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Review article

Energy and the Alzheimer brain

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ABSTRACT

The high energy demands of the poorly myelinated long axon hippocampal and cortical neurons render these neurons selectively vulnerable to degeneration in Alzheimer's disease. However, pathology engages all of the major elements of the neurovascular unit of the mature Alzheimer brain, the neurons, glia and blood vessels. Neurons present with retrograde degeneration of the axodendritic tree, capillaries with string vessels and markedly reduced densities and glia with signs of inflammatory activation. The neurons, capillaries and astrocytes of the mature Alzheimer brain harbor structurally defective mitochondria. Clinically, reduced glucose utilization, decades before cognitive deterioration, betrays ongoing energy insufficiency. β-hydroxybutyrate and γ-hydroxybutyrate can both provide energy to the brain when glucose utilization is blocked. Early work in mouse models of Alzheimer's disease demonstrate their ability to reverse the pathological changes in the Alzheimer brain and initial clinical trials reveal their ability to improve cognition and every day function. Supplying the brain with energy holds great promise for delaying the onset of Alzheimer's disease and slowing its progress.

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The mature Alzheimer brain presents with a daunting display of pathology highlighted by intracellular aggregations of hyperphosphorylated tau (p-tau) and extracellular deposits of aggregated β-amyloid (βA) peptide (Wang et al., 2014b). Although repeatedly referred to as the hallmarks of Alzheimer's disease (AD) neither of these aggregations is unique to the disease (McKee et al., 2009, 2015) and, even at this late date in the history of Alzheimer's, their true nature remains an enigma. Are they epiphenomena of the aging brain, found in man and other primates (Finch and Austad, 2015) and without pathological significance or do they play a role in the ongoing deterioration of the brain? Is it possible that they actually have a neuro-protective function? How do they relate to one another and to the other well recognised features of the Alzheimer brain such as its atrophy, synaptic pathology, autophagic vesicles, granulovacuolar degeneration, neuro- inflammation and amyloid angiopathy? What accounts for the striking deterioration of the micro-circulation in the Alzheimer brain and the reduction in capillary density, loss of vascular endothelium and breakdown of the blood brain barrier (Baloyannis and Baloyannis, 2012; Brown and Thore, 2011; Zlokovic, 2011)? What causes the structural damage of the mitochondria in vulnerable neurons, astrocytes, capillary endothelial cells and pericytes (Aliyev et al., 2005; Baloyannis, 2006; Baloyannis and Baloyannis, 2012; Hirai et al. ,2001)? How do all of these pathological changes come about? The most parsimonious answer may lie in the progressive failure of the Alzheimer brain to generate the energy it needs to maintain its integrity. And therein may also be found the basis for its treatment.

1. Neurofibrillary tangles

1.1. Development and evolution

If the earliest appearance of abnormally phosphorylated tau (p-tau) marks the microscopic beginning of AD, its natural history has been suggested to start in young adulthood or even before puberty when soluble phosphorylated tau (pre-tangles) can be immunologically identified in certain brainstem and subcortical non-thalamic nuclei such as the noradrenergic locus coeruleus in particular but also in the serotonergic upper raphe, the cholinergic magnocellular nuclei of the basal forebrain and the hypothalamic tuberomamillary nucleus (Braak and Del Tredici, 2011, 2012, 2015). All of these nuclei give rise to diffuse sparsely myelinated long axons which project to the cerebral cortex and other brain regions. Phosphorylated tau can first be identified immunologically in the proximal axon of these neurons and subsequently fills the somatodendritic compartment. The soluble p-tau of this pre-tangle state is said to gradually aggregate into non-soluble fibrillary inclusions within dendrites to form neuropil threads (NTs) and within nerve cell bodies to form neurofibrillary tangles (NFTs). These insoluble argylophilic aggregates usually first appear in the trans entorhinal region in early middle age and resist removal by autophagy and other cellular mechanisms (Braak et al., 2011; Knopman, 2014). It remains debatable, however, whether the immunologically identified pre-tangle p-tau identified in brainstem and subcortical nuclei in the young is a true forerunner of Alzheimer tau and Alzheimer's disease (Attems et al., 2012; Attems and Jellinger, 2013; Braak and Del Tredici, 2013; Duyckaerts et al., 2015; Jellinger et al., 2015; Mann and Hardy, 2013). Neurons appear to be able to tolerate the presence of pre-tangles, NTs and NFTs and to survive for many decades even though they may not be functioning optimally. They tend to die prematurely leaving extraneuronal 'ghost' tangles in the neuropil. Ghost tangles, however, are always found in the company of fresh NFTs and NTs which reveal that the pathological process was ongoing at the time of death (Braak and Braak, 1997). Brain atrophy correlates well with the burden of NFTs (Josephs et al., 2008; Whitwell et al., 2008).

The pace at which tau pathology develops and spreads varies from person to person but pre-tangles, NTs and NFTs can remain localized to subcortical regions (Braak stages I/II) in some individuals until late age and only become associated with cognitive impairment and the dementia of AD when they spread to the neocortex. Little is known about the pace of this advance (Braak and Tredeci, 2011). Only after pre-tangles develop in brainstem and subcortical neurons do pre-tangles appear in the trans-entorhinal cortical region from which they spread in a systematic and sequential manner to defined regions of the brain according to their anatomical relationship to other neurones and not according to cell type. Thus, only specific neuronal circuits are targeted in AD. Abnormal tau molecules may propagate from region to region in a prion-like manner through synaptic contacts although other routes have also been proposed (Liu et al., 2012; McKee et al., 2015; Wu et al., 2013). The first transfer occurs between the subcortical terminal axons and the pyramidal cells of the trans-entorhinal region where the first signs of degeneration may be seen (Frost and Diamond, 2010). Glutamatergic cells in this region project to the entorhinal cortex which is the next region to degenerate followed by lesions of the hippocampus, amygdala and neocortex. Cortical and hippocampal pyramidal neurons which contain high levels of neurofilament protein and have long projections are particularly vulnerable to NFT formation (Braak et al., 2006a,b; Morrison et al., 1998). Thus, the pyramidal neurons most prone to NFT formation are found in cortical layers III and V which send long projections to other cortical regions and in the efferent neurons of layers II and IV of the CA1 field and entorhinal cortex. Neurofilaments in these neurons appear to participate in NFT formation as their density declines as NFTs are assembled. On the other hand, calcium −binding-protein containing interneurons are remarkably resistant to degeneration in AD. Interestingly, these interneurons rarely exhibit neurofilament immunoreactivity (Morrison et al., 1998). As will be discussed again later in this review, AD appears to begin in the CA1 region in association with the very early loss of the

microvasculature in this region (Bailey et al., 2004). The initial invasion of the trans-entorhinal and entorhinal regions by NFTs (Braak stages I and II) are subclinical and generally develop in the absence of amyloid deposits (Braak et al., 2011, 2006a,b; Braak and Braak, 1997, 1991). Signs of cognitive impairment become evident once lesions involve the hippocampus, temporal and insular cortex and anterior cingulate gyrus (Braak stages III and IV). Severe involvement of most neocortical association areas occurs during Braak stage V but the primary fields of the neocortex and to a large extent the premotor and first order sensory association areas of the neocortex remain spared of pathology. Nearly all neocortical areas show neurofibrillary changes in Braak stage VI. Signs of dementia are clearly evident in Braak stages V and VI. The sequential advance of neurofibrillary pathology inversely resembles the sequential myelination of the cortex (Braak and Braak, 1996; Braak and Del Tredici, 2015).

1.2. Neuronal vulnerability

Only a few of the many different types of neurons in the brain develop abnormal tau aggregates. Other cells, directly adjacent, retain their normal morphology (Braak et al., 2006a,b; Morrison et al., 1998). As noted earlier, most vulnerable cells have two major characteristics: they are all projection neurons with high concentrations of neurofilaments and among these only cells with disproportionately long and thin axons in relation to the size of the parent soma show a tendency to develop lesions. Tau lesions develop in phylogenetically late appearing and ontogenetically late maturing neurons that connect to one another, axon to axon (Braak and Braak, 1996; Braak and Del Tredici, 2015). Moreover, the long and thin axons of these vulnerable neurons have thin myelin sheath or remain unmyelinated. A mature myelin sheath reduces the metabolic demands on the parent cell for the transmission of impulses (Morrison et al., 2013). Thus, rapid firing projection neurons that are poorly myelinated or unmyelinated have higher energy requirements than myelinated neurons and are therefore more likely to become vulnerable to energy insufficiency, oxidative stress and its consequences (Braak et al., 2006a,b; Morrison et al., 2013). Because myelin limits axonal access to extracellular glucose, energy for axonal survival depends on supplementary lactate and ketone bodies carried along monocarboxylate transporters (Morrison et al., 2013). Morphologically, temporal studies reveal a retrograde degeneration or 'dying back' of the axodendritic tree (Braak et al., 1994; Morrison et al., 2013; Terry, 1998). This 'dying back' neuropathy likely indicates an early failure of axonal function. A decrease in the number of microtubules and a pileup of vesicles in the cell bodies suggests that an early breakdown of axodendritic transport best accounts for the 'dying back' and synaptic loss (Braak et al., 1994; Terry, 1998). Clinically, AD reflects the large number of neurons with limited functional capacity rather than massive neuronal loss (Braak and Del Tredici, 2012).

