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Targeting Mitochondria in Alzheimer disease: Rationale and Perspectives

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Abstract

A decline in mitochondrial function plays a key role in the aging process and increases the incidence of age-related disorders, including Alzheimer Disease (AD). Mitochondria - the power station of the organism- can affect several different cellular activities, including abnormal cellular energy generation, response to toxic insults, regulation of metabolism and execution of cell death. In AD subjects, mitochondria are characterized by impaired function such as lowered oxidative phosphorylation, decreased adenosine triphosphate (ATP) production, significant increased reactive oxygen species (ROS) generation, and compromised antioxidant defense.

The current review discusses the most relevant mitochondrial defects that are considered to play a significant role in AD and that may offer promising therapeutic targets for the treatment/prevention of AD. In addition, we discuss mechanisms of action and translational potential of some promising mitochondrial and bioenergetic therapeutics for AD including compounds able to potentiate energy production, antioxidants to scavenge reactive oxygen species and reduce oxidative damage, glucose metabolism and candidates that target mitophagy. While mitochondrial therapeutic strategies have shown promise at the preclinical stage, there has been little progress in clinical trials. Thus, there is an urgent need to better understand the mechanisms regulating mitochondrial homeostasis in order to identify powerful drug candidates that target “in and out” the mitochondria to preserve cognitive functions.

1. Introduction

Alzheimer disease (AD), an irreversible neurodegenerative brain disorder, is the most common cause of dementia that affects the elderly. AD is characterized by neuronal degeneration in selective brain regions involved in cognition (hippocampus, entorhinal and frontal cortex) and emotional behaviors (amygdala, prefrontal cortex, hypothalamus). An estimated 5.8 million Americans of all ages are living with Alzheimer’s dementia in 2019. This number includes an estimated 5.6 million people age 65 and older and approximately

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200,000 individuals under age 65 who have younger-onset AD. [1]. The main pathological changes observed in AD brain tissue are senile plaques (SP), neurofibrillary tangles (NFT) and loss of synapses [2]. SP are composed of filamentous aggregates of amyloid-beta peptide (Aβ), the resulting cleavage by-product of amyloid protein precursor (APP). The main species of Aβ are Aβ−40 and Aβ−42 peptides; Aβ−42 has a greater affinity to aggregate, forming the toxic Aβ oligomers and amyloid fibrils observed in AD [3]. NFT are composed of hyperphosphorylated tau protein aggregates that accumulate in the neuronal cytoplasm, leading to destabilization of microtubules and of loss of axonal transport [4]. Late-stage AD is often preceded by three stages of progression characterized by gradual increase of neuropathological hallmarks (SP and NFT) starting from preclinical AD (PCAD) to amnestic mild cognitive impairment (MCI) and early AD (EAD) [5, 6].

Research demonstrates that diabetes (T2DM), stroke, atherosclerosis, obesity, high-fat diet, metabolic syndrome and oxidative stress, among other factors, increase the risk of AD [7, 8]. The well-known hallmarks of AD: dysfunctions in glucose metabolism, bioenergetics, and in mitochondrial integrity, play distinct roles in AD pathogenesis [9–12]. Decline in glucose metabolism and mitochondrial function are detected decades prior to clinical features of the disease making them potential biomarkers and therapeutic targets for prevention [13, 14].

Mitochondria are double-membraned organelles that provide a wide variety of biochemical services to the cell. Mitochondria are responsible for large amounts of cellular energy production derived from the biochemical processes of glucose metabolism, fatty acid oxidation, and respiration. These organelles provide most of the cellular adenosine triphosphate (ATP) demand by oxidative phosphorylation [15]. The mitochondrial oxidative phosphorylation (OXPHOS) system is the final biochemical pathway producing energy in the form of ATP by consuming oxygen. From complex I and II, electrons are transferred to complex III by Coenzyme Q, the glycerophosphate dehydrogenase, and the electron transferring flavoprotein. From complex III, the electrons are transferred to oxygen via cytochrome c and complex IV. Simultaneously, an electrochemical proton gradient is built across the inner mitochondrial membrane (by complex I, III, and IV), and the generated proton motive force is used by complex V to produce ATP. Noteworthy, these organelles also critically regulate other essential cellular functions including synthesis of pyrimidines and purines, synthesis of heme, nitrogen balance regulation through the urea cycle, ketone bodies production, sex hormone production, processing of xenobiotics, redox balancing, and regulation of the apoptotic machinery. Given the significance of mitochondria to the preservation of so many pathways in cells, it is not surprising that there exist multiple levels of control that enable a cell to coordinate its net mitochondrial activity with fuel sources, biosynthetic demands, proliferation rates, and external stimuli [16].

Unfortunately, the high demand for energy that drives ATP mediated cellular functions, also generates a significant amount of reactive oxygen species (ROS), whose amounts become highly toxic in disease-related, dysfunctional mitochondria. Increased ROS can negatively affect specific mitochondrial components, including mitochondrial DNA (mtDNA), membrane lipids, and proteins involved in oxidative phosphorylation [10, 11, 17]. In conditions of uncontrolled oxidative/nitrosative stress (OS/NS) in AD pathology, proteins

are subjected to post translational modifications (PTMs) generally associated with loss of function [18].

