Neurotherapeutics (2015) 12:66–80
DOI 10.1007/s13311-014-0324-8

REVIEW

Targeting the Prodromal Stage of Alzheimer's Disease: Bioenergetic and Mitochondrial Opportunities

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Published online: 23 December 2014

Abstract Alzheimer's disease (AD) has a complex and progressive neurodegenerative phenotype, with hypometabolism and impaired mitochondrial bioenergetics among the earliest pathogenic events. Bioenergetic deficits are well documented in preclinical models of mammalian aging and AD, emerge early in the prodromal phase of AD, and in those at risk for AD. This review discusses the importance of early therapeutic intervention during the prodromal stage that precedes irreversible degeneration in AD. Mechanisms of action for current mitochondrial and bioenergetic therapeutics for AD broadly fall into the following categories: 1) glucose metabolism and substrate supply; 2) mitochondrial enhancers to potentiate energy production; 3) antioxidants to scavenge reactive oxygen species and reduce oxidative damage; 4) candidates that target apoptotic and mitophagy pathways to either remove damaged mitochondria or prevent neuronal death. Thus far, mitochondrial therapeutic strategies have shown promise at the preclinical stage but have had little-to-no success in clinical trials. Lessons learned from preclinical and clinical therapeutic studies are discussed. Understanding the bioenergetic adaptations that occur during aging and AD led us to focus on a systems biology approach that targets the bioenergetic system rather than a single component of this system. Bioenergetic system-level therapeutics personalized to bioenergetic phenotype would target bioenergetic deficits across the prodromal and clinical stages to prevent and delay progression of AD.

Key Words Alzheimer's disease (AD) mitochondria · prodromal · therapeutics · neurodegeneration · bioenergetics

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Introduction

Alzheimer's disease (AD) remains without an effective strategy to prevent, delay, or treat the disease. In 2010, the World Health Organization estimated the number of persons with AD-related dementia at 35.6 million, which is expected to triple by 2050 to over 115 million [1]. The projected number of persons with AD in the USA by 2050 is 13.5 million, and the medical costs will exceed $20 trillion over the next 40 years [2, 3]. The measurable socioeconomic annual costs of the disease on a global scale were estimated to exceed $600 billion in 2010 [1, 4]. Socioeconomic data predict that significant decreases in medical costs are possible if therapeutic development shifts to *identification* and *prevention* of AD rather than attempts to reverse AD pathology [5].

Since 1998, there have been 101 failed Alzheimer's trials [6]. Currently available drugs offer moderate symptom alleviation [6]. No therapeutic strategies have demonstrated clinically significant disease-modifying benefits to halt or reverse cognitive decline. Most of the therapeutic candidates have focused on reduction or reversal of AD pathology based on the β-amyloid (Aβ) plaque hypothesis. Several antiamyloid drug candidates have failed in late-stage clinical trials [4, 7]. Despite preclinical success in cell lines and animal models, most therapeutic candidates for AD failed to show any significant effect on cognitive function at clinical stages [6]. These

failures can be attributed to multiple factors that arise during drug development in both preclinical and clinical settings.

As multifactorial diseases present differently, responses to therapies also differ. For example, unhealthy diet and exercise may have different impacts on individuals and require different treatment strategies than those individuals predisposed to genetically inherited familial diseases [8]. Sex, genetic risks, and age are important variables that should be considered during the development stage for AD therapeutics [9, 10]. The dosing regimen, formulation, and the route of administration all have significant effects on clinical success [10]. Past approaches targeting moderate and severe AD pathology have had minimal success, in part because of the single target strategy for a multifactorial pathology. In contrast, targeting the affected biological systems at specific stages of disease progression may have greater likelihood of success in nonfamilial AD.

The presymptomatic and prodromal stages of AD are windows of opportunity likely to have the greatest impact on reducing the risk and incidence of AD (Fig. 1). Dysfunctions in glucose metabolism, bioenergetics, and mitochondrial function are consistent antecedents leading to AD pathology, including Aβ plaque and neurofibrillary tangles [11]. Dysfunctional mitochondria produce high levels of reactive oxygen species (ROS); these ROS can negatively affect specific mitochondrial components, including mitochondrial DNA (mtDNA), membrane lipids, and oxidative phosphorylation proteins [18, 19]. For example dysregulation of complex I has been correlated with tau toxicity, and dysregulation of complex IV has been associated with increased Aβ load [20–22]. Additionally, specific proteins are affected by mitochondrial dysfunction in AD, including amyloid precursor protein, presenilin 1 and presenilin 2, which reside along the mitochondria-associated endoplasmic reticulum membranes [23]. 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 [12, 13, 24]. *In vitro* and *in vivo* preclinical 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 [12, 13, 24, 25]. Importantly, clinical studies indicate that mitochondrial deficits observed in preclinical models are evident in human-derived platelets [14, 15, 26–29]. The antecedent decline in mitochondrial function and brain metabolism indicates an early and potentially causal role in AD pathogenesis. Thus, 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.