1.3. Metabolic antecedents

Much evidence suggests that these structural changes transpire in an environment of altered energy metabolism and oxidative stress that precedes the aggregation of tau. Thus, morphometric analysis reveals that mitochondrial numbers are significantly decreased in Alzheimer's disease (Hirai et al., 2001). Mitochondria in vulnerable neurons display broken cristae and a partial or complete loss of internal structure and these changes are evident even before the appearance of NFTs (Baloyannis, 2006; Baloyannis and Baloyannis, 2012; Hirai et al., 2001). A striking rise in cytoplasmic and vacuolar mtDNA and cytochrome oxidase levels betrays the increased autophagic degradation of these mitochondria or a reduced proteolytic turnover (Hirai et al., 2001). The very early oxidation of cytoplasmic RNA, evident even before NFTs can be identified, may result from the induction of hemeoxygenase by heme released from rapidly turning over mitochondria and the subsequent production of redox active Fe^{+2} (Castellani et al., 2007; Moreira et al., 2006; Honda et al., 2005; Nunomura et al., 2009, 2001, 1999). Although neuronal RNA oxidation in vulnerable neurons occurs as an age related phenomenon, more prominent RNA damage than in normal aging correlates with the onset of cognitive impairment in the prodromal stage of AD (Nunomura et al., 2012). As AD advances, the accumulation of beta-amyloid (βA) and the formation of NFTs appear to significantly reduce but not eliminate oxidative stress and suggest a protective function for these subcellular structures (Nunomura et al., 2001). Concurrent with this mitochondrial pathology and the increase in oxidative stress, and again, in the absence of paired helical filaments, a clear deficit in microtubule number and length is evident in vulnerable pyramidal neurons (Cash et al., 2003). The cognitive deficits of AD have been proposed to follow from the consequent decline in axoplasmic flow and loss of synaptic connectivity (Terry, 1998, 1996). Cytoskeletal proteins are vulnerable to the actions of 4-hydroxynonenal, a toxic product of lipid peroxidation (Montine et al., 1997; Neely et al., 1999). Signs of lipid and protein oxidation can also be identified in the Alzheimer brain before the formation of NFTs (Sayre et al., 1997).

Energy deprivation and oxidative stress appear to play key roles in the genesis of other major characteristics of the Alzheimer brain. Oxidative stress has been proposed to reduce glucose utilization by oxidizing and destabilizing hypoxia inducible factor (HIF-1), a transcription factor which regulates the expression of blood brain barrier endothelial cell glucose transporter GLUT-1 and the neuronal glucose transporter GLUT-3 and this has been held to account for the reduced expression of these transporters in the Alzheimer brain (Liu et al., 2008; Nikinmaa et al., 2004). Perhaps even more critical, oxidative stress, as will be detailed later, reduces glucose utilization by shifting intermediary metabolism away from glycolysis and oxidative phosphorylation (Mamelak, 2012). But, in either case, the overall reduction in glucose utilization in vulnerable neurons depresses the hexosamine biosynthetic pathway and reduces O-GlcNAcylation which, in turn, promotes tau phosphorylation (Iqbal et al., 2014; Liu et al., 2009, 2008; Su et al., 2010). Oxidative stress also inhibits protein phosphatase 2A, a major enzymatic regulator of tau phosphorylation. The reduced expression and activity of this enzyme in the Alzheimer brain is thought to be a key factor in the hyperphosphorylation of tau (Iqbal et al., 2014; Liu et al., 2009; Su et al., 2010; Vogelsberg-Ragaglia et al., 2001). Energy deprivation also leads to the early activation of adenosine monophosphate protein kinase (AMPK), and again, even before the phosphorylation of tau can be detected (Vingtdeux et al., 2011). In vitro studies reveal that activated or phosphorylated AMPK (pAMPK) can phosphorylate tau at residues relevant to paired helical tangle formation. AMPK activation also leads to the inhibition of mTOR which in turn triggers autophagy, a known cellular response to energy insufficiency (Salminen et al., 2011). Thus, autophagy has been shown to occur very early in AD. Autophagic and endocytic pathways share the role of delivering unneeded cellular materials to lysosomes for degradation and recycling to provide energy to the cell and building blocks for new synthesis (Ihara et al., 2012). Genes related to endocytosis are among the earliest to show up regulated transcription and endosome anomalies are the earliest specific pathology reported in the Alzheimer brain (Cataldo et al., 1997, 2000; Ginsburg et al., 2010; Ihara et al., 2012). Neuronal endosome enlargement can be identified in neocortical pyramidal cell neurons during Braak stage II when plaques and tangles are restricted to the hippocampus but cannot be detected in the brains of similarly aged individuals free of AD-like hippocampal pathology. The unfolded protein response (UPR), a sign of endoplasmic

reticulum stress, is also activated in the hippocampus and temporal cortex early in the course of AD before the formation of NFTs but not in the neocortex (Hoozemans et al., 2005, 2009). UPR activation is known to induce glycogen synthase kinase 3β activity, a major kinase for tau phosphorylation. The markers of UPR activation, pPERK, peIF2α and pIRE1α are found localized to granules with histochemical and ultrastructural characteristics of granulovacuolar degeneration (GVD), a type of autophagosome, and provide further evidence for the nutritional and energy deficiency of the early Alzheimer brain (Funk et al., 2011).

Thus, phosphorylated tau is formed and advances into neuronal cells which are metabolically compromised. Phosphorylation and the subsequent aggregation of tau occur in an oxidative environment deprived of energy (Liu et al., 2009; Su et al., 2010). NFTs display post translational modifications typical of non-enzymatic advanced Maillard reaction end products. Such Maillard modifications are initiated and potentiated during oxidative stress and would generate the cross-linked aggregates of insoluble protein characteristic of NFTs (Srikanth et al., 2011). But, as noted earlier, experimental data reveal that the formation of NFTs may actually detoxify the environment in which they are formed and have a cytoprotective function (Li et al., 2007; Nunomura et al., 2001; Smith et al., 2002). Thus, although the activation of pro-apoptotic initiator caspases is evident early in vulnerable neurons, there is a lack of effective apoptotic signal propagation to distal effectors and apoptotic cell death, which normally requires about 16–24 h for completion, doesn't happen (Avila, 2010; Li et al., 2007; Raina et al., 2003; Wang et al., 2014a; Wang and Liu, 2008). Most NFT-bearing neurons are fated to degenerate rather than undergo apoptosis (Li et al., 2007) Tau phosphorylation blocks apoptosis by stabilizing β-catenin. p-Tau appears to block the activation of downstream effect of caspases and the apoptotic cascade (Avila, 2010; Li et al., 2007; Raina et al., 2003; Wang et al., 2014a; Wang and Liu, 2008). Among its many anti-apoptotic actions, it preserves members of the Bcl-2 family and suppresses the release of cytochrome-c from mitochondria into the cytoplasm.

p-Tau thus appears to be both neuroprotective and neurotoxic. Although neurons remain viable in the presence of p-tau, they are also dysfunctional as hyperphosphorylated tau interferes with microtubule assembly and other physiological functions. Although "sick" these neurons survive and only undergo retrograde degeneration after many years. Can they heal and recover?

1.4. Hibernation

Hibernation offers another way of thinking about tau phosphorylation. While tau phosphorylation is viewed as pathogenic in AD and other neurological disorders, it occurs naturally and reversibly in hibernating animals as part of a process which protects the brain against the effects of starvation, hypothermia and energy insufficiency. During hibernation, tau phosphorylation is coupled with extensive trimming of the pyramidal dendritic tree and a reduction in the number of synaptic contacts (Arendt et al., 2015; Mamelak, 2007; Popov et al., 1992; Popov and Bocharova, 1992; Su et al., 2008). Phosphorylation and inactivation of glyceraldehyde-3-phosphate and pyruvate dehydrogenase during hibernation mediate the inhibition of glycolysis and oxidative metabolism and reduce brain glucose utilization (McCarron et al., 2001; Story and Story, 2005). All of these anatomical and metabolic changes are rapidly reversed within hours during the recurrent arousals and the returns to euthermia which punctuate hibernation in small animals. The need for these recurrent arousals to normal body temperature suggests that prolonged periods of metabolic depression may result in irreversible tissue damage. Tau phosphorylation in AD may also start as part of a global protective response to energy deprivation but in AD this metabolic depression persists. Relief never comes.

Experimental work, however, with a mouse model of AD demonstrates that the early provision of energy to the brain limits both the development of NFTs and the deposition of βA (Kashiwaya et al., 2013).

2. Beta amyloid

2.1. anatomical distribution

The anatomical distribution and temporal development of all types of extracellular βA plaques differs from that of tau based lesions and argues for the independent development of these two disease biomarkers (Braak et al., 2013; Braak and Braak, 1997; Nelson et al., 2012; Price and Morris, 1999). Tangles form preferentially in the limbic structures and well before amyloid deposits are first identified in the neocortex. Diffuse deposits of aggregated βA most frequently first appear between the ages of 30 and 40 in the poorly myelinated regions of basal temporal cortex before extending into the hippocampus, entorhinal cortex, cingulate cortex and amygdala and then into all areas of the cortex including the densely myelinated primary areas. In the mature Alzheimer brain, amyloid plaques can also be found in the basal ganglia, diencephalon, midbrain, medulla oblongata, pons and cerebellum but even in cases with high plaque density, the cortex is never completely filled with βA plaques. Again, an inverse relationship is observed between the degree of myelination and the density of amyloid deposition (Braak and Braak, 1997).