Redox proteomics techniques in AD brain allowed the identification of specific mitochondrial proteins, including some in the mitochondrial oxidative phosphorylation machinery, that are targets of oxidative modifications during the neurodegenerative process. ATP synthase alpha, manganese superoxide dismutase (MnSOD), malate dehydrogenase and VDAC were identified modified by both protein carbonyls, 3-NT and HNE-bound, in the early stages and in the late stage of AD, in MCI and EAD [19–23]. In agreement with this view, Eno1 and ATPase activities are reportedly decreased in AD brain [21]. ATP synthase, the last complex of the electron transport chain (complex V), is an essential enzyme in the inner mitochondrial membrane, and plays a key role in energy metabolism. Its oxidative modifications modify its conformation leading to the inactivation of the complex. Defective function of ATP synthase activity secondary to oxidative modification significantly contributes to lower ATP levels, possibly resulting in electron leakage and increased ROS production, suggesting an alternate rationale for the OS observed in AD [24]. Dysfunction of single complexes of the respiratory system are frequently accompanied by deleterious side effects like loss of mitochondrial membrane potential (MMP) and consequently decreased ATP levels, but also production of ROS [25]. Dysfunction of single enzyme complexes, ROS production, mitochondrial permeability transition pore (mPTP) opening, elevated apoptosis, in addition to structural alterations, and a diminished mitochondrial content are believed to critically contribute to the onset and progression of neurodegenerative pathology in AD [26, 27]. Consonant with the above, deficiency in several mitochondrial key enzymes is well documented in AD. These include enzymes involved in the TCA cycle, such as ketoglutarate dehydrogenase complex and pyruvate dehydrogenase complex as well as those involved in the electron transport chain of oxidative phosphorylation such as cytochrome oxidase. Taken together, the above discussion suggests that targeting mitochondria and brain bioenergetics could be a disease-modifying strategy to prevent and/or delay the progression of AD. Targeting brain metabolism and mitochondrial function are relevant to the hypometabolism and impaired mitochondrial bioenergetics that are among the earliest pathogenic events in AD pathology [10].

As highly dynamic organelles, mitochondria are characterized by a balance of fusion and fission, transport, and mitophagy, all of which are essential for maintaining mitochondrial integrity and function. Altered mitochondrial transport is one of the pathogenic changes in major neurodegenerative diseases including Alzheimer disease [28]. In mature neurons, ~20–30% of axonal mitochondria are motile while the remaining two thirds are stationary [29]. Long-distance transport of mitochondria along microtubules (MTs) between the soma and distal processes or synapses is dependent on MT-based motor proteins, which drive their cargoes via mechanisms requiring ATP hydrolysis [30]. Efficient regulation of mitochondrial transport is essential for recruiting and redistributing mitochondria to specific domains with high-energy demands, such as synaptic terminals. Mitochondrial transport plays a critical role in removing aged and damaged mitochondria and replenishing them with healthy ones at distal regions of neurons. Several lines of evidence support the hypothesis that impaired axonal transport plays an important role in the pathogenesis of AD [31]. Axonal

degeneration in patients with AD is characterized by swollen regions where abnormal amounts of organelles (including mitochondria) accumulate [31].

In this review we discuss current strategies targeting different traits of dysfunctional mitochondria to prevent/slow the development of AD. In particular, the following aspects will be taken into consideration (as shown in Figure 1):

1.1 Mitochondrial bioenergetics.

Glycolysis, the citric acid cycle, and mitochondrial oxidative phosphorylation are coordinated to generate ATP. Preclinical *in vitro* and *in vivo* AD models have demonstrated reduced glucose utilization and a decline in mitochondrial function, including reduced mitochondrial respiration and decreased metabolic enzyme expression and activity [32–34]. Further, a well-documented indicator of compromised mitochondrial function is oxidative stress [35] that if paralleled by decreased antioxidant defense capacity [36] exacerbates oxidative damage [35, 37]. Therapeutic candidates that target glucose metabolism and/or the electron transport chain (ETC) together with antioxidant candidates are posited to be able to rescue mitochondrial function and reduce ROS leakage, thereby modulating AD pathology and murine models thereof.

1.2 Mitochondrial homeostasis.

Prolonged deficits in bioenergetics together with elevated oxidative stress, as observed in AD, lead to activation of apoptotic pathways, aberrant mitochondrial biogenesis, impaired mitophagy, and, ultimately, neuronal death [38]. The balance between mitophagy and mitochondrial biogenesis provides an efficient mitochondrial turnover to eliminate dysfunctional mitochondria while maintaining efficient functional organelles [39]. The proper modulation of mitochondrial homeostasis by compounds able to target either its synthesis and maintenance or its degradation, in response to stresses conditions arising from AD pathology, represent a valid and effective approach to slow reduce brain damage.

2. Mitochondrial bioenergetics

2.1 Targeting ETC: J147

Several studies showed deficit of mitochondrial functions during aging and neurodegeneration [37, 40, 41]. Accumulating evidence support the notion of decreased expression and activity of enzymes involved in mitochondrial bioenergetics together with compromised electron transport chain complex activity and reduced ATP synthesis in AD [42]. In addition to the lowered mitochondrial bioenergetic, impairment of oxidative phosphorylation is associated with increased free radical production and the resultant oxidative damage [43]. These latter effects are likely to be caused by decreased activity of mitochondrial electron transport chain enzymes or F1F0-ATPase (ATP synthase complex V) in addition to reduced ATP levels, ultimately leading to neuronal cell death [44].