Current Strategies Targeting Mitochondria and Bioenergetics in AD

The integrity and viability of the bioenergetic system is a fundamental determinant of synaptic and brain function [9, 30–32]. Although the human brain accounts for 2 % of the body's mass, it consumes 20 % of the body's fuel supply for

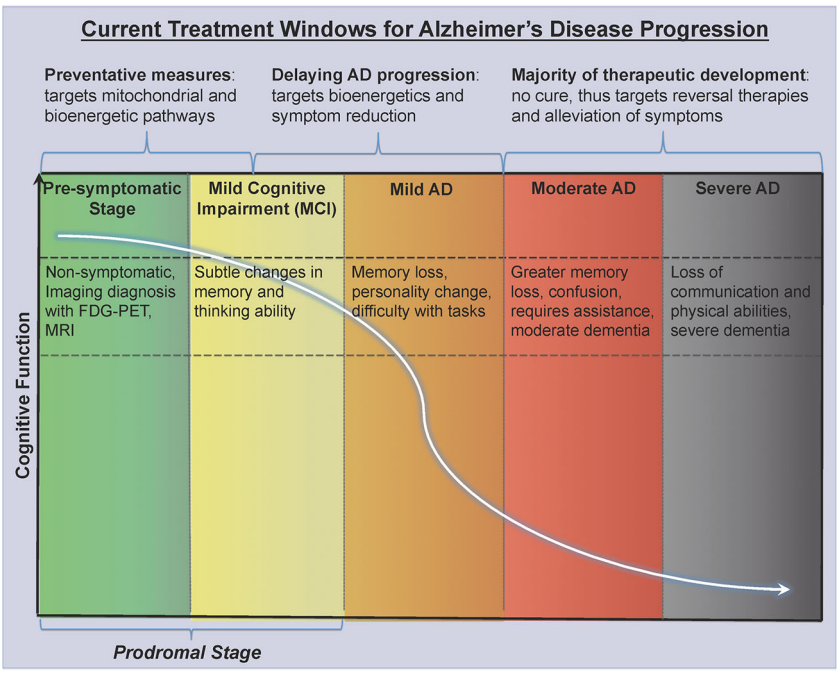

Fig. 1 The five stages of Alzheimer's disease (AD) pathology and 3 therapeutic treatment windows. The prodromal stage encompasses the presymptomatic and mild cognitive impairment stages of AD. White line = progression of cognitive decline through the 5 stages of AD [11–17]. FDG-PET = fluoro-2-deoxyglucose positron emission tomography; MRI, magnetic resonance imaging

adenosine triphosphate (ATP) production [9]. The bioenergetic system consists of obligatory processes that are tightly coupled, including substrate supply, transporters, and the catalytic machineries required for oxidative phosphorylation and ATP generation (Fig. 2). Compromised brain metabolism is an early indicator of AD in both preclinical and clinical investigations [31]. Previous studies have suggested that a decrease in brain bioenergetics may be a useful biomarker to predict disease decades before symptoms [33–36]. Decreases in mitochondrial bioenergetics, metabolic enzyme expression and activity, cerebral glucose metabolism, along with increased oxidative stress, Aβ deposits within mitochondria, and expression of ABAD are associated with the prodromal state of AD [34, 37–42].

Glucose Uptake and Substrate Supply as Therapeutic Targets

Decreased glucose metabolism is an early hallmark of the prodromal AD stage [43]. Brain hypometabolism and deficits in mitochondrial bioenergetics have long been documented in both preclinical and clinical AD research. Decrements observed in cerebral glucose metabolism using fluoro-2-deoxyglucose positron emission tomography (FDG-PET) and brain volume using magnetic resonance imaging are early signs of bioenergetic decline in the prodromal state of AD (Fig. 1) [16]. Observations from a clinical trial of the Dominantly Inherited Alzheimer's Network suggested several surrogate disease markers, including compromised FDG-PET signal in specific brain regions (posterior cingulate cortex and prefrontal cortex) vulnerable to development of AD pathology, that arise in patients with AD decades before cognitive symptoms [11–15, 17, 24, 44].

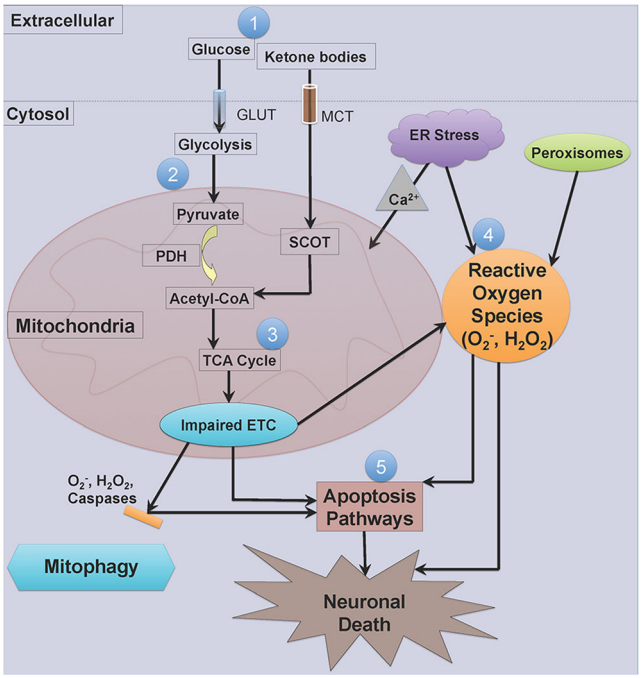

Fig. 2 Dysfunction of the brain energy production system precedes Alzheimer's disease (AD) pathology and neuronal death. Strategies to prevent mitochondrial dysfunction include multiple points of therapeutic intervention: 1) glucose or alternative fuel for substrate supply; 2) glycolysis; 3) the citric acid cycle (TCA) cycle and electron transport chain (ETC); 4) oxidative stress; 5) mitophagy and apoptosis. Mitochondrial impairments produce free radicals causing oxidative damage; reactive oxygen species and caspase proteases can block the neuroprotective mitophagy pathway. Mitochondrial dysfunction and endoplasmic reticulum (ER) stress activate apoptotic pathways that lead to neuronal loss and continuation of the AD pathology spectrum. GLUT = glucose transporter; MCT = monocarboxylate transporter; PDH = pyruvate dehydrogenase; SCOT = succinyl-coenzyme A:3-ketoacid CoA transferase