2.2. Relation to NFTs

βA accumulates very slowly over a 15 year period and plateaus at a high level in keeping with a state of equilibrium. These levels do not increase further once dementia ensues (Jack et al., 2013; Knopman, 2014). An estimated 20–40% of cognitively normal individuals between the ages of 60 and 90 have high levels of βA in their brains. Although this is inconsistent with the thesis that βA is a neurotoxin that directly impairs cognition, it has nevertheless been found that individuals with a high brain βA burden show significantly greater rates of grey matter atrophy and memory decline than those with low levels of cerebral βA (Chetelat et al., 2012; Knopman, 2014; Villemagne et al., 2013). Braak stages I/II can be identified well before the earliest deposition of βA but NFT pathology also evolves very slowly. Although Braak stages I/II are very prevalent in young people, many decades may separate these stages from Braak stages III/IV. βA deposition begins during this interval and has therefore been proposed to accelerate the topographic spread of NFTs by an as yet unknown mechanism (Duyckaerts and Hauw, 1997; Jack et al., 2014; Price and Morris, 1999). Widespread neocortical NFTs are virtually non-existent in the mature Alzheimer brain in the absence of βA deposits (Nelson et al., 2012).On the other hand, NFTs are known to occur in the complete absence of amyloid in many neurodegenerative disorders and thus the pre-existence of amyloid in any form does not appear to be an absolute requirement for the excessive phosphorylation of tau and the formation of NFTs (Reed et al., 1997). Moreover, in AD, the clearance of amyloid plaques from the brain following active immunization with βA fails to stem the progressive cognitive decline, the formation of NFTs and the ongoing neurodegeneration (Holmes et al., 2008; Yoshiyama et al., 2013). This argues that βA accumulates because the metabolic events which drive the phosphorylation of tau and the spread of NFTs concomitantly inhibit the clearance of βA. Energy failure, a function of microvascular damage, hypoxia and oxidative stress as described earlier, are the events which most readily come to mind.

These pathological events reduce the clearance of βA across the blood brain barrier (BBB) and oxidize and reduce the expression of neprilysin, one of two endopeptidases engaged in the degradation of βA (Blurton-Jones et al., 2014; Wang et al., 2003; Zlokovic, 2004).

2.3. Physiological function

βA is a normal soluble product of neuronal metabolism but despite numerous studies its actual physiological function remains elusive. Could it have a vital function? The production of βA ordinarily appears be a critical requirement for the viability and function of neurons and studies suggest that βA actually enhances memory at its physiological picomolar concentrations (Abramov et al., 2009; Morley and Farr, 2014; Plant et al., 2003). Efforts to immunologically remove βA from the Alzheimer brain have caused encephalitis in some subjects treated with active immunization and vasogenic and sulcal edema and microhemorrhages in some patients treated with passive immunization (Wisniewski and Goni, 2014).

3. Familial Alzheimer's disease

3.1. the amyloid cascade hypothesis

How did βA and specifically the aggregation prone βA42 peptide come to be identified as the great Satan of AD? βA was assigned its very prominent role in AD after genetic studies revealed that mutations in the alzheimer precursor protein (APP) and the presenilins, PSEN1 and PSEN2, were strongly associated with early onset familial AD (FAD) (Hardy and Selkoe, 2002). The presenilins are the catalytic component of γ-secretase, the membrane embedded aspartyl protease complex that partners with β-secretase to cleave APP and generate βA. Although mutations in APP and the presenilins accounted for less than 5% of all cases of AD, they were fully penetrant and therefore guaranteed the onset of the disease (Tanzi and Bertram, 2005). The great majority of the FAD mutations also conferred a similar biochemical phenotype with a significant increase in the extracellular plasma level of βA42 compared to βA40 (Borchelt et al., 1996; Scheuner et al., 1996). βA42 was found to be more prone to aggregation and appeared to be more toxic. The amyloid cascade hypothesis was subsequently formulated and proposed that an imbalance between the formation and clearance of βA initiated the degenerative process which led to the formation of NFTs, synaptic loss and the full blown pathology of AD (Tanzi and Bertram, 2005). However, it should be noted that no increase in the plasma level of βA42 has been found in late onset sporadic Alzheimer's disease (Scheuner et al., 1996).

3.2. Mutations

It is now recognized that over 200 mutations in APP and the presenilins are associated with FAD. About 180 mutations in PSEN1 alone are associated with FAD (Chau et al., 2012). Presenilin mutations alter γ-secretase activity but many of these mutations also affect intracellular calcium signalling (Bezprovzanny, 2013). Some presenilin mutations primarily affect γ-secretase function and produce a very high ratio of βA 42: βA 40 while others primarily affect the endoplasmic reticulum(ER) Ca^{2+} leak function and result in ER Ca^{2+} overload. Some mutations both increase the Aβ42:Aβ40 ratio and disrupt calcium homeostasis. Thus, clinical phenotypes of presenilin mutant families are quite heterogeneous (Castellani and Perry, 2014). Mutations with strong effects on γ-secretase function appear to segregate with phenotypes that are characterized by cotton wool plaques and paraparesis and appear to be quite distinct from AD, while mutations that affect the ER Ca^{2+} leak functions are not. The transfer of $Ca^{2+}$from the ER to mitochondria docks the mitochondria at structurally unique sites on the ER surface (MAM) and stimulates energy metabolism and the synthesis of ATP. γ-Secretase also cleaves APP at these sites to produce βA (Schon and Rea-Gomez, 2013). Is a disturbance in calcium and energy metabolism rather than the overproduction of βA42 the critical factor in the premature development of AD in these genetic disorders? This issue may shortly be clarified.

3.3. A clinical trial

A Colombian kindred with more than 5000 members carrying the PSEN1-E280a mutation and around 600 affected individuals constitutes the largest known cohort of PSEN1-FAD patients (Sepulveda-Falla et al., 2014). PSEN1-E280 carriers suffer from an early and aggressive dementia with wide clinical variability including the development of ataxia and seizures and memory impairment starting as early as the third decade (Sepulveda-Falla et al., 2014; Sepulveda-Falla et al., 2011). As in all individuals with PSEN1 mutations, those with PSEN1-E280 mutations also present with an increased βA42:βA40 ratio. Neuropathological studies reveal a high plaque load in the frontal cortex and in the cerebellum containing mainly βA42 in large diffuse and cotton wool plaques. Unlike patients with sporadic AD, patients with PSEN1-E280 also have p-Tau deposits in the cerebellum (Sepulveda-Falla et al., 2011). Signs of cerebellar motor dysfunction are an early clinical feature but start before βA deposition becomes prominent in the cerebellum. Ultrastructural analysis reveals that the number of Purkinje cells is significantly reduced and contain substantial numbers of structurally abnormal mitochondria. Moreover, these mitochondria, even when morphologically normal, are rarely localized in close proximity to rough ER in contrast to their distribution in tissue from patients with sporadic AD or controls. ER/mitochondrial tethers are defective in PSEN1-E280 tissue, calcium channels are down-regulated and calcium dependent mitochondrial transport proteins are reduced. PSEN1-E280 expression in a neuronal cell line also altered ER/mitochondrial tethering and transport. Thus impaired calcium homeostasis and mitochondrial dysfunction appear to contribute to the loss of motor coordination before the aggregation of βA and before dementia develops (Sepulveda-Falla et al., 2014). A PSEN1-E280 family has been selected for a clinical trial of a humanized antibody against oligomeric forms of βA. This trial should provide important insights into the role of the non-APP processing functions of PSEN1 in PSEN1-FAD (Sepulveda-Falla et al., 2014). What effect will neutralizing these βA oligomers have on the progress of this disease?

4. Down syndrome

4.1. Physiology and morphology

The premature development of AD in trisomy 21 or Down syndrome (DS) in which plasma levels of βA are increased and the gene for APP on chromosome 21 is triplicated provided another reason for assigning a central role to βA in the pathogenesis of AD. Down syndrome is the most common genetic cause of mental retardation. It is characterized by a general acceleration of the aging process and by the development of changes in the brain similar to AD by age 30 (Arbuzova et al., 2002; Busciglio et al., 2002). Chromosome 21 has been completely sequenced and includes genes for APP and for Cu, Zn superoxide dismutase (SOD-1) but despite numerous attempts, it has not been possible to convincingly determine whether the anatomical, physiological and functional features of the syndrome follow from an increased gene dosage effect. Moreover, the wide variation in the onset and severity of the dementia suggests that

many other factors come into play (Arbuzova et al., 2002). In DS, APP is over expressed in brain and peripheral lymphocytes throughout life (Coskun et al., 2010). Increased levels of βA42, which betray an increase in β-secretase activity, are found in the plasma and soluble βA 42 can be detected in the brains of DS subjects but not in control subjects from as early as gestational age 21 weeks (Busciglio et al., 2002; Teller et al., 1996). Despite the presence of high levels of the very aggregative solubleβA42 in the brain, diffuse βA plaques do not develop earlier than the second decade of life. The first NFTs appear in the third decade. The numerical density of NFTs and neuritic plaques increases with age and Alzheimer pathology is seen in virtually all DS individuals over the age of 35 (Sadowski et al., 1999). As in AD, the entorhinal cortex appears to be damaged early and severely in DS (Sadowski et al., 1999). The significant negative correlation between the total number of intact neurons and the percentage of neurons with neurofibrillary changes indicates that neurofibrillary degeneration is the major cause of neuronal loss. The relatively low amyloid load and the lack of correlation between the amyloid load and the neuronal loss in the entorhinal cortex suggests that the contribution of βA to the neuronal loss is insubstantial (Sadowski et al., 1999).

