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The Use of Pharmaceutical Intervention as a Mechanistic Tool to Regulate Bioenergetics and Inhibit Free Radical Oxidative Stress During the Progression of Alzheimer's Disease

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Abstract

Oxidative stress is the imbalance between antioxidants and oxidants. An increase in the level of free radicals or an antioxidant deficiency can perpetuate this phenomenon. Free radical mediated oxidative stress is demonstrated in various neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. This oxidative damage can result in a mechanistic chain reaction in which free radicals can bind to alkenes and cause overall protein damage and a decrease in energy metabolism. However, this mechanism can be halted with the use of antioxidant therapy. During the progression of Alzheimer's disease, oxidative stress is continuously elevated. Current research shows several antioxidant strategies being implemented to stop oxidative stress in Alzheimer's disease such as α-lipoic acid and acetyl L-carnitine. In addition to antioxidant therapies, antiaggregants, acetylcholinesterase inhibitors, β-secretase and γ–secretase inhibitors are also being used as pharmaceutical drugs to combat the pathological hallmarks of Alzheimer's disease. This review will describe the current pharmaceutical interventions being used to regulate energy metabolism and inhibit free radical meditated oxidative stress during the progression of Alzheimer's disease.

Keywords: Alzheimer's disease; Antioxidants; Free radicals; Oxidative stress; Pharmaceutical therapeutics

Introduction

Under normal physiological conditions, there is equilibrium between antioxidants and prooxidants. When environmental factors, stressors, or disease occur, this homeostasis can become imbalanced in favor of prooxidants, resulting in a phenomenon known as oxidative stress [1]. Oxidative stress can also occur if there is an antioxidant deficiency or excess reactive oxygen/nitrogen species production [2]. The mitochondria are the key source for free radicals [3,4]. Reactive oxygen species (ROS) are molecules that contain oxygen with higher reactivity than ground state O_2. Some examples are hydroxyl radical (OH•), superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), peroxyl radical (•OOH), hypochlorous acid (HOCl), and many others [1]. There are three mechanisms by which cells are protected from ROS: i) scavenging ROS and precursors; ii) binding catalytic metal ions needed for ROS formation; and iii) generating and upregulating endogenous antioxidant defenses. Oxidatively damaged proteins are often removed by the 20S proteosome. However, defects in the proteosome system can lead to elevated levels of oxidatively modified proteins. Reactive oxygen species levels increase as a function of age and are even higher in age-related neurodegenerative disorders [5]. It has been well established that oxidative stress is elevated in Alzheimer's disease [6,7], Parkinson's disease [8], amyotrophic lateral sclerosis [2], Huntington's disease [9] and other neurodegenerative disorders [6,10]. Alzheimer's disease (AD) is characterized by progressive neurodegeneration that results from a variety of possible environmental, genetic, and age-related factors [11,12]. The pathological hallmarks of the disease are extracellular senile plaques (deposits of amyloid β peptide) and intracellular neurofibrillary tangles (NFTs), but oxidative stress and metabolic abnormalities can precede these hallmarks as well the dementia that results from abnormal brain function [13,14]. While several biomarkers exist that may indicate the presence of the disease, conclusive evidence can only be established post-mortem [15]. Autopsy reveals the extent at which neurodegeneration has occurred and is commonly described using Braak staging methods. Braak determined that Alzheimer's disease progresses from stages I to VI with the increasing presence and distribution of NFTs and neutropil threads (NTs) [16]. This post-mortem staging is used to help differentiate between the four stages of AD: preclinical AD (PCAD), mild cognitive impairment (MCI), early AD (EAD), and late stage AD (LAD).This article will discuss specifically the use of current pharmaceutical interventions as they relate to the mechanistic recovery of energy related metabolic proteins during the progression of Alzheimer's disease.