Recent studies highlight the promising therapeutic efficacy of J147 to prevent/slow the development of Alzheimer neurodegeneration. Chin and colleagues identified mitochondrial α- F1 subunit of ATP synthase (ATP5A) as a high affinity molecular target of J147 [45].

J147, first discovered by the Schubert group [46], is a synthetic derivative of curcumin with a cyclohexyl-bisphenol A moiety, that has neurotrophic activity that curcumin lacks. J147 has been identified by an alternative drug discovery scheme, based upon efficacy in multiple cell culture models of age-associated pathologies. Initially, Schubert and colleagues showed that J147 has neurotrophic and memory-enhancing activities in rat hippocampal neurons [46]. A number of different assays have been performed to evaluate the trophic factor activity in a model of a glutamate-induced oxidative stress and amyloid toxicity. Neuroprotective properties of J147 were mainly associated with an increase in the level of brain derived neurotrophic factor (BDNF) together with the expression of BDNF-responsive proteins, including PSD95, the enhancement of long term potentiation (LTP), the reduction of oxidative stress and inflammation and reduced deposition of amyloid plaques [46]. Further, the J147 broad cognitive enhancing effects were assessed via Y-maze for working memory, Morris water and Barnes mazes for spatial memory and novel object recognition test for recognition memory [46].

Based on this promising evidence, animal studies further demonstrated that J147 administration led to enhanced memory and restored cognition in APPswe/PS1ΔE9 mice as well as in the rapidly aging senescence-accelerated mouse prone (SAMP8) dementia mouse [47, 48]. J147 treatment enhanced LTP, potentiated learning and memory in both normal and AD transgenic animals and maintained synaptic proteins while at the same time attenuated inflammatory events and reduced soluble Aβ levels in AD transgenic mice. Based on the failure of different drug clinical trials in AD, the pleiotropic activities of J147 make this compound a promising therapeutic agent in AD research. Indeed, J147 is potent, has good medicinal chemical properties for a drug that targets the CNS, is apparently safe, and is orally active.

Growing is the interest to elucidate the mechanism through which J147 is able to modulate the activity of the ATP synthase complex as reported by Chen *et al.* [46]. New emerging concepts suggest that, in addition to its well-recognized role in energy production, the mitochondrial H^+-ATP synthase is a primary hub of cellular homeostasis regulating the production of signaling molecules that sense the nucleus in response to multiple stress conditions. The activity of the H^+-ATP synthase is regulated by cellular energy demand, by the covalent modification of its subunits and by different metabolites and regulatory proteins that can interact with the enzyme [49].

Among the different subunits that associate to form the transmembrane ATPase complex, J147 binds selectively the ATP5A subunit, leading to approximately 20% decreased activity of ATP synthase [46]. The effect on ATP synthase enzyme kinetics mediated by J147 was initially tested in isolated bovine heart mitochondria. The inhibitory activity of J147 is the result of its ability to bind allosterically to ATP synthase, thereby influencing the motions and activity of the different subunits of this protein. These conformational changes regulate the activity of ATP synthase, mainly ATP hydrolysis and synthesis. However, modulation of ATP synthase activity can be achieved either by siRNA- targeted knockdown of ATP5A or by overexpression of its endogenous inhibitor, ATPase inhibitor factor 1 (IF1). This approach has been applied to test if, in both conditions, protection in different models of neurotoxicity can be elicited by J147 administration. By modulating the activity of ATP

synthase, J147 protects neuronal cells from toxic events associated with the aging brain while regulating the levels of other molecules, including ATP [46]. As noted, similar findings were obtained by overexpression of IF1 or by silencing of ATP5A. All together, these results demonstrate that J147 binds to and partially inhibits the activity of the mitochondrial ATP synthase.

Paradoxically, novel evidence suggests that inhibition of ATP synthase can evoke a retrograde, ROS-mediated pro-survival response [50], without being detrimental to the plethora of ATP mediated cellular functions. This response is thought to occur via signaling cascades initiated by increased ROS production which in turn activate HIF-1 (hypoxia-inducible factor 1)-mediated signaling [50]. The concept that mild mitochondrial stress can protect the cell from subsequent toxic insults, is a phenomenon named “mitohormesis” [51–53]. Mitohormesis is the result of adaptive intracellular changes in response to a mild mitochondrial stress that activates cytoprotective pathways to compensate for the primary causative event. These adaptive alterations result in long-lasting broad metabolic and molecular changes that finally lead to increased lifespan and health span [53, 54]. The mitohormetic response requires the activation of signaling pathways that sense mitochondrial function and inform the nucleus to trigger the adequate cellular programs to compensate for the stress [54]. This phenomenon occurs in different experimental conditions. For example, treatment of worms with low levels of paraquat increases lifespan, while treatment with higher levels of the drug actually reduces lifespan, suggesting the existence of a hormetic response when the generated ROS are mild [51, 52], in agreement with the notion that the amount of generated ROS influence lifespan. The predominant link between mitochondria and longevity may rely on a tuned balance between increased synthesis and degradation of mitochondria that results from the efficiency of the quality control machinery, reviewed in [55].

It is likely that, as part of the “mitohormetic response”, mitochondrial retrograde signaling by limiting cellular ATP availability and enhancing the production of ROS - through “partial” inhibition of the H^+-ATP synthase - contribute to preserve tissue homeostasis and healthy lifespan.