4.2. Oxidative stress

Perhaps the most striking feature of DS is the high level of oxidative stress evident very early on both centrally and peripherally. Signs of oxidative stress have been identified in red blood cells, lymphocytes, urine and cerebral neurons (Jovanovic et al., 1998; Garlet et al., 2013; Nunomura et al., 2000; Zana et al., 2006). Fibroblasts from trisomic foeti show upregulated chromosome 21 genes and down regulated nuclear encoded mitochondrial genes, structurally abnormal mitochondrial cristae, deficient mitochondrial respiratory activity and a specific inhibition of complex 1, enhanced ROS production and increased levels of mitochondrial calcium (Piccoli et al., 2013). Intracellular levels of ROS are increased 3–4 fold in DS fetal neurons and contain high levels of lipid peroxides (Busciglio and Yanker, 1995). The alterations in mitochondrial morphology observed in fetal neurons and astrocytes is coupled to decreased ATP formation and this energy deficit is proposed to ultimately account for the development of AD in DS (Helguera et al., 2013).

It has been widely assumed that a gene-dosage effect producing about a 50% increase in SOD-1 activity accounts for the pervasive signs of oxidative stress in DS (Arbuzova et al., 2002). Accordingly, it has been proposed that in the face of an inadequate antioxidant defence, the over expression of SOD-1 results in an overproduction of hydrogen peroxide followed by the subsequent generation of the ravaging hydroxyl radical and widespread organ damage (Garlet et al., 2013). However, the available evidence fails to support this thesis and it appears more likely that the increase in SOD-1 activity in DS occurs in response to oxidative stress and the high levels of O_2^- (Arbuzova et al., 2002; Arbuzova, 1998). Gene loading raises the potential for an increased protective response to O_2^-. Similarly, the over expression of APP may also be a protective response rather than a gene dosage effect. Neuronal oxidative damage appears to decrease with the deposition of βA (Nunomura et al., 2000).

4.3. Non-disjunction

The reason for the increase in non-disjunction of maternal chromosomes with age that leads to the sharp increase in frequency of trisomy 21 in mothers over the age of 30 remains unknown (Arbuzova et al., 2002, 2001; Schon et al., 2000). Meiosis, the process by which chromosomes are pulled apart, requires the energy provided by mitochondrial oxidative phosphorylation. Oocytes have by far the largest number of mitochondria and mtDNA copies of any cell (Bentov and Casper, 2013; Lagouge and Larsson, 2013). mtDNA contains genes which partially encode proteins of the respiratory chain and a significant loss of this DNA will result in dysfunctional oxidative phosphorylation and impaired energy production. mtDNA mutations and deletions accumulate with age particularly in oocytes primarily because of errors in mtDNA replication and repair (Gaziev et al., 2014; Itsara et al., 2014; Keefe et al., 1995; Lagouge and Larsson, 2013). Thus, in some older mothers, mitochondrial energy production may not be sufficient to effect normal meiosis and non-disjunction results. Since mitochondria are maternally inherited, fetal mitochondria are likewise unable to meet the energy requirements of normal growth and development. Thus advanced grand-maternal age at the birth of the mother is associated with an increased risk of DS in the infant (Aagesen et al., 1984). The great majority of mothers between the ages of 19 and 29 who give birth to infants with Down syndrome had mothers older than 30 (Malini and Ramachandra, 2006). The relevance of insufficient mitochondrial energy production in the development of both Down syndrome and AD is underscored by the fivefold increase in the eventual development of AD in mothers under the age of 35 who give birth to children with Down syndrome (Schupf et al., 2001, 1994).

5. Energy metabolism

5.1. Genetics

After advancing age, having a parent or first degree relative with AD is the most significant risk factor for developing AD (Mosconi et al., 2010). The predominance of genetic over environmental factors in the development of the disease is revealed by twin studies which show a greater than 80% concordance rate of the disease in monozygotic twins (Gatz et al., 1997; Raiha et al., 1997). Children of AD mothers are at higher risk for developing AD than children of AD fathers and epidemiological studies show that maternally inherited AD may account for over 20% of all late onset AD (Mosconi et al., 2010). However, the genes involved in maternally inherited AD do not follow an autosomal pattern of inheritance and penetrance does not appear to be high as many children of mothers with AD do not develop the disease. Given the findings in Down syndrome, it might be expected that defects in mtDNA and corresponding defects in the electron transport and energy metabolism would play a prominent role in the development of AD. mtDNA would be equally inherited by male and female children and, indeed, brain ^{18}F FDG PET studies reveal that clinically asymptomatic male and female children of AD mothers but not fathers are at risk of developing brain hypometabolism early in life decades before clinical signs develop. These cognitively normal adults were also found to have reduced platelet mitochondrial cytochrome oxidase activity (COX electron transport chain complex IV) (Mosconi et al., 2011). Inheritance of defective mtDNA may therefore influence the probability of eventually developing AD.

5.2. mtDNA

Most mitochondrial DNA mutations are not inherited but arise during the course of life. The frequency of mtDNA mutations and deletions has been shown increases with age and it is now appreciated that there is an up to fivefold increase in the frequency of mtDNA mutations in the human brain over the course of 80 years of life (Gaziev et al., 2014; Kennedy et al., 2013). However, disturbed tissue energy homeostasis is only likely to develop if the frequency of mutations and deletions exceeds a critical threshold and under these circumstances cells protect themselves by reducing the number of dysfunctional mitochondria and by activating mitochondrial dynamics and biogenesis. Mitochondrial quality

control and renewal are essential for energy homeostasis. Mitochondrial dynamics through fission and fusion play a key role in the exchange of components between damaged and functionally normal mitochondria. High levels of mitochondrial morphological alterations inhibit fusion and fission. The selective degradation of damaged mitochondria by mitophagy (autophagy) preserves and renews functionally active mitochondria but mitophagy decreases with age. In any case, to date, it has been difficult to establish the exact role of mtDNA deletions in pathogenesis of AD. Although it has been proposed that mutations and deletions in mtDNA impair the operation of the respiratory chain and interfere with the production of energy, many studies fail to observe differences in intracellular ATP levels between wild type cells and cells with mutated DNA despite clearly defective mitochondrial ATP synthesis machinery (Szczepanowska et al., 2012). Lower ATP synthesis in mitochondria does not have to be followed by reduced cytosolic ATP levels if glycolysis is intact. Under resting conditions this may be sufficient. Glycolysis is unable to meet the ATP requirements of the cell only when the demand for energy is increased or the supply of glucose is reduced. Under those conditions cellular ATP levels will fall. A gradual and progressive reduction in glucose utilization is a characteristic feature of the Alzheimer brain.

5.3. APOe4

Expression of the APOe4 allele is recognized as the strongest genetic risk factor for Alzheimer's disease although it is neither necessary nor sufficient for its development. Possession of the apolipoprotein e4 (APOe4) allele significantly increases the risk of developing Alzheimer's disease and decreases its age of onset. At least one APOe4 allele is found in about 15–25% of the general population and at roughly twice this frequency or even greater in patients with Alzheimer's disease (Tanzi and Bertram 2005; Zlokovic, 2013). Just how APOe4 increases the risk of Alzheimer's disease is uncertain but its unique unstable structure may play a prominent role. APOe has 3 isoforms, APOe2, APOe3 and APOe4. All 3 isoforms are synthesized in the brain primarily by astrocytes to support lipid transport and membrane repair but they can also be synthesized in neurons in response to injury and stress. Carriage of the APOe2 genotype decreases the risk of Alzheimer's disease (Slooter et al., 1998; Verghese et al., 2011). APOe2 has two cysteine residues and is a much stronger antioxidant than APOe4 which has no cysteine residues (Miyata and Smith, 1996). Brain levels of the lipid peroxidation products malondialdehyde and hydroxynonenal are higher in carriers of the APOe4 allele (Montine et al., 1997; Ramassamy et al., 1999). NFTs are more frequently found in the brain early in the course of AD in carriers of the AOPe4 allele (Ghebremedhin et al., 1998). Studies in neuronal cell cultures show that APOe4 promotes oxidative stress because it is exclusively subject to proteolysis in neurons and the generation of neurotoxic fragments which decrease the levels and activity of neuronal mitochondrial respiratory enzymes and mitochondrial motility (Chen et al., 2011; Mahley and Huang, 2012; Zhong and Weisgraber, 2009). ^{18}F FDG PET studies show that compared to non-carriers, asymptomatic carriers of the APOe4 allele show reductions in cerebral glucose utilization in brain regions typically affected by AD (Reiman et al., 2004, 2001). These reductions can be found decades before the possible onset of AD.

5.4. Glucose utilization

Despite the strong evidence for genetic defects in the regulation of mitochondrial energy metabolism, Alzheimer's presents clinically in the later years of life. Even in Down syndrome, where mitochondrial deficits, high levels of oxidative stress and even high levels of βA have been recognized in the fetal brain, cognitive decline first makes its appearance in the fourth and fifth decades of life. A young brain seems to be able to cope with oxidative stress and compensate for suboptimal mitochondrial function. The decline in cerebral glucose utilization in vulnerable brain regions many years preceding the development of clinical concerns may herald the breakdown of this compensatory process in the face of persistent levels of oxidative stress and mitochondrial failure. Under these circumstances, vulnerable neurons may deploy the response of all eukaryotic cells to oxidative stress by turning down the production of reactive oxygen species. Glucose utilization is diverted away from glycolysis and oxidative phosphorylation towards the pentose phosphate shunt and the regeneration of nicotinamide adenine dinucleotide phosphate (NADPH) (Mamelak, 2012). This diversion acts as an immediate protective response against oxidative stress and the mitochondrial generation of reactive oxygen species. NADPH provides the reducing power for most antioxidant and redox regulatory enzymes including glutathione/glutaredoxin, thioredoxin, heme oxygenase-1 and the aldo-keto- reductases. These are the major enzymatic systems controlling cell redox homeostasis. In response to oxidative stress, glucose utilization is directed away from energy formation towards reductive biosynthesis and the formation of lipids, proteins and nucleic acids (Mamelak, 2012). In the mature Alzheimer brain, glucose-6-phosphate dehydrogenase activity, the first step in the pentose phosphate pathway required for the production of NADPH, is increased by about 50% but a significant increase in activity is also evident in the brains of patients with minimal cognitive impairment (Soucek et al., 2003; Sultana et al., 2008).