Energy Metabolism

In addition to the hallmarks of Alzheimer's disease, senile plaques composed of amyloid beta peptide and neurofibrillary tangles composed of hyperphosphorylated tau protein, this disease is also characterized by oxidative stress and metabolic dysfunction that can precede both disease hallmarks [13,14]. The intricate relationship between these two characteristics, oxidative stress and metabolism dysfunction, has historically revealed itself in a very cyclic manner. A substantial portion of oxidative stress is generated by the mitochondria during regular metabolism, and this oxidative stress also serves as a disruptor of this same metabolism as excess reactive oxygen species (ROS) and reactive nitrogen species (RNS) production begin to outweigh the

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many compensatory mechanisms aimed to keep these oxidative species regulated [17]. This is evidenced by oxidative damage to many key metabolic proteins during the preclinical stage and each of the three clinical stages of AD [18-25]. This "chicken or the egg" –type genesis of AD pathology by oxidative damage and metabolic dysfunction is by no means a perfect mechanism and many of its details have been challenged. One recent proposal brought forth by Sun describes a lack of nutrient and oxygen availability as a key factor that promotes a protective response by the neuron to down-regulate metabolism [26].

Regardless of exactly what role oxidative stress plays in the pathogenesis of AD, there is a large body of accumulating evidence that shows key proteins involved in glycolysis, TCA cycle, electron-transport chain, and antioxidant capabilities of the cell become oxidized at various stages throughout the progression of the disease [18-22,25,27,28]. A summary of these oxidized enzymes is listed in Table 1. In order to understand the progression of AD, it is important to relate changes in metabolic function with the pathological characteristics of the disease. Patients with PCAD, also referred to as asymptomatic AD (ASYAD), show no signs of cognitive decline but present some of the neuropathological symptoms of AD. Braak scores range typically between III and IV due to the presence of NFTs and NTs [29,30]. MCI can be classified as amnestic or nonamnestic to distinguish between those with impaired memory and those without. Peterson defines MCI as being characterized by cognitive impairment and decline not related to age, no dementia, and no significant impairment in daily living [31]. Amnestic MCI patient autopsies are more common than non-amnestic patient autopsies and typically have Braak stages of III or IV, demonstrating a marked amount of neurodegeneration [32]. MCI transitions into EAD as memory continues to decline and other cognitive functions show impairment. Braak staging also increases compared to MCI, with autopsied patients having scores of IV or V. Markesbery et al. have described EAD and amnestic MCI as being virtually identical neuropathologically with the exception of neuritic plaques being elevated in EAD [33].Dementia progresses during the transition from EAD to LAD, affecting nearly every aspect of an individual's life. Braak scores of V and VI and increased Aβ deposits are associated with this stage of the disease [34].

Amyloid Beta Peptide (Aβ) and Tau

Much progress has been made in developing transgenic mouse models of AD pathology for interpretation. Specifically, models aimed at identifying the relationship between the hallmark proteins of Alzheimer's disease, Aβ and tau, have provided valuable insight into the mechanisms by which these proteins interfere with normal

Enzyme	Role	Nitration[1]	HNE-Modificatio [2]	Carbonylation[3]	Up-Regulated[4]	Down-Regulated[4]	Decreased Activity[5]
FBA	Glycolysis	MCI, EAD	LAD	EAD	PCAD, LAD		
TPI	Glycolysis	EAD, LAD	EAD				
GAPDH	Glycolysis	LAD		PCAD			
PGK	Glycolysis		MCI				
PGM	Glycolysis	EAD		EAD			
Enolase	Glycolysis	MCI, EAD, LAD	MCI, EAD, LAD	LAD	LAD		EAD
PK	Glycolysis			PCAD			MCI
LDH	LAF	LAD	MCI				MCI
Aconitase	TCA Cycle		LAD		PCAD		LAD
MDH	TCA Cycle	MCI	EAD				
COX	ETC					PCAD	
ATPase	ETC	EAD, LAD	MCI, EAD, LAD	PCAD		LAD	MCI, EAD, LAD
GDH	Metabolism/ Excitotoxicity	EAD					EAD
CK	Metabolism			LAD			LAD
Cu/Zn SOD	Antioxidant			PCAD	PCAD		EAD*
MnSOD	Antioxidant		EAD, LAD		LAD		EAD*
GST	Antioxidant	MCI	LAD		LAD		LAD
CR	Antioxidant		MCI				
Prx2	Antioxidant	EAD					
Prx6	Antioxidant	MCI	LAD				
MRP	Antioxidant	MCI	LAD				