At the substrate level, glucose transport across the blood–brain barrier (BBB) into neurons and glial cells require glucose transporters glial GLUT1 (55 kD and 45 kD), neuronal GLUT3, and insulin-dependent GLUT4 [31]. Glycolysis, the citric acid cycle, and mitochondrial oxidative phosphorylation are then coordinated to generate ATP [31, 32]. Compromised glucose uptake and metabolism provide a therapeutic target for AD prevention and intervention. Therapeutic candidates that target glucose metabolism could address the hypometabolic phenotype. If glucose hypometabolism in brain is a causative factor in development of AD, then detection, prevention, and reversal of bioenergetic decline represent a therapeutic target window for AD [45]. Insulin is a therapeutic candidate to promote glucose metabolism in the brain (Table 1) [46, 47]. 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 [46]. Additionally, insulin-sensitive glucose transporters (GLUT4) are expressed in regions supporting memory and cognitive function [46]. Insulin resistance, which is the reduced sensitivity of insulin in targeted tissues important for cognitive function, increases the risk of dementia [47]. Impaired insulin responsiveness and dysfunctional glucose utilization have been documented in postmortem AD brains [48, 49]. Intranasal insulin was tested in a randomized, double-blind, placebo controlled clinical study of 64 participants with mild cognitive impairment (MCI) and 40 participants with mild-to-moderate AD. Insulin-induced modest recovery of memory function and preservation of glucose uptake [50, 51]. A larger-scale Phase II/III trial is currently underway to examine the effects of intranasally administered insulin on cognition, entorhinal cortex and hippocampal atrophy, and cerebrospinal fluid biomarkers in amnestic MCI or mild AD (ClinicalTrials.gov identifier: NCT01767909).

In addition to glucose, an alternative fuel source, ketone bodies, is used for cellular processes when glucose and carbohydrate supply is low (Table 1; Fig. 2) [33, 62]. Ketone bodies are formed in the liver from fatty acid oxidation and are transported to the brain [31, 62, 63]. Ketone bodies, transported into the cell via monocarboxylate transporters, bypassing glycolysis, are subsequently utilized by a series of

Table 1 Substrate supply

Substrate supply	Mechanism/target	Preclinical experimentation	Clinical experimentation for AD	Reference
Insulin	Combat insulin-resistance, increase brain metabolism	Beneficial in mouse models for AD	Phase II/III trials underway	[46–55]
Ketone bodies	Alternative fuel for brain metabolism	Beneficial for motor function in animal models and had cognition sparing properties	Limited clinical data showed improvements in cognitive testing	[9, 31, 39, 56–61]

AD = Alzheimer's disease

ketolytic enzymes such as succinyl–coenzyme A (CoA):3-ketoacid CoA transferase instead of pyruvate dehydrogenase (PDH) to produce acetyl-CoA, which condenses with oxaloacetate and enters the citric acid cycle for energy production [31, 62]. Several therapeutic strategies aim to enhance brain bioenergetics through supplementation of ketone bodies, including acetoacetate and β-hydroxybutyrate [64, 65], or dietary induction of ketogenesis [56]. However, patient compliance on ketogenic diets is challenging owing to its high fat and low carbohydrate content. In addition, there are studies indicating that ketone bodies have little effect on AD pathology, despite benefits on motor performance [57, 66]. Two early proof-of-concept clinical studies, investigating ketone bodies for mild-to-moderate AD, reported significant improvements on multiple measures of cognition [58, 59]. Further research is required to verify whether supplementation of ketone bodies is an effective therapeutic approach for AD. Future research could develop forms of ketogenic supplementation for alternative energy.

The use of exogenous insulin and ketone bodies is mechanistically sound. However, supply of substrate or activation of a single target within the system, such as insulin receptors presumes that the entire bioenergetics system is fully functional, which is unlikely but not impossible. Supplementation with insulin or ketone bodies could promote substrate supply, (glucose or ketone bodies, respectively); however, substrate alone is unlikely to result in full recovery of the bioenergetics system or restore mitochondrial function.

Mitochondrial Bioenergetics as a Therapeutic Target

Multiple experimental paradigms, ranging from *in vitro* cell model systems and genomic analyses in animal models to postmortem autopsy of human brain and human brain imaging indicate deficits in mitochondrial function are consistent antecedents to AD development [11–13, 24]. A decline in mitochondrial function can occur decades prior to clinical diagnosis of AD and thus may serve as a biomarker of AD risk, as well as a therapeutic target [12, 24, 32, 67]. Preclinical *in vitro* and *in vivo* AD models have demonstrated a decline in mitochondrial function, including reduced mitochondrial respiration, decreased metabolic enzyme expression and activity, increased oxidative stress, and increased mitochondrial Aβ load and ABAD expression, prior to AD pathology [12, 13, 15, 24, 34, 38]. A series of mitochondrial enhancer candidates have been proposed and investigated in preclinical and clinical studies for AD prevention and treatment (Table 2).

Multiple candidate molecules target the electron transport chain (ETC). Coenzyme Q (CoQ) and its synthetic water-soluble analogue, idebenone, have been proposed for AD treatment [32, 68, 83]. CoQ is imbedded in the mitochondrial inner membrane and transports electrons from complex I/II to complex III in the ETC. In addition, CoQ can function as a ROS scavenger [68]. While CoQ supplementation has benefit in persons with CoQ synthesis disorders and in preclinical mouse models of AD, it is ineffective as a therapeutic in persons with AD [32, 65, 83]. In a randomized, double-blind, multicenter study with 450 participants with mild-to-moderate AD, Idebenone showed minimal cognitive benefit [69–71], but was not approved for treatment of AD based on results not reaching statistical significance in larger trials [70–72]. Methylene blue can enhance cytochrome c oxidase activity through direct electron donation [80, 81]. In a preclinical AD mouse model, methylene blue treatment reduced Tau-neurofibrillary tangle burden [82]. Clinical investigations of methylene blue as a treatment for AD have not been conducted. Menadione and ascorbate together can act as complex IV substrates and sustain mitochondrial ETC respiration when complex III is compromised [79]. Other compounds that enhance mitochondrial ETC and oxidative phosphorylation include nicotinamide, a precursor to the complex I substrate, nicotinamide adenine dinucleotide, and riboflavin, a precursor to the complex II substrate, flavin adenine dinucleotdie [84]. While outcomes of research on these molecules have shown promising potential in preclinical studies, their efficacy clinically is unlikely to be substantial as they target specific components of the bioenergetic system instead of the entire system. A case in point is creatine, which is proposed to increase energy storage capacity and could be used to generate ATP under high-energy demands. However, creatine failed in clinical trials and in some cases even caused negative effects [86, 87].