While the synthesis of many proteins increases in response to oxidative stress, the formation of others is repressed while still others are oxidized and inactivated (Mamelak, 2012). In the late stages of late-onset AD, the expression of key enzymes in the glycolytic and tricarboxylic acid pathways engaged in energy metabolism is either reduced or found to be oxidized and less efficient. For example, glyceraldehyde-3-phosphate dehydrogenase and enolase, the two enzymes in the glycolytic pathway engaged in the generation of ATP, are both oxidatively modified. Pyruvate dehydrogenase and α-ketoglutarate-dehydrogenase are also oxidatively inactivated. The activities of all decarboxylating dehydrogenases in the AD brain are reduced while the activities of the dehydrogenases in the second half of the cycle are increased, seemingly in compensation. This enzymatic adaptation has also been observed in other conditions of energy shortage such as chronic hypoxia and suggests the use of an alternative route for energy formation to bypass a metabolic block (Bubber et al., 2005; Caceda et al., 2001) (Fig. 1).

6. Vascular disease

6.1. Pathology

Vulnerable neurons in AD are constituents of a neurovascular unit (NVU) composed of neurons, capillary endothelial cells, pericytes and glia. All elements of this unit operate in tandem but, at some point in time, for reasons that are not well understood, the integrated functions of this unit begin to fail (Zlokovic, 2011). The failure of compensatory processes in vulnerable signalled by the very early decline in glucose utilization may initially be triggered by the metabolic failure of these perineural vascular structures rather than from the metabolically stressed mitochondria in vulnerable neurons. The ensuing deterioration of the capillary wall and the consequent loss of tissue perfusion may then be the principal cause of the early reduction in glucose utilization in AD rather than the reduced demand for neuronal energy (Love and Miners, 2016a,b; Miners et al., 2016). The development of a hypoxic environment would amplify oxidative stress and its damaging consequences

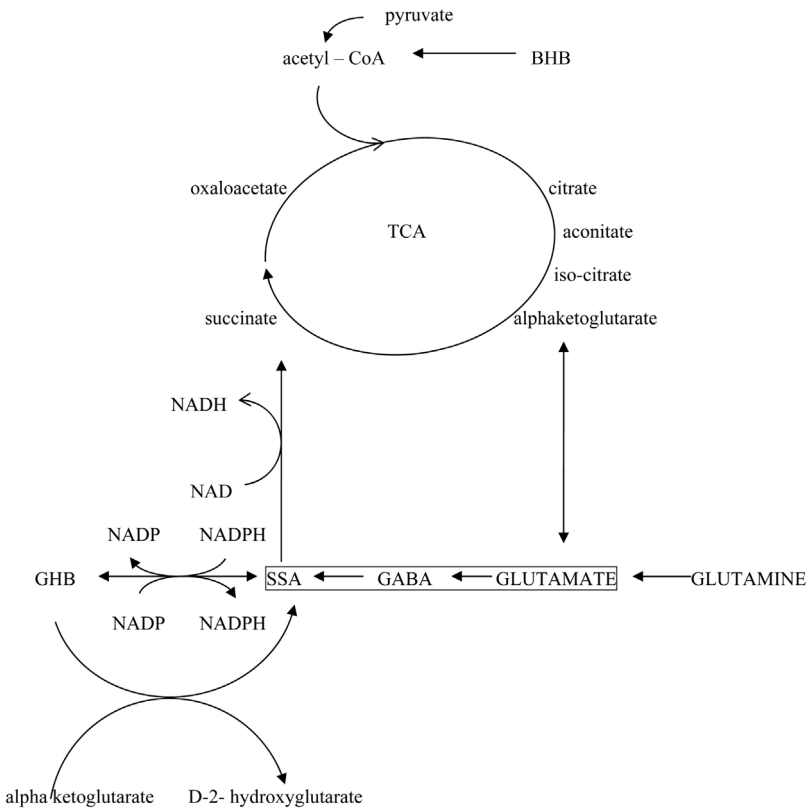

Fig. 1. Under conditions of oxidative stress, the activities of the enzymes mediating the initial steps of the tricarboxylic acid cycle (TCA) such as pyruvate dehydrogenase, aconitase, and alpha ketoglutarate dehydrogenase are reduced and the activity of succinic dehydrogenase is increased. Thus, energy formation along the initial steps of the TCA is reduced whether the source of the energy is glucose or betahydroxybutyrate (BHB). In this oxidative environment, glutamate, the brain's most common neurotransmitter, can also continue to function in its other role as a metabolic substrate and energy reservoir through its conversion to alphaketoglutarate or by its transformation to succinate along the GABA shunt (outlined). Oxidative stress increases traffic along the GABA shunt. In Alzheimer's disease, brain glutamate levels are progressively depleted. Provision of GHB may spare the consumption of glutamate and help maintain the integrity of glutamate neurotransmission. As well, through its catabolism to succinate and subsequent entry into the TCA, GHB may serve as a source of energy and, concomitantly, as a source of two important antioxidant cofactors, NADPH and NADH.
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in all cellular elements of the NVU. Abnormal mitochondria with transport chain deficiencies in AD are not limited to vulnerable neurons but have also been identified in platelets, lymphocytes and fibroblasts (Carvalho et al., 2016; Swerdlow et al., 2014) and damaged mitochondria are clearly evident in all elements of the NVU in AD (vide infra). Just when do these mitochondria begin to deteriorate and for what reason? But once they do, they would serve as a source of free radicals and could further impair the functions of these perivascular cells. Oxidative stress interferes with nitric acid's capacity to maintain capillary perfusion. It increases endothelial permeability and promotes leukocyte adhesion (Zhu et al., 2007). Oxidative stress also upregulates the endothelial production and the release of endothelin-1, a powerful vasoconstrictor. Levels of endothelin-1 are increased in the Alzheimer brain (Palmer et al., 2013). Oxidative stress also reduces the expression and activity of HIF-1 and thus the stimulus to angiogenesis and new vessel formation (Liu et al., 2008; Ogunshola and Antoniu, 2009). A vicious cycle of impaired capillary perfusion, hypoxia and oxidative stress is set in motion.

Pathology engages the Alzheimer brain's vascular system at all levels (Attems and Jellinger, 2014; Kelleher and Soiza, 2013). Reduced cerebral blood flow and/or cerebral blood flow dysregulation occurs in elderly individuals at high risk for AD even before cognitive decline, brain atrophy or the accumulation of βA (Ruitenberg et al., 2005; Zlokovic, 2011). Cerebral atherosclerosis affects the small arteries and arterioles leading to the lacunar and larger infarcts which have been identified in about a third of Alzheimer brains. Atherosclerosis of the Circle of Willis is a strong correlate of these infarcts. Among patients who meet the neuropathologic criteria of AD, those with brain infarcts have poorer cognitive function and a higher prevalence of dementia than those without infarcts. Without the neuropathologic criteria of AD, brain infarcts are only weakly associated with poor cognitive function and dementia (Snowdon et al., 1997). Small vessel disease is thought to be the cause of the white matter lesions or leukoaraiosis, increasingly detected on neuroimaging and, as well, of the capillary degeneration found in almost all AD brains. In time, cerebral amyloid angiopathy develops in more than 80% of patients with AD with widespread deposition of βA within meningeal and intracortical arteries, arterioles capillaries and, rarely, even veins. βA replaces and weakens the smooth muscle of the vascular wall and predisposes to intracerebral hemorrhages and microbleeds especially in patients with hypertension. Yet some studies find no relationship between the burden of ischemic vascular pathology and AD (Chui et al., 2012; Love and Miners, 2016a) reinforcing the concept that non-structural vascular dysfunction rather than structural abnormalities of the vessel wall initiates cerebral hypoperfusion in AD (Love and Miners, 2016a,b; Miners et al., 2016).

Electron microscopic studies of the brain in late onset AD and FAD reveal thickening and vacuolization of the vascular basement membrane, string vessels, i.e., vessels which have lost their endothelium, twisted or tortuous vessels and fragmentation of long microvessels leading to a decrease in their number and an overall decrease in capillary density (Buee et al., 1994; Fischer et al.,

1990; Szpak et al., 2007; Zlokovic, 2011). Enlarged mitochondria with disrupted cristae are common in endothelial cells, pericytes and perivascular astrocytes. The overall number and density of mitochondria is decreased and the number of mitochondrial DNA deletions is increased. Intracellular lipid granules and osmiophilic bodies are readily identified (Aliyev et al., 2005; Baloyannis and Baloyannis, 2012; Szpak et al., 2007). These microvascular changes stand in contrast to the mild alterations of the microvasculature which occur in normal aging. Again, how early can this microvascular deterioration be detected and just what sets it off?