Table 1: Oxidized proteins related to metabolism and antioxidant capacity of the cell are summarized.[1] see [19,23-25]. [2] see [19,21,22,47]. [3] see[18,41,43,105,106]. [4] see [21,47,107]. [5] see [19-22,47,105]. (HNE = 4-hydroxynonenal; FBA = fructose bisphosphate aldolase; TPI = triose phosphate isomerase; GAPDH = glyceraldehyde-3-phosphate dehydrogenase; PGK = phosphoglycerate kinase; PGM = phosphoglycerate mutase; PK = pyruvate kinase; LDH = lactate dehydrogenase; MDH = malate dehydrogenase; COX = cytochrome C oxidase; ATPase = ATP synthase; GDH = glutamate dehydrogenase; CK = creatine kinase; SOD = superoxide dismutase; GST = glutathione-S-transferase; CR = carbonyl reductase; Prx = peroxiredoxin; MRP = multi-drug resistant protein; LAF = lactic acid fermentation; TCA = tricarboxylic acid; ETC = electron transport chain).
*Overall SOD activity is reduced in EAD.

mitochondrial function. Eckert highlights the synergistic roles of Aβ and tau on down-regulating respiratory chain enzymes while promoting oxidative stress and an increased production of hyperphosphorylated tau protein in transgenic mouse models, leading to a proposed cyclic mechanism where increased Aβ deposition and neurofibrillary tangle formation is facilitated by dysfunctions in the respiratory chain that are initially brought about by increased levels of Aβ [35]. Specifically, an increase in Aβ levels, but not plaque levels, is associated with a significant decrease in the mitochondrial membrane potential as well as ATP production in 3 monthold Thy-1-$APP_{751}SL$ transgenic mice. This mitochondrial dysfunction becomes more prominent as the mice age, leading to elevations in ROS formation, increased susceptibility to Fe^{2+}-catalyzed hydroxyl radical formation, as well as decreased respiratory chain Complex IV activity[36]. Similarly, Aβ fibrils induce a fivefold increase in intracellular neurofibrillary tangle formation in a tau transgenic P301L mouse model, and proteomic analyses indicate down regulation of respiratory chain Complex I, ATP synthase, triose phosphate isomerase, malate dehydrogenase, glutathione S-transferase, and glutathione peroxidase. Significant decreases in the respiratory control ratio and ATP levels were also found with 24 month old transgenic mice [37,38]. A triple transgenic mouse model (pR5/APP/PS2) combining the Aβ and tau pathologies to facilitate significant increases in Aβ and phosphorylated tau levels, leads to several mitochondrial dysfunction markers, such as decreases in the activities of respiratory chain enzymes Complex I and Complex IV at 12 months of age [39]. Transgenic mouse models such as these serve as excellent resources for determining the exact roles of Aβ and tau in the cascade of events leading to cell death and ultimately neurodegeneration. These studies give credit to hypotheses such as the cyclic mechanism brought forth by Eckert that place mitochondrial dysfunction at the center of early AD pathology [35].

Glycolysis

Glycolytic enzymes are the most heavily targeted metabolic proteins throughout the progression of AD. Although glycolysis does not produce the majority of the energy for the cell, it generates pyruvate, which can serve as a starting material for other metabolic pathways. Proteomics research has found 70% of the enzymes involved in glycolysis to be oxidized by ROS and RNS species [18,19,21,22,25,27,40-43]. These enzymes are fructose-bisphosphate aldolase (FBA), triose phosphate isomerase (TPI), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), phosphoglycerate kinase (PGK), phosphoglycerate mutase (PGM), enolase, and pyruvate kinase (PK). Figure 1 illustrates which enzymes are oxidized in glycolysis during the progression of AD.

TCA Cycle

The TCA cycle accounts for approximately 90% of the energy produced for the cell. Thus, preserving the integrity of the enzymes involved in this metabolic pathway is integral to meeting the cell's energy demands. Neurons have very specific homeostatic requirements, such as maintaining phospholipid asymmetry, calcium regulation, and synaptic functioning. Overall energy demand for these processes in the brain is very high, as evidenced by the fact that the brain accounts for approximately 2% of body weight but uses 20% of body's glucose and over 30% of the inspired oxygen. Proteomics research has found 25% of the enzymes directly involved in the TCA cycle to become significantly oxidized during the progression of AD [19,21,23]. These enzymes are aconitase (ACO) and malate dehydrogenase (MDH).