Activation of the peroxisome proliferator-activated receptor-γ and the peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC1α) pathway promote mitochondrial biogenesis [73, 74, 83]. Therapeutic candidates in this class include peroxisome proliferator-activated receptor-γ

Table 2 Mitochondrial enhancers

Mitochondrial enhancers	Mechanism/target	Preclinical experimentation	Clinical experimentation for AD	Reference(s)
Coenzyme Q and idebenone	Accepts electron from complex I/II delivering them to complex III, scavenges ROS	Slowed cognitive decline in transgenic mouse models of AD	Failed in clinical trials insignificant effects on cognition	[68–72]
Rosiglitazone (thiazolidinedione)	Activates PGC1α	Stimulate neuronal mitochondrial biogenesis	No significance in clinical trial, poor penetration of BBB	[73–77]
Pioglitazone (thiazolidinedione)	Activates PGC1α	Reduced memory loss in mouse models of AD	Small benefit in human select groups; larger trials underway	[73–78]
Bezafibrate	Activates PGC1α	Improves bioenergetics in cell/animal models with mitochondrial dysfunction	No clinical data	[73–77]
Menadione and ascorbate	Allow ETC flux to replace defective complex III enzymes	Increased bioenergetics in animal models	No significant effects in clinical trials	[79]
Methylene blue	Tau inhibitor enhances COX activity/anti-NRTs agent	Improved bioenergetics in cell culture and animal models	No clinical data	[80–82]
Riboflavin and nicotinamide	Precursors to FADH2 and NADH	Increased mitochondrial respiration	No clinical data	[83–85]
Creatine	Cells to store creatine phosphate as alternative energy source	Increase in cell bioenergetics	Benefits for muscle strength, negative effects on cognition in clinical trials	[79, 86–88]
Exogenous TFAM	Important for mtDNA replication/transcription, administered with a mitochondrial leader sequence and protein transduction domain	Increased respiration and mitochondrial biogenesis in cell culture and mouse tissues	No clinical data	[89–91]

AD = Alzheimer's disease; ROS = reactive oxygen species; PGC1 α = peroxisome proliferator-activated receptor gamma coactivator 1-alpha; BBB = blood–brain barrier; ETC = electron transport chain; COX = cyclooxygenase; NFT = neurofibrillary tangle; FADH2 = flavin adenine dinucleotide; NADH = nicotinamide adenine dinucleotide; TFAM = mitochondrial transcription factor A; mtDNA = mitochondrial DNA

agonist thiazolidinediones, pioglitazone and rosiglitazone, as well as the PGC1α activator Bezafibrate. Activation of PGC1α by Bezafibrate was reported to improve cell bioenergetics and decrease mitochondrial dysfunction in cell culture and animal models [73, 74].

Preclinically, pioglitazone restored cerebrovascular function, reduced oxidative stress, and increased mitochondrial respiration [75–77]. Pioglitazone was initially tested in the human neuron-like NT2 cell line, where it induced mitochondrial biogenesis, increased mtDNA content and subunit proteins, and reduced mitochondrial oxidative damage [78]. Rosiglitazone stimulated neuronal mitochondrial biogenesis and reduced memory deficits in mouse models of AD [75–77]. A small clinical trial of 32 patients with mild AD showed significant improvements with pioglitazone treatment on both the AD Assessment Scale-Cognitive subscale scores and Wechsler Memory Scale-Revised Logical Memory Performance tests [92, 93]. The patients also had improved cerebral blood flow in parietal lobes [93]. A Phase III clinical trial of pioglitazone for MCI due to AD is currently underway (ClinicalTrials.gov identifier: NCT01931566). Rosiglitazone tested in MCI and early AD showed improved delayed recall [94], but failed to show significant cognitive benefits in a subsequent larger trial with over 1400 patients with mild-to-moderate AD (ClinicalTrials.gov identifier: NCT00490568) [95]. One major challenge for these candidates is they have poor BBB penetration [78]. However, if co-transported through the BBB, rosiglitazone and other thiazolidinediones could be therapeutically beneficial in preventing AD.

Another potential target of the mitochondrial biogenesis pathway is the mitochondrial transcription factor A (TFAM), which is involved in mitochondrial biogenesis, mtDNA replication, transcription, and removal of homoplasmic mtDNA mutations [96]. *In vitro* administration of TFAM reportedly increased mitochondrial respiration rates, biogenesis, and mtDNA levels [89–91]. The potential of TFAM as a therapeutic is unlikely owing to its large size and difficulty in BBB penetration [97]. However, targeting expression of TFAM could be a therapeutic strategy to enhance mitochondrial bioenergetics.

Mitochondrial enhancers have been demonstrated to be effective in preclinical models of AD (Table 2), whereas clinical trials testing this strategy directly remain to be conducted. Targeting mitochondria directly assumes that the bioenergetic system of substrate transporters and metabolism are fully functional. This is unlikely to be the case in the prodromal and later stages of the disease based on clinical FDG-PET data indicating impaired glucose metabolism decades prior to AD diagnosis. Mitochondrial function is inextricably linked to upstream substrate supply and metabolism. Thus, increasing mitochondrial function in the presence of dysfunctional substrate transport and metabolism could exacerbate

degeneration. However, therapeutic strategies that promote each functional domain of the bioenergetic system, including mitochondrial function, could have benefit.