Interestingly, recent studies have highlighted a role for ATP synthase in the regulation of mTOR and lifespan extension in flies and worms [56, 57]. Inhibition of the H^+-ATP synthase by metabolites and by other mechanisms, some still unknown, contributes to extending lifespan in different organisms through reduced mTOR signaling mainly associated with increased proteostasis reduced oxidative damage and improved insulin signaling [58, 59]. Indeed, ROS-mediated signaling is well-recognized to be a common pathway in lifespan extension. Further, inhibition of mTOR is known to occur via activation of AMP activated protein kinase (AMPK) [60], as indexed by increased phosphorylation of Thr172 on the α- subunit, lowering activity of some ATP-consuming pathways while promoting ATP synthesis through others such as fatty acid oxidation. In agreement with this view, J147 induces a time-dependent activation of AMPK (pAMPK) through Ca^{2+}/CaM-mediated activation of CamKK2. pAMPK, in turn, phosphorylates the regulatory-associated protein of mTOR (raptor) at Ser792, thus mTOR complex 1 (mTORC1). The increased Ser792 phosphorylation of raptor was observed in different cell types treated with J147 [45].

Raptor-mediated inhibition of mTORC1 activity dampens ATP expenditure by decreasing S6-kinase and resulting in reduced protein translation and increased autophagy. AMPK-mediated phosphorylation of acetyl-CoA carboxylase (ACC1) stimulates ATP production by inhibiting fatty acid biosynthesis and increasing the rate of fatty acid β-oxidation [61]. J147 decreases S6K activity and increases ACC1 phosphorylation in both cell types. Overall, these data show that the AMPK/mTOR signaling pathway, known to promote aging, is downstream of J147. Importantly, siRNA- mediated knockdown of ATP5A in MC65 cells phenocopied the effects of J147 on AMPK/mTOR signaling. All the above reported mechanisms highlight the pleiotropic properties of J47 that turns out to be effective in metabolic regulation as well as in aging and dementia.

In the elderly and in patients with AD, mitochondrial dysfunction leads to reduced levels of ATP which may contribute to disease progression [62, 63]. It is worth mentioning that partial inhibition of ATP synthase by J147 does not affect ATP levels in HT22 cells nor the composition of OXOPHOS machinery and the rate of glycolysis.

Thus, J147 is a promising novel therapeutic agent with the potential to be tested as an AD drug able to slow disease progression through neuroprotection as well as providing amelioration of cognition functions.

2.2 Targeting glucose metabolism: Insulin, Thiamet G

Brain hypometabolism and deficits in mitochondrial bioenergetics have been described in both preclinical and clinical AD studies. The observed reduction in cerebral glucose utilization, using fluoro-2-deoxyglucose positron emission tomography (FDG-PET), is an early sign of bioenergetic decay in the prodromal state of AD [14, 64]. *In vitro* and *in vivo* pre-clinical AD models indicate that deficits in mitochondrial function, metabolic enzyme expression and activity, cerebral glucose metabolism, and free radical scavenging are coupled with mitochondrial Aβ load and Aβ-binding alcohol dehydrogenase (ABAD) expression [13, 40, 41, 65]. Increasing evidence demonstrates that reduced glucose utilization and deficient energy metabolism occur early in the course of disease, thus suggesting a role for impaired insulin signaling in the pathogenesis of neurodegenerative diseases [10, 40]. Insulin plays an essential role in energy metabolism in the brain, with receptors densely populating the medial temporal regions of the brain required for memory formation. Additionally, insulin-sensitive glucose transporters (GLUT4) are expressed in regions supporting memory and cognitive function [66]. Insulin resistance, which is the reduced sensitivity of insulin in targeted tissues important for cognitive function, increases the risk of dementia [47]. Examination of postmortem AD and amnestic mild cognitive impairment brain uncovered key signs of brain insulin resistance, i.e., reduced insulin receptor (IR) and increased serine phosphorylation (inhibitory) of insulin receptor substrate 1 (IRS1), particularly in the hippocampus, cortex, and hypothalamus [59, 67, 68]. Further, the impairment of insulin responsiveness has been documented to correlate with dysfunctional glucose utilization in AD brain [69, 70]. The restoration of insulin signaling by using insulin therapy can lead to improved cognitive performances [66]. Indeed, enhancing central nervous insulin action has been shown to improve memory functions in animals as well as in humans [71, 72]. Treatments of animal models of AD by intranasal

insulin demonstrated the reduction of Aβ and tau pathology, the rescue of IR and IRS1 signaling and of mTOR pathway, and consequent increased cognitive performance [68, 73]. Since 2008 few clinical studies tested insulin treatment on MCI and AD patients. Despite a few controversial results concerning the reduction of pathological hallmarks, most of the studies demonstrated that improvement in delayed, verbal and working memory and the preservation of brain glucose uptake [74–77].

