capacity being positively correlated with cognitive MMSE early [134–136]. The exact role of CoQ_{10} in the pathogenesis of AD and the treatment of neurodegenerative diseases is yet to be clarified [96].

Oxidative stress is also thought to contribute to AD progression by inducing Aβ overexpression and accumulation, while it is unclear what is the primary cause of disease development. Oxidative stress modulates proteostasis, which is strongly impaired in AD [137]. Therefore, antioxidants are among the new clinically tested potential drugs in AD [138]. The reduced form of CoQ_{10}(H2) is a known antioxidant that also affects Aβ pathology [139]. Protective effects of CoQ_{10} and other antioxidants against Aβ accumulation in the brain and against neuroinflammation and hypoxia have been reported [140].

A study with a mouse model of AD showed that there is a relationship between changes in the hippocampus and cerebral cortex and oxidative stress, proteostasis, and bioenergetics and that CoQ_{10} may act preventively [141]. Evaluation of the therapeutic response to CoQ_{10} administration to AD patients showed efficacy in mitochondrial activation [142], but the change in CoQ_{10} levels in AD patients and its effects on improving neuropsychological assessments are not clearly confirmed [133]. Thus, the role of CoQ_{10} in the pathogenesis of AD is not fully understood.

A role for CoQ_{10} in AD pathophysiology is supported by the observation that CoQ induces tau aggregation and that CoQ is present in paired helical filaments (PHF) [143]. Cell culture studies have shown a protective effect of CoQ_{10} on Aβ neurotoxicity [131,139,144]. In a mouse model of AD, it was shown that early intervention with ubiquinol can act preventively against the deregulation of proteostasis (disorders caused by an imbalance in the protein homeostasis network - synthesis, folding and transport of proteins; by post-translational modification and degradation or clearance of misfolded proteins) in AD.

4. AD treatment

4.1. Targets of novel AD drugs

Drugs currently approved or recommended for the treatment of AD belong to the category of agents targeting neurotransmitter receptors (cholinesterase inhibitors and NMDA receptor antagonists) and Aβ (monoclonal antibodies directed against Aβ plaques, protofibrils, and oligomers). In clinical use, there are drugs aimed at suppressing or alleviating the symptoms of AD (donepezil, rivastigmine, galantamine, memantine and the memantine/donepezil combination). Two disease-modifying drugs (DMDs) targeting Aβ pathology (aducanumab and lecanemab) have recently received accelerated approval from the United States Food and Drug Administration (FDA). Attention is mainly devoted to the development of new effective and specific DMDs. However, there is also ongoing testing of symptomatic substances aimed at improving cognitive functions and neuropsychiatric symptoms in AD, and these are often drugs already approved for the treatment of other diseases or substances used in alternative and complementary medicine [145].

Oxidative stress and categories of biological processes and AD drug targets that are closely related to mitochondrial function (metabolism and bioenergetics, synaptic plasticity/neuroprotection, and cell death) are included in the CADRO classification system ("Common Alzheimer's and Related Dementias Research Ontology"; https://iadrp.nia.nih.gov/about/cadro). According to the periodic annual review of drug development for AD [138] based on an analysis of data from ClinicalTrials.gov, a total of 141 agents were tested for the treatment of AD and mild cognitive impairment (MCI) in phase 1, 2, or 3 clinical trials at the beginning of 2023 with AD. Their most common targets are inflammation (17.0%), Aβ (15.6%), synaptic plasticity/neuroprotection (12.9%), tau (9.2%), metabolism and bioenergetics (7.1%), and oxidative stress (5.0%).

