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Targeting Mitochondrial Bioenergetics for Alzheimer's Prevention and Treatment

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Abstract

Alzheimer's is a neurodegenerative disease with a complex and progressive pathological phenotype characterized first by hypometabolism and impaired mitochondrial bioenergetics followed by pathological burden. The progressive and multifaceted degenerative phenotype of Alzheimer's suggests that successful treatment strategies necessarily will be equally multi-faceted and disease stage specific. Traditional therapeutic strategies based on the pathological aspect of the disease have achieved success in preclinical models which has not translated into clinical therapeutic efficacy. Meanwhile, increasing evidence indicates an antecedent and potentially causal role of mitochondrial bioenergetic deficits and brain hypometabolism coupled with increased mitochondrial oxidative stress in AD pathogenesis. The essential role of mitochondrial bioenergetics and the unique trajectory of alterations in brain metabolic capacity enable a bioenergetic-centric strategy that targets disease-stage specific pattern of brain metabolism for disease prevention and treatment. A combination of nutraceutical and pharmaceutical intervention that enhances glucose-driven metabolic activity and potentiates mitochondrial bioenergetic function could prevent the antecedent decline in brain glucose metabolism, promote healthy aging and prevent AD. Alternatively, during the prodromal incipient phase of AD, sustained activation of ketogenic metabolic pathways coupled with supplement of the alternative fuel source, ketone bodies, could sustain mitochondrial bioenergetic function to prevent or delay further progression of the disease.

Keywords

Mitochondria; Bioenergetics; Alzheimer's disease; Ketogenesis; Hypometabolism; Oxidative Stress

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ALZHEIMER'S DISEASE – UNLIMITED COST BUT LIMITED REMEDY

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease and the leading cause of dementia among the aged population. Currently, the estimated AD patient population in the US reaches 5.4 million and is projected to at least double by the year 2050 [1]. The disease is symptomatically characterized by progressive memory deficits, cognitive impairments and personality change, which can be attributed to progressive synaptic dysfunction and the subsequent loss of neurons in vulnerable regions of the brain, including the neocortex, the limbic system and the subcortical regions [2]. From a histo-pathological view, AD is characterized by senile plaques and neurofibrillary tangles in the medial temporal lobe and cortical areas of the brain together with neurodegeneration and loss of synaptic functions [3]. According to the genetics of the disease, AD has been categorized into two major forms: familial AD (FAD) and sporadic AD (SAD) or late onset age-related AD (LOAD), with the latter being the leading cause of dementia, accounting for about 50~60% of all cases. FAD is an autosomal dominant disorder with the onset age before 65. The majority of FAD cases have been attributed to mutations in three genes, the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*)[4]. In contrast, the complete etiology of SAD has yet to be fully elucidated, with age being identified as the greatest risk factor. The prevalence of AD increases exponentially with age in people aged 65 or older [3].

Financially, the cost of Medicare for AD and other types of dementia dwarf all other Medicare beneficiaries in the same age group by 9 fold. As of 2010, the estimated cost of AD related payments is $172 billion and the cost is projected to increase exponentially in the next 20 years with more baby boomers into senile age [1].

Despite unprecedented demand for AD medications, currently no treatment exists to prevent, modify, or halt disease progression. Available drugs approved by FDA only offer moderate and temporary symptom relief [5, 6]. Therapeutic development for AD, particularly SAD, has been largely impeded due to limited understanding of the disease etiology. The prevailing "amyloid cascade" hypothesis, which was first introduced almost 20 years ago and has been enriched over the past decade, emphasizes the neurotoxic characteristics of β-amyloid (Aβ) and proposes that the deposition of Aβ initiates a cascade of neurotoxic events, including the formation of neurofibrillary tangles (NFT), prolonged inflammatory responses, increased oxidative stress and mitochondrial dysfunction, which eventually lead to cell death and dementia [7–10]. While this "amyloid cascade" hypothesis proposes a unified etiopathogenic mechanism for both FAD and SAD, findings from both basic research and clinical observations indicate a far more complex mechanism for the etiopathogenesis of SAD. Further, rather than being the cause of the disease, recent studies indicate that in SAD both Aβ deposition and NFTs may serve as reactive products that arise from increased vulnerability to genetic and environmental risk factors as a function of aging [7, 11–13]. Moreover, candidates that directly target amyloid pathways, either through passive immunotherapy against Aβ bapineuzumab) [14] or via inhibition of pathways involved in Aβ generation (Tarenflurbil, Semagacestat, or Flurizan)[15], failed to achieve efficacy in recent clinical trials, indicating the therapeutic limitation of amyloid-specific strategies. On the other hand, increasing evidence suggest that Alzheimer's disease, particularly SAD, is a

multifaceted disease that could at least be partially attributed to decline in mitochondrial function and altered brain metabolic activity.