A further mechanism that links reduced glucose uptake with impaired mitochondria is protein O-GlcNAcylation, a common post-translational modification of nucleocytoplasmic proteins [78]. It was recently recognized that O-GlcNAc levels modulate mitochondrial function, motility and distribution, with O-GlcNAc being proposed to act as a nutrient sensor [79, 80]. Several mitochondria proteins are regulated by O-GlcNAcylation, which has been shown to be markedly decreased in AD brain. Thus, aberrant O-GlcNac levels might contribute to the “mitochondrial pathology” in AD [81–83]. The pharmacological modulation of O-GlcNAcylation levels has been achieved in recent studies by different compounds able to interact with the enzymes that control GlcNAc cycling, OGA and OGT [84]. In the context of AD pathology Thiamet-G, a potent and specific inhibitor of OGA, had been tested in different *in vitro* and *in vivo* models. The treatment of mouse models of AD and tauopathy by Thiamet G led to the reduction of Aβ and tau pathology and to the rescue of cognitive deficits [85–87].

2.3 Targeting mitochondrial ROS production

Several compounds such as vitamin E and vitamin C are known to reduce the amount of ROS leaked by mitochondria [88]. Vitamin E, a lipophilic and membrane-associated antioxidant, may be a beneficial supplement for AD patients [89]. However, the therapeutic effects mediated by the administration of vitamin E are still unclear due to conflicting results. Many studies have shown a decrease in vitamin E levels in aging and dementia with a correlation to memory loss [90, 91]. Supplementation of vitamin E does increase levels of this vitamin in AD and decreases susceptibility of lipoproteins to oxidation [92]. Vitamin E was shown to decrease Aβ and tau levels in Tg2576 mice, [89]. Dysken et al. found that vitamin E could significantly slow the rate of cognitive decline in persons with mild to moderate AD [93]. However, in a study on aged male C57BL/6J mice, the supplementation of a single antioxidant had little or no effect in increasing cognitive function, and it was shown that age-related cognitive dysfunction could be reversed by supplementing the mice with vitamin E and Coenzyme Q10 (CoQ) [94]. Further, vitamin E, supplemented with vitamin C, was shown to correlate with lower prevalence and incidence of AD in the elderly population [89, 91, 92].

α-lipoic acid (LA) is a powerful antioxidant that has the ability to recycle other antioxidants such as vitamins C and E. LA is a naturally occurring cofactor of mitochondrial enzymes α-ketoglutarate dehydrogenase and pyruvate dehydrogenase, and has been found to increase acetylcholine (ACh) production and scavenge the toxic products of lipid peroxidation [95]. In a clinical trial conducted by Hager et al., nine patients with probable AD were given 600 mg of LA daily, as well as either donepezil or rivastigmine [96, 97]. Results demonstrated

that cognitive decline was slowed in these patients after the LA was prescribed in comparison to AChEIs alone.

CoQ10 is a co-factor of mitochondrial uncoupling proteins that acts as a potent antioxidant and blocks apoptosis by inhibiting the permeability transition pore (PTP) [98]. CoQ10 pretreatment prevents a decrease in mitochondrial transmembrane potential and reduces mitochondrial ROS generation [99]. Aged PS1 transgenic mice fed CoQ10 for 60 days show reduced Aβ overproduction and intracellular Aβ deposits [100].

A promising new mitochondria-targeted antioxidant is mitoquinone mesylate, more commonly known as MitoQ [101]. Mito Q was tested to prevent AD-like pathology in mouse cortical neurons in cell culture and in a triple transgenic mouse model of AD (3xTg-AD). MitoQ attenuated β-amyloid (Aβ)-induced neurotoxicity in cortical neurons and also prevented increased production of reactive species and loss of mitochondrial membrane potential ($\Delta\psi m$) [101]. MitoQ accumulates in vivo and was specifically designed to protect the mitochondrial membrane from the severe damage that can be caused by lipid peroxidation and oxidative stress [102]. The main antioxidant component of MitoQ is ubiquinone, identical to the active antioxidant found in CoQ, which is selectively taken up by mitochondria due to the membrane potential produced, resulting in an almost thousand-fold concentration of the drug inside the mitochondrial matrix [103].

3. Mitochondrial homeostasis

3.1 Targeting mitochondrial biogenesis: Resveratrol, Metformin

Recent discoveries have raised attention to mitochondrial biogenesis as a potential target to treat diseases that up to the present do not have an efficient cure. Mitochondrial biogenesis is defined as the process via which cells increase their individual mitochondrial mass. Mitochondrial biogenesis plays an important role in maintaining mitochondrial numbers, cell renewal, adapting to cell damage and the demand for energy supply. Peroxisome proliferator-activated receptor-gamma (PPARg) coactivator-1alpha (PGC-1a) has been extensively described as the gatekeeper of mitochondrial biogenesis and plays a pivotal role in the energy balance and metabolism [104]. PGC-1a interact with two key nuclear transcription factors, nuclear respiratory factor 1 and 2 (NRF1 and NRF2). NRF1 and NRF2 activate the mitochondrial transcription factor A (TFAM) and bind to promoter regions of nuclear genes encoding subunits of the four complexes in the ETC and ATP synthase, increasing the assembly of the respiratory apparatus.