In addition to its function in the TCA cycle, MDH is also involved in the malate-aspartate shuttle, which is partially responsible for efficient transfer of NADH equivalent electrons across the inner mitochondrial membrane. It is also worth noting that oxaloacetate can also be formed from pyruvate via pyruvate carboxylase, but pyruvate formation is potentially hindered in the early stages of AD by the oxidation of PK in PCAD and MCI and reduced PK activity in MCI [18,22,44]. Glutamate dehydrogenase (GDH) can form α-ketoglutarate (α-KG), another key substrate in the TCA cycle and malate-aspartate

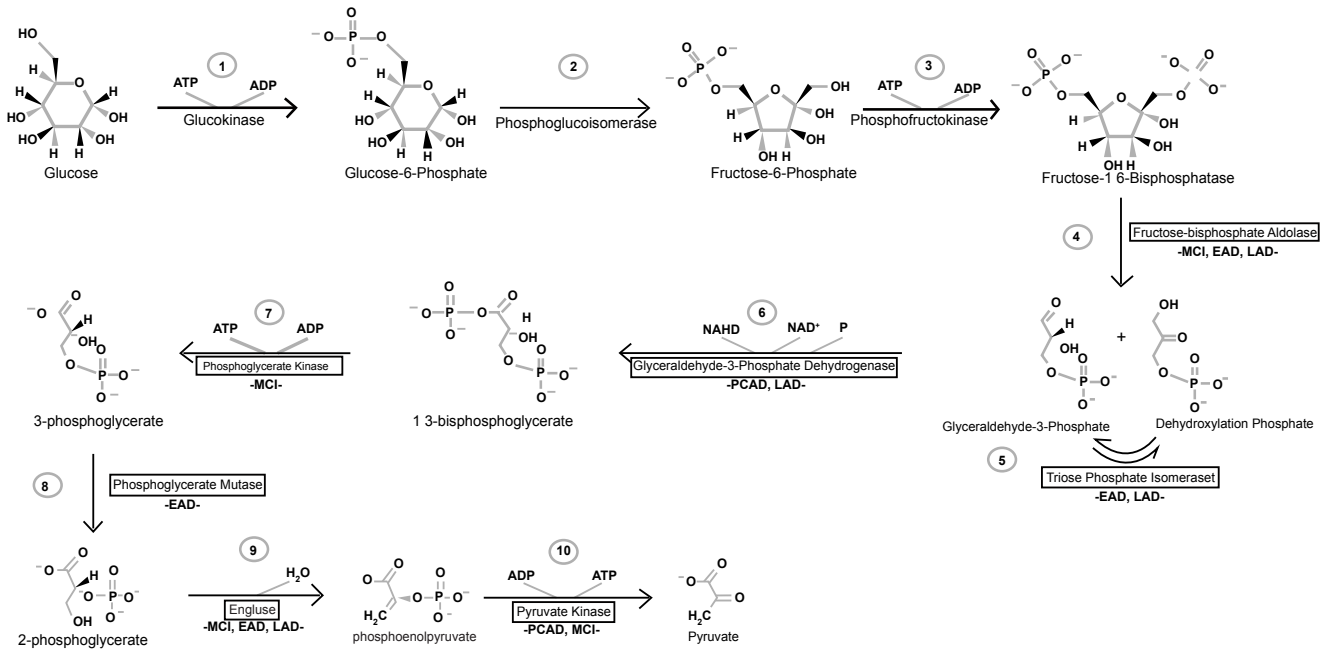

Figure 1: Summary of the glycolytic pathway. Enzymes that are oxidized during AD are boxed and the AD stages of their oxidation are listed beneath their names.

shuttle, via deamination of glutamate to yield one NADH molecule. GDH is oxidized in EAD, resulting in a reduction of enzyme activity [20]. Because GDH is responsible for keeping glutamate levels down, loss of GDH function can increase glutamate levels and lead to excitotoxicity [45]. Thus, the oxidation of MDH, PK, and GDH early in the progression of Alzheimer's disease could limit the availabilities of acetylCoA, oxaloacetate, and α-KG, limit the efficient transfer of NADH equivalent electrons across the inner mitochondrial membrane, and lead to excitotoxicity. This implicates MDH, PK, and GDH oxidation in the early metabolic dysfunction and neuronal loss that characterize AD.

