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REVIEW ARTICLE

On the central role of mitochondria dysfunction and oxidative stress in Alzheimer's disease

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Abstract

Background Alzheimer's disease (AD) is the commonest cause of dementia, with approximately 5 million new cases occurring annually. Despite decades of research, its complex pathophysiology and etiopathogenesis presents a major hindrance to the development of an effective treatment and prevention strategy. Aging is the biggest risk factor for the development of AD, and the total number of older people in the population is going to significantly increase in the next decades, suggesting that AD incidence and prevalence is likely to increase in the future. This makes the need for a better understanding of the disease to be extremely urgent.
Methods A search was done by accessing PubMed/Medline, EBSCO, and PsycINFO databases. The search string used was "(dementia* OR Alzheimer's) AND (pathophysiology* OR pathogenesis)". New key terms were identified (new term included "vitamin D, thyroid hormone, mitochondria dysfunction, oxidative stress, testosterone, estrogen, melatonin, progesterone, luteinizing hormone, amyloid-β (Aβ), and hyperphosphorylated tau"). The electronic databases were searched for titles or abstracts containing these terms in all published articles between January 1, 1965, and January 31, 2019. The search was limited to studies published in English and other languages involving both animal and human subjects.
Results Mitochondria dysfunction and oxidative stress play a critical role in AD etiopathogenesis and pathophysiology.
Conclusion AD treatment and prevention strategies must be geared towards improving mitochondrial function and attenuating oxidative stress.

Keywords Dementia pathogenesis · Alzheimer's disease · Vitamin D and dementia · Thyroid hormone and dementia · Mitochondria dysfunction and dementia · Oxidative stress and dementia · Sex hormones and Alzheimer's disease · Melatonin and dementia · Amyloid-β (Aβ) · Hyperphosphorylated tau · Alpha-synuclein (α-synuclein)

Introduction

Alzheimer's disease (AD) is the most common cause of dementia [1]. It is estimated that over 25 million people worldwide are affected by dementia, most suffering from AD, with nearly 5 million new cases reported annually [2, 3]. The main pathological changes observed in AD brain tissue are amyloid-β (Aβ) peptide, a product of the sequential cleavage of amyloid precursor protein (APP), and hyperphosphorylated tau protein, a major component of neurofibrillary tangles (NFT) [4, 5]. Also, evidence has implicated α-synuclein (α-syn) in the pathogenesis of AD [6–8]. The main species of Aβ are Aβ-40 and Aβ-42 peptides and Aβ-42 has an affinity to aggregate, forming the toxic amyloid fibrils observed in AD [9]. AD is classified into early-onset AD (EOAD, onset < 65 years) or familial AD which accounts for about 1–5% of all cases, and late-onset AD (LOAD, onset ≥ 65 years) or sporadic which accounts for > 95% of AD sufferers. Familial AD is caused by mutations in one of these three genes: APP, Presenilin-1, and Presenilin-2, and these mutations are all connected to the excessive production of Aβ1–42 [4].

Multiple lines of evidence support a critical role for mitochondria dysfunction (MtD) and oxidative stress (OS) in AD pathogenesis. Mitochondria are one of the main sources of reactive oxygen species (ROS) and nitrogen reactive species (RNS), and MtD has been implicated in the pathogenesis and pathophysiology of AD [10, 11]. MtD could result in overproduction of ROS/RNS leading to oxidative stress (OS), a condition associated with AD [12, 13]. Both MtD and OS have been implicated in AD pathogenesis and progression [14, 15].

The objective of this review is to highlight the central role of oxidative stress and mitochondria dysfunction (MtD) in AD pathogenesis and pathophysiology. This could help improve understanding of the disease and treatment strategies.