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In addition to new DMD drugs targeting the primary causes of AD onset and progression, appropriate combinations of approved drugs with adjuvant agents are also being sought and tested. These supplements, such as CoQ_{10}, ω-3 fatty acids, soy, ginkgo biloba, B vitamins, vitamin D plus calcium, vitamin C, or β-carotene have not yet been shown to prevent cognitive dysfunction in AD [133,146]. It can be expected that if adjuvants have anti-amyloid, anti-tau, neurochemical, mitochondrial, antioxidant or anti-inflammatory effects [131,147], they may also have therapeutic potential to moderate the progression of cognitive impairment in AD. Drugs in phase 2 or 3 clinical trials targeted to oxidative stress include hydralazine, icosapent ethyl, PUFA, omega-3, edavarone, and Flos gossypii flavonoids. Metabolism and bioenergetics are targeted by metformin, insulin intranasal (+ empagliflozin), dapagliflozin, empagliflozin, semaglutide, T3D-959, Chinese traditional medicine, and obicetrapib [138].

Antioxidants are only taken as adjuncts in the administration of approved AD drugs. The lack of effectiveness of antioxidants in AD therapy can be explained by their non-specific intervention in the balance between ROS activity and the activity of the antioxidant system, which can suppress the useful and necessary role of free radicals in certain areas of the brain. Nevertheless, the testing of CoQ_{10} and its analogues as a supportive therapy for AD continues to be important, mainly associated with the suppression of excessive peroxidation of membrane lipids.

A suitable target for substances that restore or increase mitochondrial function is the stimulation of mitochondrial biogenesis. Mitochondrial biogenesis is associated not only with cell division, but also with the response to oxidative stress (that is, with the demand for increased cellular energy consumption), exercise, hormones, electrical stimulation, etc. Mitochondrial biogenesis has become the target of new drugs for diseases associated with mitochondrial dysfunction, including neurodegenerative disorders such as AD. Pathways associated with mitochondrial biogenesis and activated in response to energy deficit include activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) axis, activation of AMP-activated protein kinase (AMPK), and Sirtuin 1 activation [65].

In summary, the main approach in the search for new AD disease-modifying drugs (DMD) is targeting the pathophysiological processes causing the onset of the disease, which, according to current AD hypotheses, are mainly Aβ and tau pathology, mitochondrial dysfunction, oxidative stress, neuroinflammation, disturbed neurotransmission, and disorders of brain metabolism. If we assume that age is the main risk factor for AD, then we can focus on the regulation of processes and biomarkers discussed in the oxidative stress hypothesis and in the mitochondrial hypothesis.

4.2. CoQ10 in AD treatment

Substances that act as antioxidants or increase mitochondrial bioenergetics have potential for the treatment of neurodegenerative diseases such as AD. From the point of view of the mitochondrial hypothesis of AD and the possibility of pharmacologically influencing mitochondrial dysfunction, synaptic plasticity and metabolism of brain cells, CoQ_{10} and mitochondrial proteins and lipids interacting with it also appear to be possible targets of new AD drugs. These are substances capable of regulating the availability and activity of CoQ_{10} and thus the function of the OXPHOS system.

CoQ_{10} and other antioxidants or bioenergetics stimulators may be potentially effective in the treatment of neurodegenerative diseases [148,149]. CoQ_{10} is well characterized as a neuroprotective antioxidant in animal models and in human studies of neurodegenerative disorders. CoQ_{10} has been shown to reduce oxidative stress and amyloid pathology in a mouse model of AD [150]. Age-related decline in mitochondrial function has been shown in a mouse model to be accompanied by decreased levels of mitochondrial CoQ, and exogenous administration of water-soluble CoQ can lead to restoration of mitochondrial function [151]. A number of studies have confirmed significant neuroprotective effects of CoQ_{10} in experimental biological models, but the suitability of CoQ_{10} as a biomarker or drug has not been confirmed in AD patients [133].

Given the role of CoQ_{10} in bioenergetics and antioxidant activity and the observation that CoQ_{10} has protective effects against Aβ-induced cell toxicity and impaired synaptic plasticity [144,152],

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CoQ_{10} and the processes regulated by it have strong potential as new AD drug targets [153]. Although studies in animal models of AD show significant improvements in cognition, clinical trials have not been very successful. Therefore, upregulation of brain CoQ_{10} biosynthesis appears to be more suitable for treatment of neurodegenerative disorders. An increase in CoQ_{10} biosynthesis is possible in a physiological way (cold adaptation and exercise) [107] or by targeting of isoprenoid regulation within mevalonate pathway [154], e.g. by administration of substances, such as epoxidized all-trans polyisoprenoids [95].