Oxidative Damage as a Therapeutic Target

A well-documented indicator of compromised mitochondrial function is oxidative stress [83, 85, 98–100]. Oxidative stress is primarily caused by excessive ROS produced by impaired electron transport, endoplasmic reticulum stress, and peroxisomes (Fig. 2) [24, 83, 98, 101, 102]. Decreases in enzymatic antioxidant defense capacity, including multiple superoxide dismutases (SOD), peroxiredoxins, and glutathione [103, 104], further exacerbates oxidative damage [83, 85, 98, 100]. Oxidative damage of multiple cellular components has been documented in both preclinical models of AD and in persons with the disease [102, 105]. Key enzymes involved in mitochondrial function, such as PDH and α-ketoglutarate dehydrogenase, are often targeted by ROS, leading to deceased enzyme activity and decreased efficiency of mitochondrial electron transport (Fig. 2) [106]. In AD, elevated oxidative stress is detectable in the form of lipid peroxides, 8-oxoguanine, and other oxidized proteins [107–110]. In parallel, oxidative stress has been demonstrated to increase Aβ production *in vitro* and *in vivo* [102, 109].

Several candidates have been proposed to prevent or reduce oxidative damage, and have been investigated as treatments for AD (Table 3). Deficits in plasma levels of antioxidants are well documented in patients with AD [111, 112, 140]. Early research administering antioxidants for AD treatment focused on vitamins C and E. Both these vitamins are significantly reduced in the plasma of patients with AD [111]. Multiple preclinical studies on vitamin C and vitamin E using transgenic AD mouse models indicated decreased lipid peroxidation, memory deficits, and Aβ plaque burden [114–116]. However, clinically, vitamins C and E showed limited benefits on cognitive function or delay of AD progression [117–119, 141]. Some studies indicated negative effects of high-dose vitamin E on cognitive function and increased risk for mortality [142]. A more recent randomized trial of vitamin E in veterans showed a 19 % delay in clinical progression per year [120]. In addition to vitamins C and E, several other antioxidant vitamins, including vitamins A, B_{12}, and D, have been investigated owing to their deficient levels in patients with AD [111, 113]. These vitamins failed to show significant efficacy when used in clinical settings (ClinicalTrials.gov identifier: NCT00235716), despite positive outcomes in preclinical models. Currently, these vitamins are often used in combination with other therapeutics based on their general health benefits.

Micronutrients and minerals have been investigated as potential therapeutics for AD. These include, but are not limited to, flavonoids (e.g., quercetin, morin, or baicalein), β-carotene, curcumin, zinc, folic acid, and selenium. Most of these showed little promise as an AD therapeutic on their own, but when combined together in formulations they improved cognitive function in transgenic AD mice and reduced oxidative stress [129, 130].

Curcumin is an antioxidant that has been demonstrated to induce multiple benefits in AD mouse models. In addition to its strong antioxidant ability, it has anti-inflammatory activity, reduces amyloid plaque burden, and partially restored distorted neuritis [125–128]. A current Phase II clinical trial that combines curcumin and yoga therapy aims to treat MCI (ClinicalTrials.gov identifier: NCT01811381). Resveratrol found in red grape skin is a potent antioxidant that has been shown to reduce amyloid plaque burden and improve memory deficits in transgenic AD mouse models [132, 133]. Resveratrol activates the 5'adenosine monophosphate-activated protein kinase pathway, and stimulates activity of nicotinamide adenine dinucleotide-dependent deacetylase sirtuin-1 [134, 135], which subsequently activates the PGC1α metabolic regulatory pathway and promotes mitochondrial biogenesis [136–139]. Several clinical trials are currently underway to investigate the efficacy of resveratrol, including a Phase II trial on mild-to-moderate AD (ClinicalTrials.gov identifier: NCT01504854), a Phase III on mild-to-moderate AD (ClinicalTrials.gov identifier: NCT00743743), and a Phase IV on MCI, which combines resveratrol with omega-3 (ClinicalTrials.gov identifier: NCT01219244).

There is also a set of compounds, including melatonin, that promote expression of mitochondrial antioxidant enzymes such as SOD or glutathione [121–124]. Mitoquinone mesylate (MitoQ) has been proposed for treatment of AD and other neurodegenerative diseases because its antioxidant activity localizes to the mitochondrial inner membrane to prevent oxidative damage [131]. MitoQ has shown bioenergetic benefits in AD mouse models, but the clinical benefit of MitoQ for patients with AD is yet to be determined [131].

Overall, strategies based on antioxidants and micronutrients have shown promise in transgenic AD models, but their clinical therapeutic efficacy has not been established under disease conditions. Further, their therapeutic potential in combination with factors that target the entire bioenergetic system in the at-risk and prodromal stages of the disease has yet to be investigated (Fig. 1). Therapeutics that selectively target the oxidative damage and act as free radical scavengers may offer moderate symptom alleviation if administered early in disease progress, but will not address the pathogenic cascade and therefore are unlikely to modify disease progression. Further, oxidative stress is unlikely to be causative for AD, but rather an outcome of mitochondrial dysfunction. Thus, free radical scavengers should be considered as a critical but not sufficient component of a formulation that targets the bioenergetics system.