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Mitochondria dysfunction and oxidative stress in AD

Amyloid-β (Aβ), hyperphosphorylated tau protein, and α-synuclein (α-syn)

Research indicates that MtD precedes AD pathology and mediates or plays a role in initiating pathologic molecular cascades in AD [16]. Aβ has been observed amassing in mitochondria postmortem AD brains and in the brains of AD living patients [17]. It has been observed in mitochondria prior to amyloid plaque deposition, indicating that mitochondria dysfunction plays an essential role in the etiopathogenesis of AD [17, 18]. Research indicates that Aβ blocks the transport of nuclear-encoded mitochondrial proteins to mitochondria and causes mitochondrial structural changes resulting in increased mitochondrial fragmentation, decreased mitochondrial fusion, disruption of electron transport chain, and synaptic damage [19, 20]. Evidence suggests that a lack of balance in nuclear and mitochondrial genome-encoded OXPHOS transcripts may cause a negative feedback loop decreasing mitochondrial translation and OXPHOS efficiency, triggering OS [21]. Also, research indicates α-syn plays a role in MtD in AD [6] and MtD plays an important role in promoting tau pathology in AD [22].

Furthermore, Aβ, neurofibrillary tangles, and MtD promote OS and OS is involved in the promotion of Aβ deposition, tau hyperphosphorylation, and the loss of synapses and neurons [23]. Elevated levels of OS have been found to stimulate tau phosphorylation through the activation of glycogen synthase kinase 3 (GSK-3β) [24] and influence the modification of tau protein which affects the tau fibril formation [15]. Research indicates that both MtD and OS can induce α-synuclein oligomerization and aggregation [25, 26]. Several lines of investigation have implicated melatonin, a powerful antioxidant in AD pathophysiology [27, 28]. Evidence suggests that melatonin's antioxidant properties play a critical role in AD [29, 30]. Evidence from several studies indicates that melatonin levels are significantly lower in the serum and cerebrospinal fluid (CSF) of AD patients [31–33]. Research indicates that melatonin confers a neuroprotective effect against AD via different mechanisms including inhibition of Aβ deposition, Aβ fiber formation, tau protein hyperphosphorylation, and cognitive function improvement [34]. Melatonin has been found to stimulate the nonamyloidogenic processing, suppress the amyloidogenic processing of βAPP [35], and attenuate the hyperphosphorylation of tau protein [34, 36]. Also, evidence suggests that melatonin modifies the secondary structure of the Aβ peptide and suppresses the formation of beta-sheets and amyloid fibrils [37]. Melatonin affects the secretion of soluble derivatives of APP by interfering with its maturation [38] and protects against Aβ1–42-induced neurotoxicity by decreasing the overexpression of caspase-9, caspase-3, and PARP-1 level [39]. Melatonin uses its antioxidant properties to protect against neuronal and astrocytic death induced by Aβ toxicity [40]. Melatonin has been found to protect against Aβ-induced neurotoxicity by promoting the survival of glial cells [41], reducing damage caused by OS and maintaining intracellular Ca^{2+} levels [42, 43]. Also, evidence suggests that melatonin provides neuroprotection against α-synuclein by reducing its aggregation, cytotoxicity, and oligomerization and inhibiting its fibril formation [44, 45].

Sleep disorders

Sleep disorder is common in AD and evidence suggest that disordered sleep contributes to cognitive decline and the development of AD pathology [46, 47]. Several studies have demonstrated a clear and strong relationship between MtD and sleep disorders [48, 49], indicating that MtD may contribute to sleep disorders in AD. Furthermore, evidence suggests that Aβ increases during wakefulness but sleep helps to reduce their accumulation and any disruption to the sleep–wake cycle increases OS and diminishes the clearance of Aβ [50, 51]. Research indicates that ROS in neurons play a vital role in the regulation of sleep, and a critical function of sleep is to attenuate the effects of OS [52]. Indeed, OS has been hypothesized to be the inducer of sleep which then acts as an antioxidant, attenuating the effects of OS in the body and the brain [52]. Also, melatonin plays a major role in sleep regulation. Research indicates that melatonin prevents Aβ-induced circadian alterations [53], and its supplementation ameliorates sundowning and improves sleep quality in AD patients [54, 55].

Cognitive and behavioral impairment

Cognitive impairment is an essential feature of AD pathology and MtD and OS play a critical role in cognitive impairment in AD. Research indicates that cognitive impairment is a CNS manifestation of MtD [56], and many lines of evidence suggest that mitochondrial DNA mutations play a critical role in cognitive deficits [56–58]. Findings from research indicate that certain genes disrupt mitochondrial functions and are implicated in both neurodegenerative diseases and cognitive decline [59], suggesting that MtD caused by these genes may be one of the underlying mechanisms by which they contribute to cognitive decline in AD.