The activity of PGC-1a can be regulated by two metabolic sensors SIRT1 (sirtuin 1) or AMPK through deacetylation and phosphorylation, respectively [105]. Sirtuins (SIRT1–7) comprise a NAD^+ dependent histone deacetylase family of proteins. SIRT1, SIRT6 and SIRT7 are found in the nucleus, while SIRT2 is mainly located in the cytoplasm, and SIRT3–5 are in mitochondria. SIRT1 deacetylates PGC1a and promotes nuclear transfer. [106]. AMPK is a sensor of the AMP/ATP ratio: at a low energy state, AMPK promotes PGC-1a phosphorylation and therefore regulates glucose transport, fatty acid oxidation and mitochondrial biogenesis. TFAM controls the expression of mtDNA replication and transcription and participates in mtDNA base excision repair process. [107]. Sheng and

collaborators have shown that the expression of PGC-1a, NRF1, NRF2 and TFAM are significantly decreased in the hippocampus of AD, suggesting an abnormal mitochondrial biogenesis in AD [108]. In agreement with this result, overexpression of PGC-1a can reduce mitochondrial damage and improve biogenesis.

Among the promising strategies to ameliorate mitochondrial-based diseases, it is worth noting the induction of PGC-1a via the activation of PPAR receptors by rosiglitazone or bezafibrate or modulating PGC-1a activity by targeting AMPK employing 5-aminoimidazole-4-carboxamide ribotide (AICAR), metformin, or resveratrol. AMPK, an evolutionarily conserved sensor of cellular energy status, is activated by increasing AMP levels in conditions of energy deprivation, and the enzyme consequently inhibits energy consumption and stimulates catabolic pathways. Activation of AMPK has a wide range of effects, including inhibition of mTOR and PI3K-Akt signaling. Salicylates, thienopyridone, and AICAR activate mitochondrial biogenesis through induction of AMPK [109].

Resveratrol, a molecule belonging to a phenylpropanoid family commonly found in the skins of red grapes and in red wine, activates mitochondrial biogenesis through stimulating SIRT1 or inhibiting cAMP phosphodiesterases [110]. Studies demonstrated that resveratrol can induce SIRT1 expression, increase AMPK activation, and activate PGC-1a [111, 112]. One of the major neuroprotective mechanisms of resveratrol is the activation of SIRT1 that is expressed in the adult mammalian brain, predominantly in neurons [113]. Activation of SIRT1 by resveratrol prevents Aβ-induced microglial death and contributes to improved cognitive function [114]. A diet including long-term resveratrol use reportedly reduced learning and memory impairment and decreased amyloid levels and phosphorylated tau by activating AMPK and SIRT1 [115]. A significant reduction in hippocampal neurodegeneration was observed after intracerebroventricular injection of resveratrol in an animal model, which was associated with a decrease in SIRT1 acetylation [116]. Wang et al [117] recently showed that resveratrol protected neurons against Aβ 1–42-induced disruption of spatial learning, memory, and synaptic plasticity and rescued the reduction of SIRT1 expression in hippocampal rats. A multicenter, randomized, double-blind, placebo-controlled Phase II clinical trial in individuals with mild to moderate Alzheimer disease (AD) shows that resveratrol is safe and well tolerated, and effects on AD biomarker (plasma Aβ40 and Aβ42, CSF Aβ40, Aβ42, tau, and phospho-tau 181) and volumetric MRI outcomes (primary outcomes) [118].

An alternative and promising strategy to rescue mitochondrial defects by targeting AMPK is Metformin (Met), a well-tested *in vitro* and *in vivo* compound that affects mitochondrial energy production and insulin signaling. Dysregulation of AMPK is associated with insulin resistance and T2DM and neuroinflammation. AMPK signaling plays a major role in AD progression since AMPK has been shown to regulate both Aβ generation and tau phosphorylation. The primary molecular target of Met is believed to be mitochondria, where it reduces complex I of the electron transport chain, resulting in a reduction in oxidative phosphorylation and ultimately a reduction in the synthesis of ATP [119]. Increased AMP binds to the AMPK binding domain and causes allosteric conformational change, as a result of this, the catalytic domain of AMPK is activated [119]. Considered as a promising drug for AD, Met was shown to reduce tau phosphorylation in murine primary neurons *in vitro* and *in*

vivo. In this study, Met inhibited protein phosphatase 2A activity (PP2A) rather than mTOR, via the regulatory subunit of PP2A-α4 and the ubiquitin ligase MID1. However, Met did not show a considerable effect on the phosphorylation of the AMPK. In accordance with these results, it was posited that long-term use of Met may be useful for prophylaxis and/or therapy of AD [120]. Wang et al. demonstrated that Met enhanced neurogenesis and spatial memory formation in the cultures of both human and rodent neurons by the activation of PKC-CBP pathway [121]. In another study by Chen et al. using obese mice (db/db), these researchers found that Met improved memory impairment, inhibited neuronal apoptosis, and lowered Aβ accumulation in the hippocampus. These scientists also observed that Met noticeably influenced RAGE-mediated transport of Aβ across the blood–brain barrier, but Met did not have an important effect on LRP1-mediated transport of Aβ [122]. A study conducted in human neuronal stem cells proposed that activation of AMPK via metformin is neuroprotective against Aβ [123].