Table 3 Antioxidants and micronutrients

Antioxidants and micronutrients	Mechanism/target	Preclinical experimentation	Clinical experimentation for AD	Reference(s)
Vitamin A	Oxidative stress, ROS scavenger	*In vitro* and mouse models of AD confirm mechanism	No significant effects in clinical trials	[111–113]
Vitamin B_{12}	Oxidative stress, ROS scavenger	*In vitro* and mouse models of AD confirm mechanism	No significant effects in clinical trials	[111–113]
Vitamin C	Oxidative stress, ROS scavenger	Reduced memory deficits in mouse models of AD	No significant effects in clinical trials	[114–118]
Vitamin D	Oxidative stress, ROS scavenger	Minimal effects in mouse models of AD	No significant effects in clinical trials	[111–113]
Vitamin E (α-Tocopherol)	Oxidative stress, ROS scavenger	Reduce ROS, lipid peroxidation and amyloid plaque in transgenic mouse models of AD	Multiple trials with no effect, recent clinical trial indicating delay in clinical progression, but high dose increased risk of mortality	[114–120]
Melatonin	Potent antioxidant, elevates levels of SOD and glutathione	Reduced oxidative stress increased learning ability in mouse models of AD	No clinical data	[121–124]
Curcumin	Antioxidant and anti-inflammatory activity	*In vitro* and mouse models of AD confirm mechanism	No significant effects in clinical trials	[125–128]
Folic acid	Oxidative stress, ROS scavenger	*In vitro* and mouse models of AD confirm mechanism	No significant effects in clinical trials	[129, 130]
β-Carotene	Oxidative stress, ROS scavenger	*In vitro* and mouse models of AD confirm mechanism	No significant effects in clinical trials	[129, 130]
Flavonoids	Oxidative stress, ROS scavenger	*In vitro* and mouse models of AD confirm mechanism	No significant effects in clinical trials	[129, 130]
Zinc	Reduce oxidative stress	Combined with micronutrients decreased oxidative damage/ increased bioenergetics	No significant effects in clinical trials	[129, 130]
Selenium	Oxidative stress, ROS scavenger	Mixed results when used alone, but effective in animal models in combinations	No significant effects in clinical trials	[129, 130]
MitoQ	Oxidative stress, ROS scavenger	Extended lifespan in mouse models of AD	No clinical data for AD	[131]
Resveratrol	Activation of AMPK subsequent induction of NAD+ levels stimulate activity of SIRT1	Reduces oxidative stress, reduces amyloid plaques, improves memory deficits in transgenic mouse models of AD	No major effect on cognitive function	[132–139]

AD = Alzheimer's disease; ROS = reactive oxygen species; SOD = superoxide dismutase; MitoQ = mitoquinone mesylate; AMPK = adenosine monophosphate-activated protein kinase; NAD = nicotinamide adenine dinucleotide; SIRT1 = sirtuin 1

Apoptosis and Mitophagy as Therapeutic Targets

Prolonged deficits in bioenergetics together with elevated oxidative stress lead to activation of apoptotic pathways, impaired mitophagy, and, ultimately, neuronal death [143]. Mitochondrial autophagy, often referred to as mitophagy, is a highly dynamic process for disposal and recycling of unhealthy mitochondria [143]. A balance between mitophagy and mitochondrial biogenesis provides an efficient energy transducing system required for neuronal survival [144], whereas mitochondrial dysfunction contributes to neuronal death and AD pathology (Fig. 2) [98, 123, 145]. Elevated oxidative stress and induction of apoptotic proteases can inactivate mitophagy and impair pathways required for clearance of aberrant mitochondria [83, 85, 101, 146, 147].

Several therapeutic strategies target the autophagy and mitophagy pathways (Table 4). Based on its potential to induce autophagy in several neurodegenerative disease models, Rapamycin, also known as sirolimus, is being investigated for AD [148–150]. Mechanisms of rapamycin action include removal of damaged mitochondria and cells with dysfunctional mitochondria via mammalian target of rapamycin-dependent activation of autophagy [149, 150]. Rapamycin extends lifespan in aged mice [148]. In transgenic AD mouse models, rapamycin reduced Aβ plaques and prevented cognitive decline [148, 149, 151]. However, the therapeutic development of rapamycin for treatment of neurodegenerative diseases was largely hampered by severe side effects, including lung toxicity, diabetes, and cancer [151].

Latrepirdine, also known as Dimebon, is an antihistamine that, in cell culture, reduced swelling of mitochondria under Aβ stress and stabilized mitochondrial membrane potentials [145, 152]. Latrepirdine is proposed to interact with glutamate

Table 4 Antiapoptotic and mitophagy strategies

Antiapoptotic and mitophagy strategies	Mechanism/target	Preclinical experimentation	Clinical experimentation for AD	References
Rapamycin	Targets and inhibits the mTOR complex 1	Reduced and prevented cognitive decline and Aβ levels in mouse models of AD	No clinical trials available for AD, side effects in other uses include cancer, lung toxicity, and diabetes	[148–151]
Latrepirdine (Dimebon)	Antihistamine, some mitochondrial stabilizing properties	Transgenic mouse models of AD	Phase II success improved function, but no effect in the larger Phase III; some yet to be reported	[152–157]
Lentiviral vector expressing Nrf2	Intrahippocampal injection of lentiviral vector expressing Nrf2, a master regulator of the antioxidant pathway, induces expression of antioxidant enzymes	Hippocampal cells *in vitro* and mouse models of AD	No clinical data	[158, 159]
Synthetic triterpenoids	Suppress inflammatory stress and oxidative damage by activating Nrf2 pathway	Memory retention in transgenic mouse models of AD	No clinical data	[160, 161]

AD = Alzheimer's disease; mTOR = mammalian target of rapamycin; Aβ = β-amyloid; Nrf2 = nuclear response factor 2

receptors, block voltage-dependent calcium channels, and inhibit mitochondrial permeability, thereby suppressing unnecessary mitophagy or apoptosis [153, 154]. In a Phase II clinical trial in patients with moderate AD, it significantly improved cognitive function over placebo [155]. However, these results were not confirmed as Latrepirdine/Dimebon later failed in a larger Phase III trial of patients with moderate-to-severe AD (ClinicalTrials.gov identifier: NCT00912288) [156, 157].