Other Metabolic Processes

Protein oxidation is also involved in lactic acid fermentation, creatine phosphorylation, and ATP synthesis at various stages of AD. Lactic acid fermentation, an anaerobic method of pyruvate reduction by lactate dehydrogenase (LDH), generates lactic acid for use in gluconeogenesis as well as recycling NAD^+ back into glycolysis. The free NAD^+ generated by LDH can be very important when the cell requires immediate energy at the expense of glucose via glycolysis, thus potentially implicating the oxidation of LDH in metabolic dysfunction in early stages of AD progression. Creatine kinase catalyzes the reversible phosphorylation of creatine to phosphocreatine by ATP in the intermembrane space of the mitochondria to transport high-energy phosphate groups into the cytosol. This plays a large role in cell energy homeostasis by giving the cell access to the ATP generated by mitochondria. ATP synthase (ATPase), also known as Complex V of the electron transport chain, is a multi-subunit protein involved in the substrate-level phosphorylation of ADP in the mitochondrial matrix. Figure 2 illustrates the function of ATPase. The generation of ATP by ATPase is central to proper metabolism. Unfortunately, oxidation of the components of ATPase is highly involved in each stage during the progression of AD, leading to decreased enzyme activity during MCI, EAD, and LAD [18-22,46]. Due to its role in metabolism and oxidized during each stage of AD, ATPase is likely a key player in the progression of this disease.

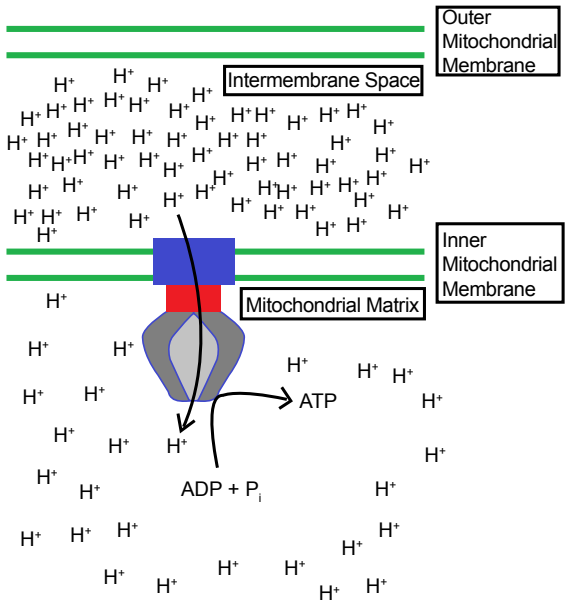

Figure 2: Depiction of the electromotive force for ATP production by ATP synthase.

Antioxidant Enzymes

Since metabolic function is the primary source of ROS production, and because these ROS play such a significant role in metabolic protein function, antioxidant enzymes are thus implicated in the progression of AD [17]. Several antioxidant enzymes exist to maintain a reductive environment in the cytosol and mitochondria. A number of these proteins are oxidized during AD. Specifically, glutathione-S-transferase (GST), carbonyl reductase (CR), multidrug resistant protein 3, various superoxide dismutase (SOD) isoenzymes, and peroxiredoxins (Prx) are all oxidized at various stages of the disease [19-23,47]. GST detoxifies toxic species such as HNE so it is crucial for maintaining the integrity of proteins susceptible to HNE oxidation. Like GST, CR can also reduce HNE as well as carbonyl containing compounds. Superoxide is generated as a result of electron passage through the electron transport chain, so keeping mitochondrial SOD levels is very important for protecting metabolic proteins from oxidation.

Pharmaceutical Interventions

While there are several treatment options for Alzheimer's disease, current therapeutic interventions are limited in their functionality, measurements, and effectiveness. There are currently no options available that stop or reverse the disease. Treating the two neuropathological hallmarks of AD, extracellular senile plaques and intracellular neurofibrillary tangles, has become a major area of focus for drug development [48-50]. Other treatment options aim to counteract the symptoms of AD by increasing neurotransmitter levels (specifically acetylcholine) or acting on neurotransmitter receptors to limit excitotoxicity [51-54]. Because metabolic abnormalities can precede the cognitive impairments associated with AD, and because cytosolic and mitochondrial oxidative stress are well-documented in the disease, early pharmaceutical and diet intervention in these areas is of utmost importance [13,14,55,56]. A general overview of treatment options is listed in Table 2.