MITOCHONDRIAL DYSFUNCTION AND β-AMYLOID – A VICIOUS CYCLE

The fundamental role of mitochondria in cellular bioenergetics and survival has been well established [16–18]. The evidence for mitochondrial dysfunction as a pivotal factor in age-associated neurodegenerative diseases such as Alzheimer's and Parkinson's continues to mount [16, 19–22]. Perturbations in mitochondrial function have long been observed in samples derived from clinically confirmed AD patients, including altered mitochondrial morphology, compromised enzyme complexes in the Krebs cycle, and reduced cytochrome c oxidase (COX) activity [23–28]. Later, the “cybrid model” of AD, generated by transferring mtDNA from human AD patients into cell cultures that are devoid of endogenous mtDNA (ρ^0 cells), exhibited symptoms that recapitulated previous findings in clinical AD specimens, including decreased mitochondrial mobility, increased oxidative stress, decreased COX activity, decreased mitochondrial membrane potential, and increased Aβ production, therefore provided further evidence for involvement of mitochondria and mtDNA in AD etiopathogenesis [29, 30]. Moreover, increasing evidence indicates that mitochondria are direct targets of Aβ. Aβ has been demonstrated to accumulate within mitochondria and interact with a mitochondrial protein, Aβ̃ binding-alcohol-dehydrogenase (ABAD), resulting in decreased COX activity and increased oxidative stress [31–33]. Further, the Aβ induced neurotoxicity requires functional mitochondrial respiratory chain [34] and is further exacerbated in synergy with mitochondrial dysfunction in similar AD cybrid models [35].

While the neurotoxic mechanisms of Aβ converge upon mitochondria, compromised mitochondrial function, particularly inhibition in mitochondrial bioenergetics and increase in oxidative stress, exacerbates the degenerative process by increasing Aβ generation thereby generating a vicious cycle in which excessive Aβ accumulation and -prolonged mitochondrial dysfunction synergize to activate a cascade of neurodegenerative pathways, including disturbed cytoskeleton network and lysosomal pathways [36–39].

MITOCHONDRIAL BIOENERGETIC DEFICITS IN AD – AN EARLY AND POTENTIALLY CAUSAL EVENT

Multiple levels of analysis and multiple experimental paradigms that range from genomic analyses in animal models and postmortem autopsy of human brains to *in vitro* cell model systems to brain imaging in humans, demonstrate that dysfunction in glucose metabolism, bioenergetics and mitochondrial function are consistent antecedents to development of Alzheimer pathology [13, 40–42]. The decline in brain glucose metabolism and mitochondrial function can appear decades prior to the onset of histopathologcial and/or clinical features and thus may serve as a biomarker of AD risk as well as therapeutic target. Studies using multiple preclinical *in vitro* and *in vivo* AD models demonstrated antecedent decline in mitochondrial function prior to the development of Alzheimer’s pathology, including decreased mitochondrial respiration, decreased metabolic enzyme expression and activity, decreased cerebral glucose metabolism, increased oxidative stress, and increased

mitochondrial Aβ load and ABAD expression [40–45]. Further, the antecedent decline in mitochondrial function deteriorates with AD progression [31, 32]. Consistent with basic science findings, many clinical observations also report antecedent abnormality in cerebral glucose utilization decades prior to the onset of AD [46–52]. In addition to the distinct pattern of brain hypometabolism observed in clinical confirmed AD patients, multiple positron emission tomography (PET) studies demonstrated that the antecedent decline in glucose utilization, particularly in the hippocampal and entorhinal cortical regions, preceded the clinical diagnosis of AD by years and predicted the cognitive decline in normal aging [50] or the progression of patients from mild cognitive impairment (MCI) to AD [53] with high accuracy. Recent clinical studies revealed a significant overlap between brain regions that exhibited abnormal glucose metabolism and regions that are most vulnerable to development of AD pathology [54–56], providing further evidence of the association between disturbed glucose metabolism and AD pathogenesis.