Reduced availability of CoQ_{10} can be eliminated by dietary administration of this substance. The process of CoQ_{10} absorption and bioavailability is complex and strongly depends on the formulation of the preparation [155]. CoQ_{10} and its analogues, idebenone and MitoQ, are used in the treatment of mitochondrial disorders and in the supportive treatment of neurodegenerative diseases associated with mitochondrial dysfunction, such as AD [108]. CoQ_{10} is well tolerated and safe, but not approved for treatment of AD [156]. The therapeutic application of CoQ_{10} is limited by its insolubility in water. Various preparations of CoQ_{10} have been developed to improve solubility and bioavailability.

The synthetic analogue of CoQ_{10} idebenone (hydroxydyecylubiquinone) acts as an antioxidant and an electron carrier in ETS. Idebenone has protective effects against many toxins [157], but inhibits complex I [158]. In some studies it showed therapeutic effects on AD progression [159], but in other studies no effect of idenbenone on cognitive decline in AD [160] or on biomarkers related to Aβ and tau pathology in AD was demonstrated [91].

The administration of mitoquinone (MitoQ), which passes through membranes more easily and concentrates in the mitochondria thanks to the attached triphenylphosphonium to ubiquinone, seems promising. MitoQ has protective effects against mitochondrial damage [161] and appears promising in suppressing AD symptoms. In experiments with cell cultures and a mouse model of AD, MitoQ was found to increase synaptic connectivity and neurite outgrowth, prevented Aβ induced oxidative stress, and improved memory retention [162–164].

In summary, To evaluate the effect of CoQ_{10} on the activity of the OXPHOS system, or on mitochondrial dysfunction associated with impaired electron transport in the ETS in AD, data from *in vivo* measurements are not yet available. However, *in vitro* measurements using isolated mitochondria suggest that exogenously supplied CoQ_{10} can increase mitochondrial respiratory rate. It can be hypothesized that the antioxidant activity of CoQ_{10}, which protects mitochondrial membranes from oxidative damage, and the increase in electron transfer efficiency due to the incorporation of CoQ_{10} into the inner mitochondrial membrane contribute to this increase in ETS efficiency. From this point of view, it appears as a perspective synthesis and testing of (i) analogues of CoQ_{10} with good bioavailability in brain mitochondria, (ii) substances aimed at regulating CoQ_{10} biosynthesis, and (iii) substances aimed at increasing the activity of CoQ_{10} in the Q cycle, including those that affect the formation of supercomplexes containing complex III.

5. Discussion and Conclusions

Based on the findings on which the mitochondrial hypothesis of AD and the oxidative stress hypothesis are based, mitochondrial ETS, especially CoQ_{10} and the processes mediated by it, appear to be a promising target for new AD drugs. The uptake of dietary CoQ_{10} into tissues is limited, as CoQ_{10} is localized in the membranes of the central hydrophobic part of the lipid bilayer; thus, the space available for CoQ_{10} and similar lipophilic compounds is limited. CoQ_{10} diffusion in lipid bilayer may represent the rate-limiting step of electron transfer [165].

CoQ_{10} concentration decreases with aging, with the availability and redox status of CoQ_{10} playing a role in the oxidative stress associated with aging [166–169]. Increased availability of CoQ_{10} may have neuroprotective effects through antioxidant and bioenergetic effects. However, a systematic review did not confirm a decrease in plasma CoQ_{10} in AD patients [133]. Also, the decrease in mitochondrial respiratory rate in platelets with age was not different in AD patients compared to age-matched healthy controls [61]. These results indicate that mitochondrial dysfunction (potentially associated with reduced availability and activity of CoQ_{10}) in AD is associated with the onset of the

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disease rather than its progression. CoQ_{10} supplementation may then slow age-related neurodegeneration, but does not act as a causal cure for AD.