3.2 Targeting mitochondrial uncoupling proteins (UCPs)

The uncoupling proteins (UCPs) are transporters, present in the mitochondrial inner membrane, that mediate a regulated discharge of the proton gradient that is generated by the respiratory chain. This energy-dissipation mechanism can serve functions such as thermogenesis, maintenance of the redox balance, or reduction in the production of reactive oxygen species. Recent findings have elucidated roles for UCPs in neuronal plasticity and resistance to metabolic and oxidative stress [124]. UCPs are induced by bioenergetic challenges such as caloric restriction and exercise and may protect neurons against dysfunction and degeneration. The pharmacological uncoupler, 2,4-dinitrophenol (DNP), which was once prescribed to over 100,000 people as a treatment for obesity, stimulates several adaptive cellular stress response signaling pathways in neurons, including those involving the neurotrophic factor BDNF, the transcription factor CREB, and autophagy. Preclinical data show that low doses of DNP can protect neurons and improve functional outcome in animal models of AD. Moreover, data particularly from a study of a mouse model of AD (APP/PS1 double mutant transgenic mice) demonstrated that daily administration of a very low dose of DNP (0.5 mg/kg) for 4 months ameliorated spatial learning and memory deficits in a water maze task, with striking results on short-term memory [124].

3.3 Targeting mitophagy: Rapamycin, Latrepiridine, Nicotinammide

Mitochondrial autophagy, also known as mitophagy, is a highly dynamic process for removal and recycling of corrupt mitochondria [125]. A balance between mitophagy and mitochondrial biogenesis offers an efficient energy transducing system essential for neuronal survival, whereas mitochondrial dysfunction contributes to neuronal death [15, 41, 64, 126]. Elevated OS and induction of apoptosis can deactivate mitophagy and weaken pathways required for clearance of aberrant mitochondria [40, 127, 128]. In parallel, mitochondria and their physical dynamics play a vital role at several stages of autophagy from initial assembly of the autophagosome to autophagy-mediated cell death [129]. mTOR complex is directly involved in the regulation of mitophagy by its direct interaction with the ULK1 complex that regulates the formation of the phagophore [58]. Further, mTOR was found to be associated with mitochondria, and under differential redox-based modulation stimulates mitochondrial

respiration and regulates the balance between glycolytic- and mitochondrial-generated ATP [130]. In AD, the aggregation of dysfunctional neurons is caused in part by the obstruction of the clearance of impaired mitochondria, accompanied by concomitant rise in oxidative stress. In particular, dysfunctional autophagolysosomes play a crucial role in producing compromised mitophagy [131–133]. Generally, autophagy/mitophagy is damaged by the mutations in PSEN1 gene [134], which cause the alkalization of the lysosome and lessened activity of lysosomal hydrolases [135]. Diverse features including elevated Parkin displacement to mitochondria, aggregation of autophagosome-lysosomes containing undigested mitochondria take place in AD brains, supporting the idea that aggregation of autophagosomes may characterize low lysosomal effectiveness [136].

Further, evidence from post-mortem AD brains and brains from mouse models of the disease indicates that mTOR is increasingly active in hippocampus and in other brain areas [59, 137–139], leading to defective autophagosome formation. Pharmacological agents and lifestyle interventions aimed at improving mitochondrial health and enhancing mitophagy have been evaluated in animal models and, in some cases, in MCI or AD patients [40, 140]. Rapamycin a selected inhibitor of mTORC1 has been extensively shown to reduce cognitive decline in several mouse models of AD and of AD-like dementia [141–144]. The molecular mechanisms through which the compound and its derivatives exert it effectiveness encompass autophagy/mitophagy rescue, as indexed by the significant increase of LC3 II/I and other autophagy related proteins, including Atg5, Atg7, and Atg12, due to rapamycin-mediated suppression of mTOR signaling [141–144]. Therefore, the increased autophagy-related clearance of toxic aggregates and of damaged mitochondria in mice neurons led to the reduction of AD pathological hallmarks, including oxidative damage and insulin resistance, and to improved cognitive performances. Our groups recently demonstrated that intranasal administration of rapamycin decreased oxidative damage to brain protein and improved cognition, while brain-resident AD pathological hallmarks were decreased in a Down syndrome mouse [156]. These promising results await human trials, a delay primarily due to concerns related to whether long-term usage of rapamycin is tolerable in terms of potential side effects associated with immune suppression.

Latrepirdine, an antihistamine drug also known as dimebon, showed an anti-AD effects in *in vitro* and *in vivo* studies [40, 145, 146]. In cell culture and in AD mouse models, latrepirdine led to diminution of mitochondria defects and Aβ toxicity by regulating the autophagic pathway. In a Phase II clinical trial in patients with moderate AD, latrepirdine significantly improved cognitive function [147]. However, these results were not confirmed in a Phase III clinical trial [148]. Consequently, this agent seems not be promising for AD therapy.

Nicotinamide, the precursor of nicotinamide dinucleotide (NAD^+), was shown to reduce the pathology of AD in animal models through a mechanism including elevated brain bioenergetics, mitochondria functionality, and autophagy [149, 150]. Nicotinamide led to reduced Aβ and tau pathologies through increased mitochondrial response to oxidative stress, induction of autophagy, and improved activation of PI3K–Akt, MAPK/ERK1/2, SIRT1 and CREB pathways [151].

Several other compounds with structural similarities to resveratrol, RSVA314 and RSVA405, were found to inhibit mTOR activity and to promote the degradation of Aβ by the autophagic-lysosomal machinery [152].

Evidence from studies of rodents reported that caloric restriction, intermitting fasting and vigorous exercise affect signaling pathways in neurons in ways that reduce both mitochondrial damage and production of ROS [153, 154]. Fasting and exercise may increase the numbers of well-functioning mitochondria in neurons by activating pathways that stimulate mitochondrial biogenesis and mitophagy [155].