ACTIVATION OF ALTERNATIVE FUEL SOURCE – COMPENSATION WITH DISEASE PROGRESSION

In parallel with the decline in glucose metabolism in AD, there is a generalized shift away from glucose-derived energy production, which is associated with a decrease in the expression of glycolytic enzymes coupled to a decrease in the activity of the pyruvate dehydrogenase (PDH) complex [24]. Alteration in brain metabolic profile in AD is further evidenced by concomitant activation of compensatory pathways that promote the usage of alternative substrates, such as ketone bodies, to compensate for the decline in glucose-driven ATP generation. We have previously reported that in the female 3xTgAD mouse model, pre-pathological decrease in PDH expression and mitochondrial bioenergetics were paralleled by increased expression of succinyl-CoA:3-ketoacid coenzyme A transferase (SCOT) at a young age (3 months), indicating early activation of ketogenic pathways to compensate for compromised PDH capacity, provide alternative sources of acetyl-CoA, and consequently maintain energy-conservation mechanisms required for ATP generation [57]. Consistently, previous clinical observations have also demonstrated the projectile of substrate switch along with AD progression. While there is a 100:0 ratio of glucose to other substrates utilization in young controls, there is a 2:1 ratio in incipient AD patients compared to a ratio of 29:1 in healthy elderly controls [58]. Cerebral utilization of ketone bodies requires supply from the peripheral ketogenic organ, the liver, or local synthesis of ketone bodies, potentially by astroglia via fatty acid oxidation [59]. Concomitant with the increase in ketone utilization in aging and AD brains, AD patients demonstrated various degrees of compromised brain white matter integrity [60–62]. In a preclinical AD rodent model, white matter degeneration was observed in the corpus callosum, fornix and hippocampus [63]. Lesions in white matter integrity suggests either hyper-activation of the fatty acid oxidation pathway for local astroglial ketone production or incompetency for lipid synthesis due to competition between consumption of ketones/ acetyle-CoA for bioenergetics and lipid synthesis [59].

BIOENERGETIC DEFICITS AND OXIDATIVE STRESS – WHEN IT RAINS IT POURS

Impairment of mitochondrial bioenergetics and oxidative phosphorylation (OXPHOS) is often closely associated with increased free radical production and the consequent oxidative damage. As the major source for cellular reactive oxygen species (ROS), mitochondria generate free radicals as the by-product during OXPHOS [64, 65]. On the other hand, oxidative damage to mitochondrial membranes and proteins is well documented to impair mitochondrial OXPHOS efficiency and result in increased electron leak as observed by increased hydrogen peroxide levels and higher oxidative stress [33, 66]. Key enzymes involved in mitochondrial bioenergetics, such as α-ketoglutarate dehydrogenase complex (αKGDHC) and the pyruvate dehydrogenase complex (PDHC), often are the targets of oxidative modifications, which lead to deceased enzyme activity and increased production of free radicals [67, 68].

Overproduction of reactive oxygen species and higher oxidative stress is characteristic of AD brains [13, 69]. In AD patients, significant increase in oxidatively modified molecules, such as lipid peroxide, 8-oxoguanine, and oxidized amino acid, have been identified in vulnerable brain regions [70, 71]. In preclinical AD animal models, increased generation of ROS, such as hydrogen peroxide, and elevated oxidative damage on cellular components have also been demonstrated to precede the development of AD pathology [40, 72–76]. In fact, increase in oxidative stress has been demonstrated to increase β-amyloid production *in vitro and in vivo* [77– 79].

CURRENT ALZHEIMER'S THERAPEUTICS – A MILESTONE YET TO BE ACHIEVED

Alzheimer's disease is a complex disease with a prolonged trajectory of etiopathogenic changes in brain bioenergetics decades prior to the clinical onset of the disease. Therefore, targeting only the pathological aspect, particularly the β-amyloid pathway, is insufficient to achieve full efficacy to prevent, delay, or even reverse the disease progression.