Also, evidence suggests that age-related memory impairments are connected to a decline in brain and plasma antioxidant defense mechanism [60, 61]. Damage from OS has been observed in the postmortem frontal cortex of AD patients, indicating that it plays a role in executive dysfunction and cognitive decline in AD [62–64]. Furthermore, higher melatonin levels have been found to be associated with a lower prevalence of cognitive impairment in the elderly [54, 65]. Research indicates that melatonin can modulate plasticity in hippocampal pyramidal neurons [54], and evidence suggests that melatonin plays a role in hippocampal neurogenesis [66, 67]. Also, evidence suggests that melatonin slows hippocampal pathological

progression and relieves amygdala-dependent emotional memory in AD [68]. Fear conditioning is impaired in AD [69], and melatonin has been found to restore this impairment by promoting the extinction of conditional cued fear without disturbing its acquisition or expression [70].

Also, behavioral changes have been noted in AD patients. Several studies have noted aggressive behavior in AD patients [71–74]. AD patients have been found to be at a higher risk of displaying aggressive behaviors than healthy individuals or those with mild cognitive impairment [72]. Research indicates that dementias are strongly associated with aggressive and impulsive behaviors, and this behavior worsens with disease progression [71]. Notably, elevated levels of OS have been found to be associated with intermittent explosive disorder and aggression [75]. OS decreases the expression of MAO-A gene [76], whose low activity has been implicated in violence and aggression [77]. Evidence suggests that antioxidants are effective against aggression [78], impulsivity, and emotional instability [79, 80]. Antioxidant treatment of violent and aggressive male youth has been shown to reduce aggressive and violent behaviors, and improve social adjustment [81]. Autism, which is a state of elevated brain OS [82], is associated with inhibitory deficits or behavioral impairments [83, 84], and antioxidant therapy has been shown to reverse these impairments [85, 86]. Several studies have independently concluded that OS is the underlying molecular mechanism behind the behavioral deficits observed in aging [87, 88]. Also, a genetic reduction in antioxidant function in mice has been found to increase aggressive behavior [89]. All these point to the fact that OS might be the underlying driver of aggressive and impulsive behavior observed in AD pathology.

HPA axis and cortisol

Hypothalamic–pituitary–adrenal (HPA) stress axis dysregulation plays a key role in AD, and it has been associated with depression and hippocampal atrophy [90, 91]. Chronic stress is considered a risk factor for AD and evidence suggests that OS and MtD underlie its pathophysiology in AD [92]. Research indicates that mitochondrial DNA damage is strongly associated with impaired HPA-axis hyperactivity and negative feedback [93]. Evidence suggests that mitochondria play a role in HPA axis and influences the body's integrated response to psychological stress both at the cellular and organismal levels [94]. Acute and chronic stressors modulate many aspects of mitochondrial biology, and chronic stress exposure can result in MtD [95, 96], suggesting HPA-axis hyperactivity could promote MtD.

Also, evidence suggests that OS is the culprit in HPA-axis dysfunction as part of the aging process [97]. Research indicates that activation of the HPA axis induces OS [98] and OS could result in impaired HPA axis [97]. In addition, evidence suggests that melatonin modulates HPA-axis dysregulation [99].

Cytokines and neuroinflammation

Research indicates that inflammation plays a crucial role in the development and progression of AD neurodegeneration and different cytokines, including interleukins, TNF-α, TGF-β and IFN-γ, IL-1β, IL-6, IL-12, and IL-18, play a critical role in AD pathogenesis [100, 101]. Cytokines can influence APP by affecting its expression levels and amyloidogenic processing and/or Aβ aggregation. Also, cytokines and chemokines can influence kinases' activities, leading to abnormal TAU phosphorylation [102].