4. Conclusions

Mitochondrial function is significantly disturbed in AD and there is growing interest in understanding how altered mitochondrial activities may be targeted to inhibit/slow the neurodegenerative process in AD, as well as other brain disorders. Proper modulation of mitochondrial turnover to eliminate dysfunctional mitochondria while maintaining efficient functional mitochondria in response to stresses, may be relevant in managing neurodegeneration in AD. Indeed, it is likely that mitochondrial homeostasis reflects efficient bioenergetic metabolism as well as the inverse regulation-two faces of the same coin. Thus, novel mitochondrial targeted therapeutics should have the potential to act simultaneously on the two aspects of mitochondrial function. Among putative candidates, J147 have demonstrated a great potential but also other compounds including metformin, antioxidants and rapalogs have the ability to modulate both mitochondria self-renewal and energy production. Further studies are needed to confirm the ability of some of the mentioned compounds for translation into clinics as well as the development of novel promising agents able to selectively target the mitochondrion.

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KEYPOINTS

- Deficit of mitochondrial function (energy metabolism, cell death, mitophagy) is a key pathological feature of neurodegeneration in Alzheimer disease and other brain disorders.
- Adenosine triphosphate (ATP) is the major energy currency molecule of the cell.
- Mitochondrion-targeted therapies aim to preserve mitochondrial homeostasis (biogenesis and degradation) and energy metabolism (ATP synthesis).
- Promising drugs for AD treatment have shown the ability to potentiate energy production, to scavenge reactive oxygen species and reduce oxidative damage, to improve glucose metabolism and mitophagy.

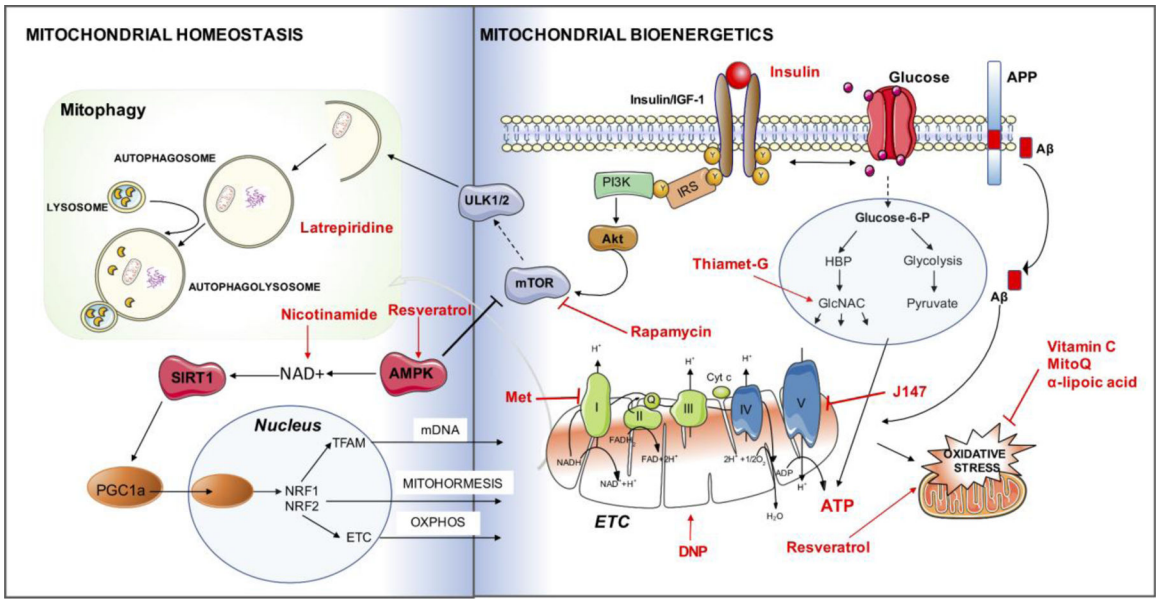

Figure 1.

Proposed scenario of current strategies targeting different traits of dysfunctional mitochondria in Alzheimer disease (AD), including mitochondrial bioenergetics and mitochondrial homeostasis. In the right part, therapeutic candidates that target glucose metabolism and/or the electron transport chain (ETC) are reported in red. J147 targets α- F1 subunit of ATP synthase (ATP5A) modulating its activity. Insulin rescues insulin resistance occurring in AD and improves glucose utilization. Thiamet G is a potent and specific inhibitor of OGA, an enzyme that controls GlcNAc cycling. Reduced GlcNAc levels are associated with reduced glucose uptake and result in altered mitochondria function. Vitamin C, MitoQ and a lipoic acid are antioxidant therapeutic candidates, used as beneficial supplements for AD patients. DNP (2,4-dinitrophenol) is a pharmacological uncoupler targeting UCPs present in the mitochondrial inner membrane. In the left part of the figure, therapeutic candidates targeting mitochondrial homeostasis that involves mitophagy and mitochondrial biogenesis, are shown in red. Resveratrol activates mitochondrial biogenesis by induction of SIRT1 or inhibition of cAMP phosphodiesterases. Metformin (Met) reduces ETC complex I activity, ultimately resulting in reduced ATP synthesis. Rapamycin is a potent and selective mTOR inhibitor able to regulate mitophagy. Latrepiridine and nicotinamide are both regulators of the autophagy pathway.