Recently, Eli Lilly announced cessation of its phase III clinical trial of semagacestat, a γ-secretase inhibitor, as the drug candidate failed to achieve efficacy in slowing disease progression and was associated with worsening of clinical measurement of cognitive function [80]. Similarly, other Aβ targeting candidates, tarenflurbil, tramiprosate and flurizan, also failed in Phase II or phase III clinical trials [80–82], although these candidates have been demonstrated to lower or reduce Aβ production in preclinical and early phase clinical studies [80–82]. Further, the clinical potential of the γ-secretase inhibitors are often complicated by its off-target interferences on the Notch signaling pathway.

Another category of anti-Aβ therapeutics includes Aβ42 vaccines, monoclonal Aβ antibodies and polyclonal antibodies. These candidates act via an immunotherapeutic mechanism to promote the clearance of amyloid. Yet, the active immunization approach, such as the amyloid vaccine AN-1792 (Elan/Wyeth), was discontinued due to increased risk of severe meningoencephalitis in the patients despite the trend towards positive efficacy it achieved

[83]. On the other hand, bapineuzumab (Elan/Wyeth), a passive immunization monoclonal antibody of Aβ, failed to achieve expected efficacy in a Phase II clinical trial, although it did exhibit some benefits in AD patients who did not carry the APOE4 genetic risk factor [83]. Other Aβ antibodies are currently under various stages of clinical trials and the efficacy is yet to be determined. Similarly, candidates that target Tau pathology as disease modifying therapeutics for AD are still in the early stage of development despite the potential benefits exhibited in preclinical animal studies.

Aside from the anti-Aβ/tau strategy, antioxidants have been proposed as potential therapeutics for AD. Analyses on specimens obtained from AD patients and various preclinical animal models clearly documented elevated oxidative damage on cellular components [40, 70–76]. The therapeutic potential of antioxidants is further supported by vast epidemiological analyses that demonstrated a positive correlation between the usage of antioxidant, particularly vitamin E and C, and cognitive function. Further early administration of antioxidants such as curcumin or vitamin E, has been demonstrated to suppress amyloidogenesis in several preclinical AD rodent models [84, 85]. However, multiple randomized clinical trials of high dosage of vitamin E usage failed to achieve significant efficacy [86], indicating the therapeutic limit of using exogenous antioxidants to scavenge oxidative insults rather than suppress the generation of oxidative insults.

THERAPEUTICS TARGETING MITOCHONDRIA AND BIOENERGETICS

Alzheimer's is a neurodegenerative disease with a complex and progressive pathological phenotype characterized first by hypometabolism and impaired mitochondrial bioenergetics followed by pathological burden. The progressive and multifaceted degenerative phenotype of Alzheimer's suggests that successful treatment strategies need to be equally multi-faceted and stage specific. Increasing evidence indicates an antecedent and potentially causal role of mitochondrial bioenergetic deficits and brain hypometabolism coupled with increased mitochondrial oxidative stress in AD pathogenesis. Mitochondrial deficits have been demonstrated to activate a cassette of neurotoxic events that all contribute to synaptic dysfunction, pathology development and eventually neuronal loss and cognitive impairment [33, 66]. Further, deficits in mitochondrial bioenergetics and brain metabolism exhibit a stage-specific trajectory with disease progression, which was first evidenced by the decline in glucose uptake and utilization that takes place decades prior to AD onset, followed by parallel activation of pathways to use alternative fuel substrates, ketone bodies, to compensate for the decline in glucose metabolism [40, 57]. As disease progresses, exacerbated decline in glucose utilization and exhaustion of available ketone reservoir leads to further disturbance of mitochondrial function and activation of fatty acid oxidation (FAO) pathway that eventually results in white matter generation and neuronal death observed in AD [16, 60, 62, 87]. This unique trajectory of glucose-ketone-FAO progression of brain mitochondrial metabolic alteration provides an ideal therapeutic target that is both disease modifying and stage specific (Fig. 1).