Notably, MtD in microglial cells has been found to inhibit portions of the IL-4-induced alternative response, which is associated with a reduction of inflammation [103], suggesting that MtD in microglial cells might contribute to pro-inflammatory mediator expression and neuronal death in neurodegenerative diseases including AD [104]. Furthermore, evidence suggests that OS and inflammation are inextricably linked. Neuroinflammation leads to increased OS which causes subsequent inflammation [105], and antioxidants protect neurons by reducing OS and chronic inflammation in AD [106]. Chronic OS triggers alterations in the differentiation and number of $CD4^+$ T cells, leading to an increase in Th1 and Th17 response and contributing to the development of neuroinflammation and poor inflammatory response in neurodegenerative diseases such as AD [107]. Evidence suggests that altered regulation of microRNAs cause neurodegeneration in AD and OS and pro-inflammatory cytokines act together to modulate the expression of microRNAs [106]. Antioxidant treatment has been shown to attenuate cytokine-induced inflammation, suggesting that OS promotes their activity [108]. Research indicates that melatonin has strong anti-inflammatory properties [109, 110]. Evidence suggests that melatonin modulates the expression of different inflammatory mediators including both pro- and anti-inflammatory cytokines [111, 112].

Psychiatric disturbance

Neuropsychiatric symptoms are common and an essential component of AD pathology [113, 114]. MtD has been hypothesized to be the etiological basis of neuropsychiatric disorders [115, 116], and numerous lines of evidence suggest that MtD plays an important in psychiatric disorders [117–123], indicating that it might contribute to AD psychiatric disturbances. Indeed, research indicates that psychiatric symptoms are a presenting feature of mitochondrial disorders [118, 124]. Animal research has found that the deletion of certain mitochondrial genes in the 22q11.2 genomic region results in symptoms associated with neuropsychiatric diseases [125].

Also, several lines of evidence indicate that OS plays a critical role in psychiatric disorders [126–131], indicating that

it may contribute to such disorders in AD. Indeed, OS has been hypothesized to be a convergence point for genetic and environmental susceptibilities in both neurodegenerative and psychiatric disorders [132].

Neurotransmitters

Neurotransmitters are altered in AD including GABA and glutamate. Research indicates that MtD plays an important role in glutamate-induced neuronal excitotoxicity [133], by impacting upon the ability of the neuron to withstand excitotoxic stress [134, 135]. Findings from research indicate that cytosolic Ca^{2+} elevations and mitochondrial Ca^{2+} overload, the hallmarks of excitotoxic conditions, are paralleled by MtD [133]. Furthermore, evidence suggests that OS contributes to glutamatergic excitotoxicity in AD by modifying key components of the glutamate system, and Aβ plays an essential role in this process [136, 137]. Also, melatonin affects the glutamate–GABAergic system. It regulates the NMDA receptor [138] and controls intracellular free Ca^{2+} by directly binding to calmodulin [139]. Melatonin has been found to protect against Aβ neurotoxicity by decreasing glutamate excitatory tonus, and the activation of GABA receptors [140].

Vitamin D

Several lines of investigation have found an association between VD deficiency and risk of AD [141–143]. Evidence suggests that VD and its receptors (VDR) regulate APP processing pathway, are co-localized with APP in neurons, and play a critical role in Aβ homeostasis and the prevention of Aβ toxicity [143–146]. Also, evidence suggests that VD inhibits α-synuclein aggregation [147].

Notably, VD receptors protect mitochondria optimal function and play a central role in protecting cells from OS [148]. VD has strong antioxidant properties [149, 150]; its deficiency/insufficiency is associated with increased OS [151]. All these point to the fact that VD deficiency promotes OS and MtD in AD.

Hormones (TH and sex hormones)

Several hormones have been implicated in AD pathology including thyroid hormones (TH) and sex hormones (luteinizing hormone (LH), progesterone, estrogen, and testosterone). Research indicates that thyroid dysfunction plays an essential role in AD pathology [152]. TH decreases the expression of APP genes in the brain and its reduced activity on the APP gene increases APP expression and the number of processed APP products [153–155]. Hyperthyroidism has been associated with AD [156], and research indicates that hypothyroidism increases vulnerability to the development of amyloid deposits [157]. Furthermore, thyrotropin-releasing hormone (TRH) has been found to be depleted in AD brains [158]. Evidence suggests that TRH suppresses tau phosphorylation in hippocampal neurons and reduced TRH gene expression results in elevated tau and GSK-3β, a critical enzyme necessary for the phosphorylation of tau and tau protein [159]. TRH administration results in significant reduction in tau phosphorylation in hippocampal neurons [158, 159].