The microvascular abnormalities of the Alzheimer brain show regional and laminar selectivity and are primarily found in layers III and V of the temporal and to a lesser extent the frontal cortex (Buee et al., 1994). These layers are highly vascularized and contain the vulnerable large pyramidal neurons of AD. The highest density of microvascular pathology is found in the CA1/subiculum. This region is exquisitely sensitive to ischemia and severely involved early in AD in keeping with the demonstrated reduction in glucose utilization found at that stage of the disease (Mosconi et al., 2005). In a case study of the brain of a 20 year old subject with Down syndrome, this microvasculature pathology, rarely seen in normal young controls, was observed in the absence of amyloid plaques or NFTs (Buee et al., 1994). Remarkably, in a detailed study of the vulnerable hippocampal CA1 region, loss of the microvasculature appeared to be present even before neuronal loss (Bailey et al., 2004). On the other hand, another insight into the relationship between neurons and the microvasculature is provided by a recent study using two lines of PS1 FAD-mutant transgenic mice which develop microcirculatory changes closely resembling those seen in AD with thin, irregular abnormally looped and string vessels. The FAD-mutant transgene was expressed in neurons in both lines. There was no detectable expression in vascular endothelial cells or glial cells. The study therefore suggests a role for neuronal to vascular signalling in the genesis of the microvascular pathology associated with AD (Gama Sosa et al., 2010).

6.2. Blood brain barrier

The time course of the microvascular alterations in AD and their relationship to the neuronal changes remains to be established but the studies cited above suggest that microcirculatory pathology may be present even before the advent of the characteristic hallmark lesions of AD. Since all elements of the neurovascular unit (NVU), the neurons, endothelial cells, pericytes, smooth muscle cells and glia, act in concert, they are likely impacted simultaneously by the vicious cycle of reduced cerebral perfusion and hypoxia which ensues in the wake of vascular disease (Grammas et al., 2011; Zlokovic, 2011). The NVU regulates cerebral blood flow and maintains the microvasculature, transports oxygen, nutrients and energy metabolites into the brain and clears toxic metabolites from the brain. The presence of damaged mitochondria in all the cellular constituents of the neurovascular unit in AD speaks to the breakdown of these integrated functions. Under normal circumstances, the endothelial cells that surround the capillary vessel lumen in the brain are connected to one another by tight junctions and form a blood brain barrier (BBB) that limits entry into the brain of red blood cells, leukocytes and many different plasma constituents. Although small lipophilic molecules, oxygen and carbon dioxide can freely diffuse across the BBB, the high number of mitochondria in endothelial cells attests to the great demand for energy in these cells. The passage of many nutrients across the blood brain barrier such as hexose sugars, amino acids, monocarboxylic acids, nucleosides, amines and vitamins requires active ATP-dependent carrier mediated transport. Energy is also required for the synthesis of pro and anticoagulant proteins, extracellular matrix proteins, inflammatory mediators, growth factors, proteases and vasoconstrictor/dilation factors.

Hypoxia depletes cellular ATP levels and impairs these transport and homeostatic mechanisms. For example, in the face of limited supplies of ATP, glutamate cannot be effectively cleared from the interstitial space and triggers neuronal excitotoxic damage (Zlokovic, 2011). The increased levels thrombin, prostaglandins, leukocyte adhesion molecules, cytokines and chemokines found in brain microvessels isolated from individuals with AD create a toxic inflammatory environment which impinges on all elements of the neurovascular unit. The vicious cycle of hypoxia/hypoperfusion accelerates when hypoxia activates vascular matrix metalloproteinase which digests tight junction proteins and basement membrane extracellular matrix proteins and disrupts the blood brain barrier. Hypoxia reduces the expression of the mesenchyme homeobox 2 (MEOX2) in brain endothelial cells and increases the expression of the myocardin gene in vascular smooth muscle cells. MEOX2 regulates vascular differentiation and remodelling while myocardin contributes to the development of a hyper-contractile cerebral arterial phenotype. The altered expression of these vascular specific genes causes vessel regression, endothelial hypoplasia and hypoperfusion (Wu et al., 2005). Faulty signal transduction between endothelial cells and pericytes leads to the loss of pericytes and to further disruption of the BBB. With the breakdown of the BBB, red blood cells enter the brain and deposit iron and add to the level of oxidative stress.

6.3. βA uptake and clearance

The passage of serum proteins like albumin, thrombin, fibrin and plasminogen across a porous BBB each has its own unique toxic consequences. But now, as well, βA, synthesized in the periphery, can pass across the capillary wall and into the brain. Recent studies confirm the importance of peripheral βA as a precursor of brain βA (Dries et al., 2012; Sagare et al., 2011; Sehgal et al., 2012; Sutcliffe et al., 2011). The receptor for advanced glycation end products (RAGE) serves as the portal for the entry of βA into the brain in the form of either monocytes laden with βA or free unbound plasma peptide. RAGE is expressed mainly at the luminal surface of the endothelium but also on all cellular elements of the NVU. Its expression is increased in response to oxidative stress and increases with the advance of AD (Yan et al., 1996; Miller et al., 2008). RAGE mediated transport of βA into the brain activates endothelial cells and produces an inflammatory response while at the same time generating endothelin-1 which further suppresses blood flow. Circulating βA is largely bound by soluble low density lipoprotein receptor-1 (sLRP1) and this normally prevents its free access to the brain but the oxidation of sLRP1 in AD compromises its ability to bind βA. Free levels of plasma βA then rise and enter the brain by RAGE mediated transport. The entry of peripherally derived βA contributes to the development of cerebral amyloid angiopathy (Eisele et al., 2010). Thus, while peripherally generated βA is a source of central βA, βA, whether peripherally derived or centrally manufactured, can also be cleared from the brain and back into the blood by binding to LRP1 on the abluminal side of epithelial cells even though LRP1 normally internalizes its ligands and directs them towards lysosomes for degradation. LRP1 mediates the rapid efflux of free unbound βA or βA bound to APOE2 or APOE3 from the brain's interstitial fluid. On the other hand, APOE4 inhibits this transport and thus promotes the accumulation of βA in the brain.

Unfortunately, the high levels of oxidative stress in the Alzheimer brain oxidize LRP1 and reduce its expression. Oxidized LRP1 cannot bind or transport βA and these alterations in LRP1 function therefore contribute to the retention of βA. The decrease in LRP1 levels in vascular smooth muscle cells may account in good part for the development of cerebral amyloid angiopathy in AD and

in normal elderly as well (Bell et al., 2008; Sagare et al., 2013; Zlokovic 2011, 2013). All cellular elements of the NVU express different βA degrading enzymes such as neprilysin and matrix metalloproteinases and these also contribute to βA clearance. But again, the oxidation of neprilysin in aging and even more so in the Alzheimer brain reduces its ability to metabolize and clear βA (Wang et al., 2003).

6.4. β-amyloid origins

Peripheral and central βA appear to exist in a dynamic equilibrium and there is now reason to believe that the levels of βA in the brain can be reduced by agents which enhance its clearance from the brain or which interfere with its synthesis in the liver (Dries et al., 2012; Sagare et al., 2011; Sehgal et al., 2012; Sutcliffe et al., 2011). These findings suggest that targeting the periphery offers an effective approach to reducing brain βA levels and the behavioral deficits attributed to the accumulation of this peptide. However, not all experimental work supports this dynamic equilibrium as the studies with intravenous neprlysin demonstrate (Henderson et al., 2014). To date, efforts to directly eliminate βA from the brain with monoclonal antibodies have had toxic consequences and, in any case, have not prevented the advance of the disease (Holmes et al., 2008; Yoshiyama et al., 2013). The 2016 announcement of solanezumab's failure in large clinical trials to be any more effective than placebo casts further doubts on the amyloid cascade hypothesis and about the role of βA in the pathogenesis of AD (Eli Lilly website). As the studies summarized above reveal, the accumulation of βA in the brain is a late event in the development of AD and is preceded by a long period of progressive energy starvation rooted in vascular disease.

6.5. Hypertension and vascular disease

Although the inheritance of defective mitochondria and the APOe4 allele may predispose to the development of microcirculatory abnormalities, many other factors contribute to the development of vascular disease during the course of life. Epidemiological and clinical studies document the relevance of vascular pathology to both aging and AD and specifically the early development of this pathology in the hippocampus (Attems and Jellinger, 2014; Brown and Thore, 2011; Montagne et al., 2015a,b; Zlokovic, 2011). Observational studies have documented that high blood pressure particularly in mid-life appears to be associated with an increased risk of late-life cognitive impairment and AD (Reitz and Mayeux, 2014). These epidemiological studies have been complemented by numerous investigations which demonstrate that hypertension and the pressure induced mechanical stress which it generates leads to the increased production of ROS in blood vessel walls. The potent vasodilator properties of endothelial nitric oxide and its ability to inhibit platelet and leukocyte adherence to blood vessel walls are lost when it is efficiently oxidized by the superoxide radical to produce the reactive peroxynitrite radical. Peroxynitrite, in turn, acts on nitric oxide synthase to further increase the levels of superoxide and amplify the level of oxidative stress (Faraci, 2005, 2011). Recently, experimental work in mice has demonstrated that the oxidative stress generated by hypertension increases circulating levels of AGEs, recruits RAGE in hippocampal and cortical brain vessels and leads to the deposition of amyloid plaques(Carnevale et al., 2012). Brain levels of AGE and RAGE expression also increase naturally with age and, as noted earlier, even more so in AD (Miller et al., 2008; Srikanth et al., 2011; Yan et al., 1996). Thus, as outlined earlier, hypoperfusion and hypoxia follow in the wake of vascular disease and set in motion the chain of metabolic events which accelerate the development of AD. Can this chain of events be prevented or interrupted?