Treatment of Senile Plaques

Treatment of senile plaques involves decreasing the formation and aggregation of the Aβ peptide, the main component of these plaques. In relation to oxidative damage, especially mitochondrial oxidative damage, early treatments for reducing Aβ formation may play a critical role in slowing the progression of AD. Amyloid precursor protein (APP) is a transmembrane protein that plays a role in long term potentiation, neuronal plasticity, and memory loss [57]. Cleavage of APP is accomplished by three different enzymes (Figure 3). Specifically, β-secretase and γ-secretase are involved in cleaving APP at the two sites required to produce the insoluble Aβ peptide, so they are targets for inhibition to decrease Aβ formation [58,59]. APP cleavage by γ-secretase is nonspecific and forms Aβ peptides of varying lengths. The peptides with lengths of 40 amino acids (Aβ40) and 42 amino acids (Aβ42) play a central role in plaque formation because their ratio has been implicated in how Aβ aggregation occurs [60]. Aβ42 acts as an insoluble seed that promotes the aggregation of Aβ peptides, whereas Aβ40 has been shown to inhibit Aβ deposit formation [61-63]. Thus, methods to decrease the Aβ42/Aβ40 ratio via modulating γ-secretase activity may become very useful strategies in treating AD as they evolve

Signs and Symptoms	Treatment	Effect
Senile Plaque Formation	β-secretase inhibitor	Decreases the formation of Aβ by inhibiting cleavage of APP by β-secretase [51]
	γ-secretase inhibitor	Decreases the formation of Aβ by inhibiting cleavage of APP by γ-secretase [52]
	PKC activator	Decreases the formation of Aβ by increasing cleavage of APP within the Aβ domain by α-secretase via up-regulation by PKC activation [53]
	Antiaggregant	Inhibits aggregation of Aβ into oligomers [54,55]
	Vaccination	Causes an immune response by which the body targets Aβ for degredation [56-58]
	ApoE inhibitor	Allows for removal of Aβ by blocking attachment of ApoE to Aβ [59]
Neurofibrillary Tangle	CDK5 inhibitor	Inhibits phosphorylation of tau protein by CDK5 [60]
	GSK-3 inhibitor	Inhibits phosphorylation of tau protein by GSK-3 [61]
	ApoE inhibitor	May inhibit phosphorylation of tau protein by GSK-3 via signal blocking [62,63]
	Antiaggregant	Inhibits aggregation of tau protein [64]
Low Acetylcholine Levels	AChE inhibitor	Increases levels of acetylcholine by inhibiting its degredation by AChE [45-48]
Oxidative Stress	Antioxidant	Breaks or inhibits free radical chain reactions by scavenging unpaired electrons [65,66]

Table 2: A summary of current treatment options for AD and their effects. (Aβ = amyloid beta peptide; AChE = acetylcholinesterase; ApoE = apolipoprotein E; APP = amyloid precursor protein; CDK5 = cyclin-dependent kinase 5; GSK-3 = glycogen synthase kinase 3; PKC = protein kinase C).

[60]. Activation of α-secretase also inhibits Aβ formation by cleaving APP within the Aβ domain [64]. Once formed, Aβ aggregates form oligomers of various sizes as well as the plaques that are traditionally associated with AD. Interference with this aggregation takes place at each stage of the process, with several compounds targeting early aggregation and others targeting larger assemblies of oligomers [65,66]. Apolipoprotein E (ApoE) is a lipoprotein used to in triglyceride catabolism. Although several alleles exist for this lipoprotein, the E4 allele is a risk factor for AD. Inhibiting apolipoprotein E has also been explored, as this protein hinders the removal of Aβ [67]. A relatively new area of research involves vaccination against Aβ, which has shown promising results in mouse models, and to some extent, in human trials [68-70]. Petrushina demonstrated that this type of immunotherapy can selectively decrease the formation of insoluble Aβ plaques without affecting the levels of soluble Aβ or causing cerebral microhemorrhages that have previously been encountered [70,71]. However, human clinical trials highlighted other dangers associated with immunotherapy when several patients undergoing this treatment strategy developed meningoencephalitis, causing the trials to be halted. While levels of Aβ plaques were found to be lower in treated patients at autopsy, cerebral inflammation was also found and cognitive decline was not prevented as a result of plaque clearance [69].