Also, sex hormones have been found to attenuate Aβ-induced mitochondrial deficits and AD tauopathy [160]. Findings from research indicate that they possess significant α-synuclein anti-aggregation properties and fibril-destabilizing effects [161]. Estrogen has been found to elevate the levels of soluble amyloid beta-protein precursor alpha (sβAPPα), the secreted form of AβPP, and to reduce cerebral Aβ levels [162]. Estrogen and progesterone have been found to modulate the expression levels of several Aβ clearance factors [163]. Furthermore, findings from research suggest that there is increased estrogen receptor-α–tau interaction in AD brain, indicating that the sequestration of ERα by tau abnormality is at the heart of the loss of estrogen neuroprotection in AD [164]. Estrogen has anti-inflammatory properties and is involved in the inhibition of proinflammatory cytokines, as well as the regulation of cytokine- and chemokine-mediated neuroinflammatory response in the CNS [165, 166]. Also, low levels of endogenous progesterone have been associated with dementia and supplementation has been demonstrated to reduce total tau levels [167]. Evidence suggest that LH modulates the processing of Aβ precursor protein and Aβ deposits in the brain and may promote the development of AD through amyloid-dependent mechanisms [168, 169]. Evidence suggests that low testosterone level is associated with an elevated risk of AD development in elderly men [170], and in brain levels of AD men, testosterone has been found to be inversely correlated with soluble Aβ [171]. Research indicates that testosterone attenuates Aβ toxicity through estrogen-independent mechanisms [172, 173]. In men with AD neuropathology, testosterone supplementation has been found to stimulate the secretion of the nonamyloidogenic APP fragment, sβAPPα and reduce neuronal secretion of Aβ peptides [174]. Furthermore, androgen deprivation therapy has been found to elevate plasma levels of Aβ and the risk of developing AD [175].

Notably, evidence suggests that TH reduces OS and can improve mitochondrial function [176], indicating that its dysfunction could promote OS and MtD. Research indicates that OS plays an essential role in the pathogenesis of different thyroid diseases [177]. Hyperthyroidism promotes a high metabolic rate triggering OS [178], and hypothyroidism is recognized to be a state of OS [179] suggesting that OS might the underlying mechanism that drives TH dysfunction in AD pathology. Also, evidence suggests that mitochondria are essential in steroidogenesis, and sex steroid hormones can regulate mitochondrial biogenesis and function, indicating that

impairment of mitochondrial function could affect optimal sex steroid hormones action and vice versa [180]. Research indicates that sex hormones modulate OS in AD [181] and evidence suggests that OS can reduce testosterone and gonadotropin levels [182]. Several lines of evidence indicate that testosterone can decrease OS and cell damage [183, 184]. Research has described the antioxidant properties of estrogen indicating that it attenuates OS [185]. Furthermore, findings from animal research indicate that antioxidant (melatonin) modulates the number of estrogen and progesterone receptors [186]. Evidence suggests that melatonin suppresses LH in postmenopausal women [187]. In addition, melatonin increases thyroglobulin mRNA and protein expression, and protect against thyroid disorder by ameliorating OS involved in thyroid diseases [188, 189]. All these points to the fact that MtD and OS may be the underlying mechanism that drives TH and sex hormones role in AD pathology.