Candidates that potentiate mitochondrial bioenergetics and enhance brain glucose metabolism are expected to prevent the antecedent decline in brain glucose metabolism, promote healthy aging and therefore prevent AD. Interestingly, many candidates within this

category are naturally occurring herbals and small co-factors, which often are on the GRAS (generally considered as safe) list. R-α-lipoic acid, an important co-factor for key mitochondrial metabolic enzymes, including PDH, KGDH, and branched chain α-ketoacid dehydrogenase (BCKDH), has been demonstrated to upregulate mitochondrial bioenergetics, promote glucose metabolism, and suppress oxidative stress due to its potent antioxidant capacity [88]. Resveratrol, a redox active ingredient in grapes and wine, improves brain energy metabolism and reduces amyloid accumulation in preclinical animal models [89–92]. Both R-α-lipoic acid and resveratrol are currently under clinical trials for their efficacy in AD prevention and treatment [88, 93]. Other important regulators of mitochondrial metabolic activity include B-vitamins which are also co-factors of key metabolic/mitochondrial enzymes. These naturally occurring compounds often possess antioxidant properties. All together, these compounds exhibit potential to promote brain glucose utilization, potentiate brain metabolic activity, and simultaneously suppress oxidative damage with relatively low toxicity, which make them ideal candidates for development of nutraceutical cocktails to promote brain metabolism during healthy aging and therefore prevent AD.

While the preventive strategy focuses heavily on the enhancement of brain glucose metabolism, the shift towards an alternative fuel source, ketone bodies, observed in both preclinical AD models and in AD patients provides a second therapeutic window that targets the specific glucose – ketone transition stage to sustain brain metabolic activity and therefore prevent or delay further exacerbation in brain bioenergetic deficits. Ketone bodies are mainly synthesized in the liver and are well documented to serve as alternative energy substrates for the heart, muscle, and brain. Ketogenic pathways have been demonstrated to exist in astrocytes [94, 95]. Epidemiological analyses indicate a positive association between dietary intake of ketones/consumption of ketogenic diets and reduced risk for AD [59, 96]. The switch from glucose as the primary fuel to the alternative of ketone bodies in the AD brain was the basis for Accera to develop Ketasyn, which is converted to ketone bodies in the liver for subsequent use by the brain. This approach capitalizes on the brain's relative inability to utilize glucose and its dependency on ketone bodies. Phase II clinical trial in Alzheimer's patients and in individuals suffering from age-associated memory impairment has been completed and both groups showed improvement in memory function using the ketone body alternative fuel source (http://www.acerapharma.com).

While increasing ketone body supply provides more substrate to the brain to utilize as an alternative fuel, the therapeutic efficacy could be limited due to a diminished brain capacity to utilize ketone bodies. To address the issue of deficits in the ketogenic metabolic pathway, our group investigated the efficacy of the ketogenic modulator, 2-deoxy-d-glucose (2-DG) to increase brain capacity to utilize ketone bodies as fuel. Results of these analyses demonstrated that dietary 2-DG intake induced ketogenesis, sustained mitochondrial bioenergetics, and reduced pathology in the triple transgenic Alzheimer's (3xTgAD) mouse model [97]. Based on these clinical and preclinical findings, a combination of nutraceutical and pharmaceutical modulators that simultaneously enhance mitochondrial bioenergetics while sustaining availability and utilization of an alternative fuel substrate (ketone bodies), could prevent further decline in brain metabolism and to delay progression of AD.

SUMMARY

Alzheimer's is a progressive and complex neurodegenerative disease that requires therapeutic development to target beyond histopathological aspects of the disease. Increasing evidence indicates an antecedent and causal role of mitochondrial bioenergetic deficits and brain hypometabolism coupled with oxidative stress that initiates multiple neurotoxic events in AD etiopathogenesis. The essential role of mitochondrial bioenergetics and the unique trajectory of alterations in brain metabolic profile provides the foundation upon which to construct a bioenergetic-centric strategy that targets disease-stage specific pattern of brain metabolism to prevent AD and/or delay the disease progression.