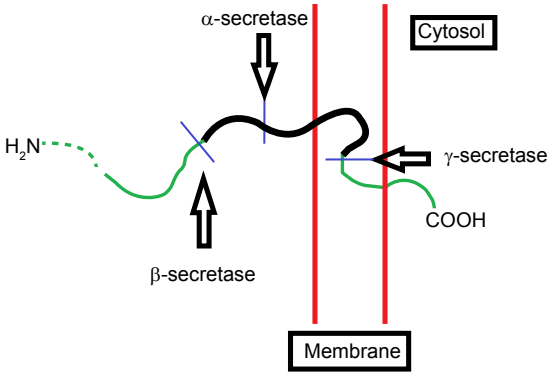

Figure 3: Cleavage of APP at different locations to promote or inhibit the formation of Aβ peptide (illustrated as the black fragment).

Treatment of Neurofibrillary Tangles

Neurofibrillary tangles are composed of hyperphosphorylated tau protein. Similar to treatment options for senile plaques, reduction of NFTs has been investigated using enzyme inhibitors as well as antiaggregant compounds that block the aggregation of tau protein [72]. Hyperphosphorylation of tau has been attributed to re-entry into the cell cycle by neurons, which has been observed in AD, because tau hyperphosphorylation is common during embryonic cell development but not in differentiated cells [73]. Hyperphosphorylation of tau is known to occur via cyclin-dependent kinase 5 (CDK5) and glycogen synthase kinase 3 (GSK-3), both of which have been targeted for inhibition [74,75]. ApoE may also become a target for inhibition specifically for its role in signaling GSK-3 [76,77]. Recent research has shown a direct relationship between cell cycle dysregulation (likely as a result of oxidative stress), hyperphosphorylation of tau, and AD progression [78]. Thus, treating only NFT formation, instead of upstream regulation defects, may only slow the progression of AD and not prevent or reverse the disease.

Neurotransmitter Availability

When neurons die as a result of neurodegeneration, levels of neurotransmitters inevitably fall and consequently promotecognitive decline. In particular, acetylcholine has been the major neurotransmitter targeted for increase by means of acetylcholinesterase (AChE) inhibition. In 1985, Davies highlights the central role of acetylcholine in learning and cognitive function [79]. For this reason, 80% of FDA-approved treatments (i.e. Exelon®, Razadyne®, Cognex®, and Aricept®) for cognitive impairment in Alzheimer's disease target the degradation of acetylcholine by the enzyme acetylcholinesterase, with the fifth treatment, Namenda®, antagonizing N-methyl-D-aspartate (NMDA) receptors to decrease excitotoxicity [51-54]. While increasing the availability of neurotransmitters may temporarily increase cognition, this type of treatment addresses AD-related symptoms and not the pathology of the disease.

Antioxidant Therapies

Oxidative stress manifests itself through a variety of mechanisms during the progression of AD. More importantly, oxidative stress

precedes both traditional pathological hallmarks of AD, senile plaque formation and neurofibrillary tangles, leading in part to the formation of the "two-hit hypothesis" postulated by Zhu in 2004 [14,80,81]. This hypothesis places oxidative stress and cell cycle dysregulation at the forefront of the pathological onset of AD. Changes in metabolism have also been observed to occur before the appearance of the cognitive deficits of AD, and these kinds of changes can be caused by mtDNA mutation after exposure to reactive oxygen species (ROS) via changes in mitochondrial fission and fusion processes [13,82-84]. Control of mitochondrial fission and fusion is known to directly affect energy production and ROS formation [82,85]. Thus there is a potential cyclic mechanism by which early oxidative stress causes changes in mitochondrial fission and fusion control via mtDNA mutation, which in turn creates more ROS and exacerbates the shift toward an oxidative environment that the cell can't overcome. A similar mechanism introduced in 2000 incorporates energy insufficiency and Ca^{2+} dyshomeostasis into the mechanism by which ROS and mitochondrial damage perpetuate one another [86]. These mechanisms offer insight into how important and possibly manageable the progression of AD can be if biomarkers for these disruptions in cell homeostasis are discovered early enough.