Other factors

Many recognized risk factors of AD are well documented to promote OS and MtD, indicating that they might be their link to the disease. As an example, cholesterol, a risk factor of AD, has been found to induce OS [190, 191] and inhibition of mitochondrial complexes (I and II) activity has been observed in the cortex of genetic models of hypercholesterolemia [192, 193]. Cholinergic dysfunction is associated with AD and several lines of evidence suggest that OS is the cause of cholinergic dysfunction [194, 195]. Evidence indicates that obesity and obesity-related comorbidities (e.g., insulin resistance, leptin dysfunction, hyperglycemia, and type 2 diabetes) increase the risk of cognitive impairment and AD [196–198]. Research indicates that obesity results in MtD [199] and is a state of chronic OS [200, 201]. Smoking has been implicated in the risk of AD and evidence suggests that OS may underlie its pathophysiology in AD [202, 203]. Moreover, research indicates that in AD, there is increased accumulation of metals in the brain (Fe, Al, and Hg), and evidence suggests that they cause MtD [204, 205], and OS underlies their role in AD pathogenesis and pathophysiology [206, 207].

Discussion

Currently, AD ranks number six in the cause of death in America and it is the fifth leading cause of death in elderly Americans (65 years or older) [208]. In the USA, after cancer and coronary heart disease, AD is the third most costly disorder exceeding $US100 billion annually [208]. The cost of AD was approximately $US216 billion in 2012 in the USA and it is expected to surpass $203 billion in 2013 [208]. Furthermore, the world faces an unprecedented global epidemic of AD as the number of elderly people in the population increases [209]. Currently, someone in America develops AD every 68 seconds, but by 2050, that is expected to drop to as low as every 33 seconds, or nearly a million new cases annually [210]. Globally, the incidence of AD is expected to rise dramatically from the current 36 million sufferers to as much as 115 million by 2050 [211]. The projected spike in AD prevalence and the associated health, social, and economic burden that accompanies it makes the need to better understand the etiopathogenetic and neuropathophysiological basis of the disease to be extremely critical as such understanding is crucial to reducing its burden and arresting its projected spike.

The current review's elucidation of the role of MtD and OS in AD pathology is an effort in that direction. MtD and OS play a central role in AD pathology and influence all facets of the disease and underlie the pathogenic mechanism of many factors. There are, however, certain limitations in this review that must be addressed. The review proposes that many AD risk factors including smoking, obesity, diabetes, cholinergic dysfunction, thyroid dysfunction, VD, sex hormones, and depression are connected to AD via MtD and OS. Although it is true that these conditions promote MtD and OS and MtD and OS might be the likely pathogenic mechanism behind their association with AD, there is no direct and definitive proof that this is the case. Clearly, more research is needed to know their definitive pathogenic mechanism in AD.

Recommendations

The understanding that MtD and OS play a central role in AD pathology means that treatment strategies should be geared toward improving mitochondrial function and reducing or reversing OS. To this end, clinicians should check and treat thyroid dysfunction, total antioxidant capacity (TAC), melatonin levels, VD deficiency, sleep-related disorders, depression, and CoQ10 levels in AD patients and those showing early signs of AD pathology. Assessing serum CoQ10 levels should be considered as lower serum CoQ10 level could be useful for predicting the development of AD [212].

Cessation of activities or behavior that promote OS and increase in activities or behavior that promote antioxidant defense should be recommended. Lifestyle changes to reduce OS such as exercising to maintain ideal body weight and abstinence from alcohol and smoking should be recommended for the elderly. Also, a diet with high glycemic index or high glycemic load should not be advised because evidence suggests that it increases OS [182, 213]. Instead, a Mediterranean diet (MeDi) should be recommended as evidence indicates that it decreases OS [214, 215], and adherence reduces the risk for AD [216–218] and is associated with lower mortality in AD [217]. To slow cognitive decline and the risk of AD, cognitive and leisure activities should be encouraged for people 60 and older [219]. Cognitive training in the form of reading and solving arithmetic problems should be encouraged to improve cognitive function [220]. To improve sleep,

melatonin treatment and a warm shower performed before bedtime should be recommended [221].

Finally, although the risk factors for AD have increased in the last few decades, research indicates that the prevalence and inferred incidence of dementia and severe cognitive impairment might have decreased in higher income countries, and the scale of the reduction is substantial [222]. This reduction is believed to be mediated by societal changes such as improvements in education, and prevention and treatment strategies in recent decades [222]. This shows that improved prevention, treatment, and education can change AD incidence projections. So more must be done in this direction especially in low- and middle-income countries.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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