Nuclear response factor 2 (Nrf2) and Nrf2/antioxidant response element have been proposed as a therapeutic target for autophagy and mitophagy. In transgenic AD mouse models intrahippocampal injections of the lentiviral vector expressing Nrf2 decreased Aβ plaque, reduced learning deficits, and protected against Aβ-induced cell death [158, 159]. Synthetic triterpenoids have been demonstrated to induce expression of Nrf2 and to protect against cell death in both *in vitro* and *in vivo* experiments [160, 161]. Development of strategies that target this Nrf2/antioxidant response element pathway are at an early stage and require substantial translational research.

Preclinical strategies targeting autophagy and mitophagy pathways in AD models have shown cognitive benefits (Table 4). However, substantial preclinical discovery and translational research remain to be conducted to advance this therapeutic target. Targeting the apoptotic and mitophagy pathways alone as a therapeutic strategy does not address the causative mechanisms leading to disrupted mitophagy and elevated apoptosis. Though the research in this area of AD therapeutics awaits translational validation, apoptotic regulation and removal of dysfunctional mitochondria is critical to restoration of bioenergetic capacity in brain.

Systems Approaches for AD Prevention and Treatment

Alzheimer's is a neurodegenerative disease with a complex and progressive pathological phenotype characterized by antecedent hypometabolism, impaired mitochondrial bioenergetics, and oxidative damage followed by apoptotic and pathological burden. The progressive and multifaceted degenerative phenotype of AD suggests that successful treatment strategies would be equally multifaceted with a systems biological approach. Several systems biology approaches for AD prevention and treatment are in development (Table 5).

One of the widely accepted therapeutic strategies to prevent AD is diet and exercise. The systems-wide neuroprotective benefits of caloric restriction and exercise include activation of adaptive cellular stress responses, enhancement of DNA repair, promotion of mitochondrial biogenesis, and induction of neurotropic factors [162]. Previous preclinical studies using multiple forms of caloric restriction led to reduced abdominal fat mass, decreased cellular oxidative damage and proinflammatory cytokines [163–165, 194], and improved learning and memory function [60].

Exercise has also been investigated for its direct benefits for patients with AD. Exercise activates a full systems effect, including promotion of hippocampal neurogenesis, reduction of brain inflammation, and increased PGC1α levels, mtDNA, proteins in ETC, and neurotropic factors [167–172]. Interestingly, a recent study demonstrated that the benefits of exercise were associated with elevated lactate levels and could be partially replicated by treatment with lactate [168].

Another lifestyle strategy for AD prevention is the Mediterranean diet (MeDi). MeDi, opposed to the Western diet, is characterized by the abundant consumption of plant foods such as vegetables, fruits, breads, potatoes, legumes, nuts,

Table 5 Systems strategies

Systems strategies	Mechanism/target	Preclinical experimentation	Clinical experimentation for AD	References
Restricted-calorie diet	Decrease oxidative damage and increase lactate levels	Controlled daily caloric restriction reduced oxidative stress *in vivo*	Reduced oxidative damaged	[60, 162–166]
Exercise	Decrease oxidative stress, increased mitochondrial function	Decrease in oxidative damage and amyloid plaque levels *in vivo*	Increased cognitive function, weight, and general health	[135, 136, 162, 165, 167–172]
Mediterranean diet	Plant foods, e.g., fruits, vegetables, roots, and grains	NA	Epidemiological studies in several countries	[113, 173–181]
17-β-estradiol	Decrease oxidative stress, increase glycolytic metabolism, increase mitochondrial respiration	Decrease in oxidative damage and amyloid plaque levels, increase in mitochondria bioenergetics *in vitro* and *in vivo*	Transdermal patch aims to improve cognition, possible adverse side effects	[9, 33, 110, 182–189]
Clioquinol and PBT2	Multifaceted antifungal drug; metal chelator of Zn and Cu targeting Aβ plaque reactions	Reversal of cognitive deficits in AD transgenic mice	Currently in clinical trials	[85, 190–192]
Souvenaid	EPA, 300 mg DHA, 1200 mg Phospholipids 106 mg Choline, 400 mg Uridine monophosphate, 625 mg Vitamin E, 40 mg Selenium, 60 μg Vitamin B_{12}, 3 μg Vitamin B_6, 1 mg Folic acid, 400 μg	Protects *in vivo* system against Aβ toxicity in rat Aβ infusion model and transgenic mouse models of AD	Small-scale human trials; improve cognitive function and enhance synaptic activity with EEG	[112, 113, 193]

AD = Alzheimer's disease; NA, not available; Aβ = β-amyloid; EPA = eicospentaenoic acid; DHA = docosahexaenoic acid; EEG = electroencephalography

and seeds; olive oil as the source of fat; moderate amounts of dairy, fish, poultry, and eggs; low intake of red meats; and wine during normal meals [173, 174, 195]. The nutrients within the MeDi influence biological mechanisms affecting vascular, antioxidant, and inflammatory pathways [175, 176]. MeDi was demonstrated to reduce risk of heart disease, decrease markers of oxidative stress, and lower inflammatory markers; hence, MeDi adherence might delay age-related cognitive decline [177–180]. MeDi has shown a trend of benefiting cognitive function when assessed in population studies in 7 different countries [196]. Mechanistically, the cognitive benefits of the MeDi have been attributed to the synergistic interactions between antioxidants, B vitamins, omega-3 fatty acids, and other compounds [181, 197]. Questions remain about whether the benefits of the MeDi could be attributed to specific ingredients rather the complete diet [196]. Investigations on the mechanisms of MeDi action could identify key active ingredients that can be further developed into therapeutics for AD prevention and treatment.