7. Treatment

7.1. Vascular protection

Numerous attempts have been made to delay the onset or treat AD with the use of anti-hypertensive agents or statins to prevent the development of vascular disease and improve blood flow to the brain. And indeed, there is evidence that the use of angiotensin receptor blockers in particular but also angiotensin converting enzyme inhibitors, calcium channel blockers and diuretics do reduce the incidence of AD (Ashby and Kehoe, 2013; Chuang et al., 2014). However, conflicting findings with both antihypertensive agents and statins have raised questions about their effectiveness and even about their mechanism of action (Barone et al., 2014; Kelley and Glasser, 2014). In elderly patients, reducing blood pressure may actually impair memory and advance signs of AD (Glodzik et al., 2014).

7.2. Anti-oxidants

Great efforts have been made to at least slow the progress of AD if not improve overall function with the use of anti-oxidants. A recent review summarizes this undertaking (Mecocci and Polidori, 2012). The authors describe past and ongoing trials of Vitamin E, flavonoids, resveratrol, curcumin, pramipexole, latrapirdine, ubiquinone, lipoic acid, idebenone, ginkgo biloba, N-acetyl-cysteine and conclude that the findings to date, although conflicting, do not warrant the use of anti-oxidants to treat AD. Iron chelation has also been proposed to control oxidative stress in AD but there is no published data on its clinical efficacy (Liu et al., 2010). It has been argued that small molecule antioxidants are ineffective because they are distributed throughout the body and only a small fraction is taken up by mitochondria. Consequently, antioxidants that selectively target mitochondria have been developed by conjugating antioxidants like vitamin E or quinone to a lipophilic cation such as triphenylphosphonium to form mitovitamin E and mitoquinone. These conjugated molecules achieve 100–500 fold greater concentrations within mitochondria and have shown promise in preclinical studies and some human trials, but, again, there are no published results of trials in AD (Jin et al., 2014). Methylene blue, a potent redox agent that concentrates in mitochondria and facilitates the flow of electrons along the respiratory chain has been shown to increase mitochondrial ATP production and reduce ROS formation. This makes it a potentially useful agent for the treatment of AD and, indeed, a controlled trial demonstrated significant improvements in cognition and cerebral blood flow (Gonzalez-Lima et al., 2014; Wischik et al., 2015).

7.3. Beyond anti-oxidants

Although reduction of oxidative stress has been a common goal in the management and treatment of AD, it is recognized that oxidative stress is not specific to AD and that it can be found in almost all of the major neurodegenerative diseases such as Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis (Bonda et al., 2014). Aging is a common factor in all of these disorders and oxidative stress increases with age, but in each of these conditions oxidative stress appears to be driven by distinct metabolic events. In Parkinson's disease, for example, oxidative stress is localized primarily to the substantia nigra and basal ganglia where cells may be exposed to ROS generated by the metabolism of dopamine. In AD, high levels of oxidative stress are found in the hippocampus and cortex but not in the cerebellum, midbrain

and pons (Sultana and Butterfield, 2013). These high levels may be attributed to the high energy requirements and metabolic needs of the long axons and multiple synapses in these regions. Oxidative stress alone cannot be the principle cause of the cognitive deterioration in AD. In Down's syndrome, for example, high levels of oxidative stress are evident early on and even in utero but cognitive deterioration only develops decades later (Busciglio and Yankner, 1995; Nunomura et al., 2000). The decline in glucose utilization in the temporal regions in Alzheimer's decades before cognition deteriorates hints at an early failure in energy metabolism. Energy consumption and energy production are reduced. The consequent increase in oxidative stress sets in motion a vicious cycle of reduced glucose utilization and increased oxidative stress which starves the brain (Hertz et al., 2015; Mamelak, 2012). Two factors add to the specific vulnerability of the hippocampal region. The most severe changes in the cortical microvasculature in the Alzheimer brain are found in the hippocampus and may be detected even before any significant neuronal loss (Bailey et al., 2004; Buee et al., 1994). Capillaries in the hippocampal CA-1 region appear to be particularly vulnerable to the damaging effects of hypoperfusion (De Jong et al., 1999). Moreover, this region is exquisitely sensitive to ischemia-hypoxia and damage secondary to excitotoxic glutamate release (Lavenex et al., 2011).

Is there any way to simultaneously protect all elements of the neurovascular unit, neurons, capillaries and astrocytes, against the damaging effects of hypoxia, glutamate toxicity and oxidative stress?

7.4. Beta and gamma hydroxybutyrate

β and γ-hydroxybutyrate, uniquely, may be able to address the two major vulnerabilities of the poorly myelinated long axon neurons which emanate from the hippocampal region of the brain: insufficient energy to maintain functional integrity and the consequent development of oxidative stress with all its sequelae. In animal models of AD, ketone diets and ketone esters, which raise serum levels of D-β-hydroxybutyrate (BHB), reduce brain atrophy, decrease brain levels of βA and p-Tau, alleviate anxiety, lability and improve cognition (Kashiwaya et al., 2013; Gonzalez-Lima et al., 2014; Zhang et al., 2013). At the cellular level, ketone esters reduce oxidative stress and increase ATP production (Gonzalez-Lima et al., 2014; Zhang et al., 2013). Ketogenesis either reduces processing of APP or increases the degradation of β-amyloid by increasing the activities of α-secretase and the insulin degrading enzyme (Van der Auwera et al., 2005; Wang et al., 2005). Ketone bodies may be considered a superfuel for the brain with powerful anti-oxidant properties as an added bonus (Veech, 2004). They increase cerebral blood flow and are utilized in preference to glucose (Hasselbalch et al., 1996; Veech, 2004). Moreover, studies in mild to moderate Alzheimer's disease have shown that, unlike glucose, brain ketone uptake is not different from that in healthy age matched controls (Castellano et al., 2015; Cunnane et al., 2016; Nugent et al., 2014). The mouse model studies supplement clinical trials which demonstrate that even the mild ketosis associated with low serum levels of BHB in the 0.3–0.4 mM range produced by the oral administration of C-8 fatty acid triglycerides may significantly improve cognition in some patients (Henderson et al., 2009; Henderson and Poirier, 2011). Normal plasma levels of ketone bodies are ≤0.2 mM. A recent case study demonstrates that BHB serum levels can be maintained for months in the 5.0–7.0 mM range with the oral application of the synthetic ketone ester D-3-hydroxybutyl-D-3-hydroxybutyrate. Dramatic improvements in cognition and every day function ensued and minimental state scores rose from 12 to 26/30 (Newport et al., 2015).

The physiological properties of BHB are particularly germane to the metabolic aberrations of AD. A progressive failure of glucose utilization is a prominent feature of Alzheimer brain. Ketones can serve as an alternate source of energy for the brain and can provide up to 60% of the brain's energy needs (Hashim and VanItallie, 2014; Owen et al., 1967). Indeed, BHB has a substantially greater energy of combustion than pyruvate and thus makes more energy available for ATP synthesis (Veech, 2004). Moreover, ketones can bypass the metabolic block to glucose utilization associated with reduction in pyruvate dehydrogenase activity in AD and energize the cell by providing acetyl-CoA to the tricarboxylic acid cycle (TCA) (Fig. 1). In this regard, ketones can overcome the resistance of the Alzheimer brain to insulin which normally promotes energy metabolism by activating pyruvate dehydrogenase. Intranasal insulin, for example, has been shown to increase brain ATP and phosphocreatine levels in humans (Jauch-Chara et al., 2012). Ketones increase tissue sensitivity to insulin (Kashiwaya et al., 2010; Mamelak, 2012). This may account for the current interest in the use of insulin sensitizers such as the incretin liraglutide, metformin and the PPAR-Δ/γ dual nuclear receptor agonist T3D-959 to improve cognition and function in AD (Chen et al., 2016; Tong et al., 2016).

Aside from a source of energy, ketones are signaling metabolites that alter the expression of genes engaged in energy metabolism, oxidative stress, memory and learning (Newman and Verdin, 2014). Transcripts associated with glycolysis, the citric acid cycle, oxidative phosphorylation, the ATP synthase complex and glucose-6-phosphate dehydrogenase are all upregulated in the hippocampus by ketogenic diets (Bough et al., 2006; Noh et al., 2004). Micrographs of the dentate-hilar region of the hippocampus reveal an almost 50% increase in mitochondrial profiles concentrated mostly in dendrites and axon terminals where the demand for energy is high. The coordinate induction of energy metabolism genes and mitochondrial biogenesis lead to an increase in cell energy reserves with significantly greater phosphocreatine/creatine ratios without changing ATP levels. Ketones also increase the expression of monocarboxylic acid transporters in the vascular epithelial lining of the blood brain barrier and facilitate their own uptake by the brain (Pifferi et al., 2011) This confers a particular advantage for ketones as an energy source in AD given the dependence of the long axon neurons in this disease on monocarboxylic acid transporters for their fuel (Morrison et al., 2013). Ketones have also been shown to increase global histone acetylation and to activate the oxidative stress resistant factors FOXO3A and MT2 and induce the formation of superoxide dismutase and catalase (Shimazu et al., 2013). Ketones upregulate the enzymes involved in glutathione (GSH) biosynthesis. They greatly increase hippocampal mitochondrial GSH and GSH/GSSG ratios and protect mtDNA from oxidant induced damage. Levels of lipoic acid, a thiol antioxidant, are also significantly increased (Jarrett et al., 2008). Ketones reduce the cytosolic NADP/NADPH couple and thus promote the reduction of GSH and the increased efficacy of other NADPH dependent anti-oxidative systems (Veech, 2004). Ketone body metabolism oxidizes the mitochondrial co-enzyme Q couple. The major source of mitochondrial free radical generation is the Q-semiquinone. The half reduced semiquinone reacts with O_2 to form free radicals. Oxidation of the Q couple decreases the amount of semiquinone and reduces free radical formation. Ketones may also reduce oxidative stress by inducing the formation of uncoupling proteins (Kashiwaya et al., 2010).