Successful attempts at reducing oxidative stress, reducing changes in mitochondrial dynamics, and restoring cognitive function have used a supplemental combination of the antioxidants acetyl L-carnitine (ALCAR) and R-α-lipoic acid (LA) [87-91]. These endogenous compounds are involved in maintaining efficient metabolism of glucose and fatty acids. Structures for ALCAR and LA are shown in Figure 4. L-carnitine is involved in transporting long-chain fatty acids into the mitochondria for β-oxidation and transporting shorter fatty acid chains out of the mitochondria. By transporting short-chain fatty acids out of the mitochondria, L-carnitine is also involved in freeing coenzyme A (CoASH) for use in the TCA cycle via carnitine acyltransferase (CAT). LA is required as a coenzyme for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. ALCAR and LA have been shown to work synergistically to improve CAT binding and activity, which are reduced in aged rat brain [89]. ALCAR alone has also been shown to increase antioxidant enzyme activity as well as total antioxidant capacity in the plasma of healthy people, making it a viable candidate for early, safe intervention long before biomarkers for AD appear [92].

Future Directions

The role of inflammation in the pathogenesis of AD has become a central target for therapeutic intervention, involving such pharmaceutics as non-steroidal anti-inflammatory drugs (NSAIDs), immunotherapy options, and other means of destroying Aβ plaques [66,68,93]. The specific roles of various conformations of Aβ peptide as neurotoxins as well as mediators of beneficial cellular processes significantly impact the direction of anti-Aβ treatments [94]. Current literature suggests that progress has been made in developing Aβ antibodies that are specific to soluble and insoluble conformations [95]. A multi-treatment approach may prove to be invaluable in the coming years, as indicated by Gotz, as therapeutic strategies targeting tau protein also become more sophisticated [38]. This is evidenced by several transgenic mouse models of individual and combined Aβ- and tau-induced AD pathologies in relation to mitochondrial dysfunction [35-37,39,96-99]. Given the natural abilities of certain antioxidants to protect mitochondria from ROS-induced oxidative damage, future therapeutic strategies would likely benefit from treatments targeting not only the reduction of AD pathological hallmarks, but also the strengthening of protective mechanisms that are inherent to the neuron [91].

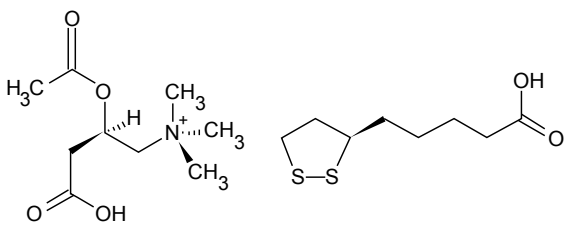

Figure 4: Structures for ALCAR (left) and LA (right).

Conclusions

Oxidative stress occurs when there is an imbalance between oxidants and antioxidants in a system. Free radicals from ROS and RNS are highly elevated in during the progression of Alzheimer's disease, while antioxidant enzymes have shown loss of protein function, reduced activity, and sometimes compensatory up-regulation to meet cellular demands. Therefore, increased oxidative stress can result from these free radicals causing cognitive decline in PCAD, MCI, EAD, and AD patients supporting the hypothesis of free radicals as an underlying contributor to Alzheimer's disease [100-103]. Among the metabolic and antioxidant enzymes reviewed, the glycolytic enzymes are the primary targets of oxidative damage. Because glycolysis is an upstream process relative to the TCA cycle and electron transport chain, glycolytic enzyme oxidation and accompanying loss of activity may serve as a trigger for downstream metabolic defects that occur early in the progression of AD. Although there are several hurdles in developing successful treatments for Alzheimer's disease[104], namely understanding the pathogenesis and successfully approaching the factor(s) involved in progression, early intervention and treatment efficacy are the most important factors that influence changes in the progression of AD. Current treatments have been met with little effectiveness, although vaccination against Aβ and early supplementation of ALCAR and LA may provide more promising results in the future. Combining therapies such as these at an early stage may prove to be a very effective therapeutic strategy once more progress has been made in clarifying AD pathogenesis.

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