Other than these lifestyle strategies there are also systems approaches for improving bioenergetics and mitochondrial function. One of the most investigated therapeutics in women is estrogen-containing hormone therapy. 17-β-estradiol (E_2) activates multiple signaling pathways in the brain, including mitogen-activated protein kinase, phosphatidylinositol-3-kinase, G protein-regulated signaling, c-fos, protein kinase C, and Ca^{2+} influx, which all are connected to neuronal function and survival [9, 182]. The ovarian hormone loss in menopause has been linked with cognitive decline that increases the risk for AD [9, 33, 110, 182–186]. E_2 treatment induced a significant increase in expression of glucose transporters and promotes aerobic glycolysis by increasing gylcolytic enzyme activity of hexokinase, phosphofructokinase, and pyruvate kinase [187, 188]. Further, E_2 activates PDH, enhances activities of the ETC complexes, and promotes ATP generation. The neurological benefits of E_2 are further enhanced by suppression of the oxidative stress via enhanced antioxidant capacity. E_2 also reduces AD pathology by both decreasing the production and increasing the clearance of Aβ species [182]. The systems biology of E_2 action in the brain has led to the design and development of brain-specific candidates of selective estrogen receptor modulators that activate the systems level of estrogenic mechanisms in the brain without the proliferative side effects in the periphery [110, 183, 185, 186].

Clioquinol is a therapeutic candidate for treatment of AD with bioenergetic system benefits. Acting as a chelator for copper and zinc ions, clioquinol had significant success in preclinical studies with transgenic AD mouse models. Binding of metal ions is required for Aβ aggregation and Aβ-induced free radical release in mitochondria [190]. A second-generation clioquinol molecule, PBT2, is in Phase II clinical trials (ClinicalTrials.gov identifier: NCT00471211). PBT2

reportedly decreased Aβ levels and improved performance on 2 cognitive function tests [191, 192]. In addition to metal chelation, PBT2 has a second mechanistic action to increase Aβ clearance, increasing activity of matrix metalloproteases including neprilysin, insulin degrading enzyme, and tissue plasminogen activator [191, 192].

Souvenaid was originally developed to improve nutrient deficiencies common in patients with AD and contains high doses of the omega-3 fatty acids eicospentaenoic acid and docosahexaenoic acid [112]. The formulation also acts as a ketogenic dietary supplement with high fat content to provide ketone bodies to the brain. The formulation also contains antioxidants; vitamins A, C, E, riboflavin, and folic acid; selenium; and ions required for membrane potential balancing and mitochondrial function, including sodium, potassium, chloride, calcium, and zinc [193]. In a 24-week double-blind sex-balanced clinical trial with 259 patients aged 51–89 years (mean 74 years) with mild AD, Souvenaid significantly improved memory and synaptic connectivity measured by electroencephalography [193]. However, in a clinical trial with patients with moderate-to-severe AD, no significant improvement was associated with Souvenaid treatment [112, 193], suggesting that the intervention window is early in AD progression.

System-wide approaches for therapeutic intervention have greater potential for clinical success in chronic progressive neurodegenerative diseases like AD. Systems biology therapeutic strategies address dysfunction of multiple components of the bioenergetic system and thus have a higher probability for efficacy. Future approaches will need to address early antecedent deficits in substrate supply, mitochondrial function, and apoptotic pathways in the bioenergetic system to avoid development of severe irreversible AD pathology.

Summary and Concluding Comments

The bioenergetic system is a complex network of pathways responsible for energy production required for neurological function and health. Current preventive strategies to target brain mitochondria focus on antioxidants, antiapoptosis agents, and bioenergetic enhancement. Several of these strategies have shown efficacy in preclinical investigations; however, most interventions have not translated to success in preventing, delaying, or reversing cognitive decline in clinical investigations.

A large body of evidence indicates that targeting one component of a neurobiological system does not create a course of correction nor does it reverse a system failure. For example, targeting oxidative stress does not alleviate the glucose hypometabolism or mitochondrial dysfunction, which are likely to be the primary failure points of the system from which oxidative stress emerges. Attempts to target the bioenergetic system in AD face the challenge of a dynamic adapting system that requires biomarkers specific to the bioenergetic state and precision therapeutics that target the bioenergetic phenotype during the window of opportunity.

The prodromal/preclinical state is a critical window in which to prevent progression to AD (Fig. 1). This window of opportunity is likely to be addressed through a combination of dietary supplements and nutraceuticals. Dietary supplements are defined as products that intend to supplement diet containing ≥1 of several dietary ingredients: vitamins, minerals, herbs, amino acids, concentrates, metabolites, or combinations of such [198]. Nutraceuticals, which may include 1 or many of the components in dietary supplements, intend to aid in prevention or treatment of disease or disorder [198]. Nutraceuticals hold promise as effective modifiers of multifaceted cellular pathways that are defective in the prodromal state of AD. Numerous vitamins and natural compounds elicit effects on specific targets of the bioenergetic system in the brain; some micronutrients may offset the deficiencies often associated with early AD [111, 112]. Natural compounds combined into a synergistic formulation could provide an effective nutraceutical-based mode of prevention for AD and other neurodegenerative disorders. Effective strategies that target the prodromal AD window could combine the benefits of bioenergetic system enhancers to promote glucose metabolism, reduce oxidative stress, and sustain normal mitophagy. The systems biology-based therapeutic strategy to prevent early bioenergetic deficits in the brain could have a major impact on future incidence of AD.

Acknowledgments This work was supported by National Institute on Aging (NIA) grants R01AG032236 (to R.D.B.), P01AG026572 (to R.D.B.), and R01AG033288 (to R.D.B.). We thank Dr. Ronald Irwin for helpful discussions throughout the process of developing this review.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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