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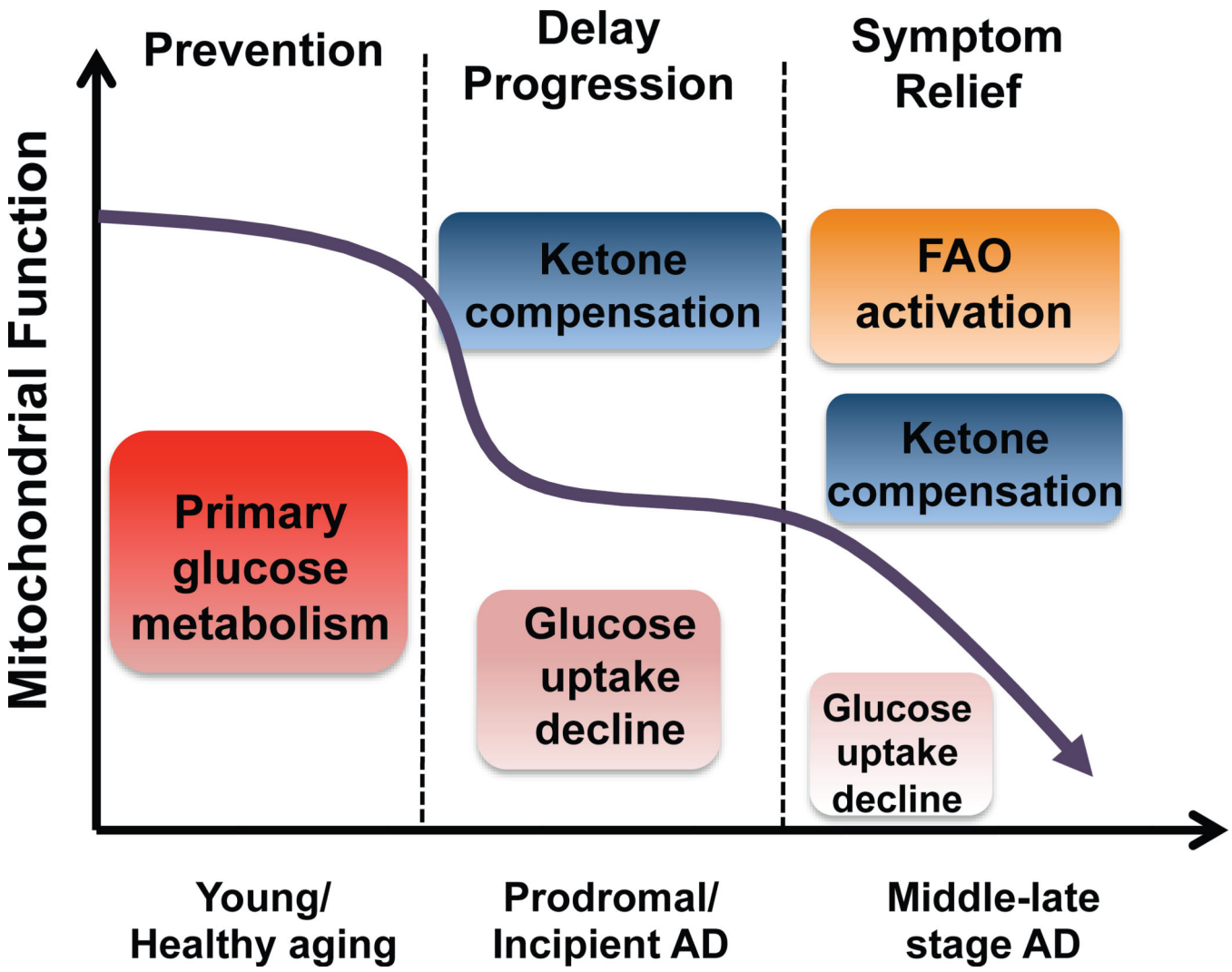

Fig. (1). Trajectory of mitochondrial function, substrate utilization during AD progression and therapeutic strategy

At young age or during healthy aging, brain metabolic activity is largely supported by glucose the primary fuel source whereas in prodromal and incipient AD the antecedent decline in glucose metabolism is paralleled by compensatory activation of ketogenic pathways, which later diminishes and progresses to local fatty acid oxidation leading to white matter degeneration observed with disease progression. The prevention strategy aims to enhance the glucose driven mitochondrial bioenergetics to promote healthy aging and prevent AD. Alternatively, in prodromal and incipient AD, sustained activation of ketogenesis provides prolonged supplement of the alternative fuel source, ketone bodies, and therefore sustains mitochondrial bioenergetic function and prevents/delays further progression of the disease. At the middle to late stage of AD, rather than modifying disease progression, treatments merely offer symptom relief.