When we tested in vitro the effect of CoQ_{10} and other antioxidants on mitochondrial respiration using a model of isolated brain mitochondria, only the addition of CoQ_{10} caused an increase in respiratory rate [170]. It can be hypothesized that the increase in ETS activity may be achieved by direct incorporation of CoQ_{10} into the IMM, rather than the antioxidant action of CoQ_{10}. It can be assumed that the improvement of mitochondrial function in AD is possible by increased CoQ_{10} biosynthesis and increased mitochondrial biogenesis, rather than dietary CoQ_{10} supplementation, which does not ensure an increase in CoQ_{10} in IMM brain mitochondria. To increase the availability of CoQ_{10} in the brain and in brain mitochondria, its exogenous administration and biosynthesis stimulation can be combined, as exogenous supplementation of CoQ_{10} is safe and does not affect its endogenous biosynthesis [171].

Age-associated mitochondrial dysfunction (measurable as a decrease in ETS capacity or a decrease in respiratory reserve) together with the effects of ApoE4 may be at the start of Aβ and tau pathology, oxidative stress, and neuroinflammation in the late-onset sporadic form of AD. Targeting new AD drugs on the activity and efficiency of ETS, specifically on the availability and activity of CoQ_{10} in the inner mitochondrial membrane and on the regulation of redox processes in the ETS associated with CoQ_{10}, can therefore be considered a promising research approach. The direct in vitro effects of CoQ_{10} on increasing mitochondrial respiration [170] suggest that the regulation of CoQ_{10} biosynthesis could be a promising direction in the development of new AD drugs.

In conclusion, the specific pathophysiology of AD is primarily associated with Aβ and tau pathology. According to the mitochondrial hypothesis and the oxidative stress hypothesis, mitochondrial dysfunction and oxidative stress are involved in the pathogenesis of AD, which can be both initiating and accompanying processes in the pathophysiology of AD and the development of neurodegenerative processes in AD. The approach of targeting new AD drugs to the availability and activity of CoQ_{10} is underpinned by the role of CoQ_{10} in the cellular antioxidant system and in mitochondrial bioenergetics. Increasing the availability and activity of CoQ_{10} is possible by its exogenous administration; using biological models of isolated brain mitochondria, cell cultures, and animal models of AD, both antioxidant and bioenergetic effects of CoQ_{10} have been demonstrated. However, the effects of antioxidants are shown to be insufficiently effective in AD therapy in humans, and exogenous administration of CoQ_{10} does not yet allow its reliable increased utilization by brain mitochondria. From this point of view, targeting new AD drugs to increase mitochondrial bioenergetics by regulating mitochondrial biogenesis or CoQ_{10} biosynthesis in the brain appears to be a more appropriate pharmacological strategy. Regulation of the activity of the OXPHOS system through increasing the efficiency of electron transfer in the ETS using CoQ_{10} and cyt c appears promising. However, targeted pharmacological intervention in this electron transfer requires a deeper understanding of normal and pathological processes in the OXPHOS system, including those associated with the assembly of respiratory complexes into respirasomes and function of supercomplexes in electron transfer efficiency by CoQ_{10}.

Considering the role of CoQ_{10} in bioenergetics and lipid peroxidation, it is advisable to continue studying the possibilities of AD therapy by regulating the activity of CoQ_{10} in the OXPHOS system. In the context of the mitochondrial hypothesis and the oxidative stress hypothesis, stimulation of mitochondrial biogenesis and CoQ_{10} biosynthesis appears to be a promising target for new AD drugs. In the early stages of AD development, the stimulation of mitochondrial bioenergetics and the antioxidant action of CoQ_{10} could prevent the development of Aβ and tau neurotoxicity. However, even in the later stages of the disease, the effects of CoQ_{10} on mitochondrial bioenergetics could slow the progression of the disease.

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