The neuroprotective utility of ketone bodies is now being widely explored (Gonzalez-Lima et al., 2014; Newman and Verdin, 2014). Fasting has been used as an anticonvulsive therapy since ancient times and the ketogenic diet has been in clinical use for over a century. Ketogenic diets have been shown to raise brain levels of brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) critical for learning, memory and neurogenesis (Yao et al., 2011). BDNF levels are reduced in the temporal region of the Alzheimer brain (Lee et al., 2005). Ketogenic diets have been

shown to improve learning and memory and reduce amyloid and tau pathologies in mouse models of AD (Kashiwaya et al., 2013; VanItallie, 2015). Ketogenic diets have also been shown to improve neuronal and mitochondrial survival in animal models of Parkinson's disease (Cheng et al., 2009; Tieu et al., 2003). BHB has been shown to protect cultured neurons in models of Alzheimer's and Parkinson's disease (Kashiwaya et al., 2000). Ketone bodies mitigate brain damage in experimental models of traumatic brain injury, hypoxia and ischemia (Appelberg et al., 2009; Puchowicz et al., 2008; Suzuki et al., 2002, 2001). Ketosis appears to protect the ischemic brain by increasing intracellular succinate which in turn upregulates hypoxia inducible factor (HIF)-1α to promote angiogenesis and neuroprotection. BHB has also been shown to protect hippocampal cultures from hypoglycemia, hypoxia and N-methyl-D aspartate-induced neurotoxicity (Samoilova et al., 2010). D-BHB has been shown to reduce oxidative stress in distinct cortical areas and subregions of the hippocampus and efficiently prevent neuronal death in the cortex of hypoglycemic animals (Julio-Amilpas et al., 2015). While D-BHB can both stimulate ATP production and reduce oxidative stress, its non-physiologic isomer, L-BHB, has no effect on energy production.

Gammahydroxybutyrate (GHB), an endogenous metabolite found in every living cell, bacterial, protozoal, plant and animal, shares BHB's neuroprotective properties and has also been shown to have widespread cellular protective effects in heart, skeletal muscle, pancreatic β-cells, lung, liver, gut and kidney in addition to the brain (Mamelak and Hyndman, 2002; Mamelak, 2012, 2007). The application of GHB profoundly reduces cerebral glucose utilization but not the brain's oxygen consumption and hence reveals GHB's capacity to serve as an alternate fuel. Much the same as ketones, the brain appears to prefer GHB to glucose as an energy source (Haller et al., 1990).

GHB is a product of the GABA shunt and is generated when oxidative stress impedes the formation of energy through the glycolytic pathway and the initial steps of the citric acid cycle (Fig. 1). Its metabolism generates succinate, NADH and NADPH to provide energy and antioxidant power to the cell. In the heart, for example, GHB completely prevents the cardiac necrosis, mitochondrial swelling and the accumulation of dense deposits in mitochondria produced by the oxidative stress generated by exposing the heart to high levels of the catecholamine, isoproterenol (see illustration in Kolin et al., 1993; Mukherjee et al., 2012). Brain, pretreated with GHB, maintains ATP at normal levels even under hypoxic conditions (MacMillan, 1978). GHB strongly protects neuroblastoma cells from oxidative stress induced by direct exposure to hydrogen peroxide (Wendt et al., 2014). GHB has been shown to protect cerebral neurones from global ischemic damage as well as from the focal ischemic damage induced by the local injection of kainic acid, an excitotoxin, or endothelin-1, the powerful vasoconstrictor (Lavyne et al., 1983; Ottani et al., 2003; Sadasivan et al., 2006; Sims and Heward, 1994). GHB, like BHB, is transported across cell membranes by monocarboxylic acid transporters enabling it to directly nourish the energy challenged long axon neurons of the Alzheimer brain. Equally important, GHB is taken up by astrocytes and by the vascular epithelial cells of the BBB (Roiko et al., 2012). GHB has also been shown to protect the vascular endothelium. In gut, for example, GHB maintains microvascular perfusion in the face of ischemic reperfusion injury and significantly reduces the accumulation of white blood cells in the microvasculature (Boyd et al., 1994, 1990). Leukocyte adherence and microvascular stasis are considered important contributors to ischemic reperfusion injury. In liver, reperfusion injury significantly increases serum levels of hepatic enzymes and serum levels of endothelin-1. Endothelin-1, in addition to its vasoconstrictor properties, strongly promotes leukocyte adhesion. The apoptotic index rises, tissue malondialdehyde levels markedly increase and superoxide dismutase activity falls. GHB reverses all of these effects (Wei and Xia, 2004). GHB's endothelial protective effects owe in part to its unique capacity to reduce oxidative stress, activate the pentose phosphate pathway and increase the production of NADPH which in turn maintains endothelial NO production (Leopold et al., 2003). NO contributes to vascular homeostasis by inhibiting vascular smooth muscle contraction, platelet aggregation and leukocyte adherence. In all cells, activation of the pentose phosphate pathway generates NADPH and promotes lipid and nucleic acid biosynthesis and cell repair. Among its many antioxidant functions, NADPH is required for reducing and detoxifying the reactive ketone and aldehyde precursors of AGEs (Mamelak and Hyndman, 2002). GHB thus acts in concert with repair mechanisms already operating in the Alzheimer brain (Mamelak, 2012).

In distinction to BHB, GHB is a weak GABAB receptor agonist and its actions at this receptor account for many of its unique pharmacological properties such as its sedative effect and inhibitory effect on dopaminergic neuronal activity in the brain (Mamelak, 2007). In the mouse, the acute administration of GHB has been shown to produce a rapid long lasting increase in the hippocampal level of phosphorylated cAMP-responsive element binding protein (CREB) (Ren and Mody, 2006). The activation and phosphorylation of CREB induces the transcription of many genes critical to learning, memory and cell growth (Lonze and Ginty, 2002). GHB, like BHB is a histone deacetylase inhibitor and the epigenetic changes which occur in response to the inhibition of histone deacetylases with the repeated administration of GHB have been shown to lead to the overexpression of the neprilysin gene in neuroblastoma cells as well as in the APPSWE mouse model of AD. GHB reduces brain levels of βA in this mouse model and also prevents the cognitive decline. The increased expression of neprilysin likely accounts for the decline in brain βA levels (Blurton-Jones et al., 2014; Klein et al., 2015, 2009).

8. Conclusion

Many microorganisms naturally synthesize polymers of BHB and co-polymers of BHB and GHB and store these remarkable molecules to meet the need for carbon, energy and antioxidant power under adverse conditions (Bach et al., 2009; Dawes and Senior, 1973; Doi et al., 1990). Can these molecules serve the same purpose in the toxic environment of the Alzheimer brain? The synthesis of ketone esters of D-BHB and the manufacture of controlled release formulations of GHB represent initial steps in the development of these 4 carbon molecules into clinically useful cytoprotective agents (Newport et al., 2015; Flamel Technologies- website). As matters stand, GHB has already been used nightly for many years by large numbers of patients to treat narcolepsy (Mamelak, 2009). Many of these patients are elderly and have been using GHB safely for decades without major untoward effects. As of 2015, GHB has been prescribed to more than 60,000 patients (Xyrem-website). A search of the published scientific literature using the Medline and Embase literature databases did not identify any published case reports about the development of Alzheimer's disease or Parkinson's leading to the discontinuation of Xyrem. Similarly, as of today, the Jazz Pharmaceutical Drug Safety and Pharmacovigilance Program has not identified Alzheimer's or Parkinson's as safety signals for Xyrem. Alzheimer's and Parkinson's diseases are also only very rarely reported in the product manufacturer's Drug Safety database (Jazz Pharmaceuticals-Medical Information Department). These data encourage the view that the use of Xyrem may delay the development of these neurodegenerative disorders. Formal epidemiological studies are required to determine the incidence and prevalence of Alzheimer's and Parkinson's in long term users of GHB. Recently, other investigators

familiar with the neuroprotective effects of GHB have also proposed trials of its use in the prevention of Alzheimer's disease (Maitre et al., 2016).

Any effective treatment for AD must be able to provide carbon, energy and antioxidant power to repair and rebuild vulnerable cells. Anti-oxidants alone, as discussed earlier, are not sufficient. Removing βA may be hazardous and, in any case, does not appear to stem the progress of the disease (Holmes et al., 2008; Wisniewski and Goni, 2014; Yoshiyama et al., 2013). Any effective treatment must be able to protect all elements of the vulnerable neurovascular unit, be it the endothelium, pericytes, astrocytes and neurons and must especially be able to maintain the structure and function of the mitochondria which power these cells. All of these elements are vulnerable in AD. BHB and GHB have this capacity. Clinical trials are expected to be undertaken shortly to demonstrate that BHB and GHB, alone or together, can delay the onset of AD and slow its progress. But, an early start is required lest irreversible damage occurs.

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