

**Cerebral Hypoperfusion and Glucose Hypometabolism: Key Pathophysiological
Modulators Promote Neurodegeneration, Cognitive Impairment,
and Alzheimer's Disease**

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Article Outline

Abstract

1. Introduction

2. Conditions That Promote Cerebral Hypoperfusion and Glucose Hypometabolism

- 2.1 Aging
- 2.2 Intermittent Hypoxia/Obstructive Sleep Apnea
- 2.3 Hypertension
- 2.4 Obesity/ Metabolic syndrome
- 2.5 Vitamin B12/Folate Deficiency
- 2.6 Diabetes Mellitus
- 2.7 Depression
- 2.8 Traumatic Brain Injury

3. Framework Highlighting Pathological Ramifications and Cognitive Vulnerability Owing to Chronic hypoperfusion and hypometabolism

- 3.1 Diverse Comorbid Conditions Trigger Vascular Pathology
- 3.2 Cerebral Amyloid Angiopathy (CAA)
- 3.3 Blood–Brain Barrier (BBB) Dysfunction
 - 3.3.1 Disruption of Glucose Uptake Impairs BBB Integrity
 - 3.3.2 BBB Disruption Promotes Neuronal Loss
 - 3.3.3 Hypoperfusion and Neuronal Death
- 3.4 Cerebral Hypometabolism
- 3.5 Brain Atrophy: A Defining Impairment in Multiple Risk Factors
 - 3.5.1 Aging
 - 3.5.2 Obesity
 - 3.5.3 Homocysteine
 - 3.5.4 Sleep Deprivation
 - 3.5.5 Chronic Alcohol Abuse
- 3.6 Elderly and Cognitive Impairment

4. Cerebral Hypoperfusion: Therapeutic Approach

- 4.1 Reperfusion-Rehabilitation Approach
- 4.2 Pharmacological Approach
- 4.3 Nutraceutical Approach

5. Concluding Remarks

References

Abbreviation

A β - amyloid beta

AD - Alzheimer's disease

BBB - blood-brain barrier

BFVs - Blood flow velocities

BOLD - blood-oxygen level dependent

BP - High blood pressure, hypertension

CAA - cerebral amyloid angiopathy

CBFV - Changes in CBF velocity

CSD - Chronic sleep deprivation

CMRglc - cerebral metabolic rate of glucose

CMRO₂ - cerebral metabolic rate of oxygen

CV - Cerebrovascular

CRP - C-reactive protein

DMN - default-mode network

EC - entorhinal cortex

fMRI - Functional MRI

FDG - 2-[¹⁸F]fluoro-2-Deoxy-D-glucose

GluRs - glutamate receptors

HbA(1c) - Glycosylated haemoglobin

Hhcy - hyperhomocysteinemia

HIF-1 α - Hypoxia-inducible factor 1-alpha

ICAM-1 - Intercellular adhesion molecule 1

LTP - long-term potentiation

MCP-1 - monocyte chemoattractant protein

MetS - metabolic syndrome

MDD - major depressive disorder

MMP - matrix metalloproteinase

MCI - mild cognitive impairment

MMSE - Mini-Mental State Examination (MMSE)

MRS - magnetic resonance spectroscopy

NO - nitric oxide

NOS - nitric oxide synthase

NFT - neurofibrillary tangles

PCC - posterior cingulate cortex

PET - positron emission tomography

PIB - Pittsburgh compound B

rCBF - regional cerebral blood flow

ROS - reactive oxidative stress

SPECT - Single photon emission computed tomography

SPs - senile plaques

T2DM - type 2 diabetes mellitus

TBM - tensor-based morphometry

TGF- β 1 - transforming growth factor- β 1

VaD - vascular dementia ()

VCAM-1 - vascular cell adhesion molecule 1

WMH - white matter hyperintensities

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Significance

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Aging, hypertension, diabetes, hypoxia/OSA, obesity, vitamin B12/folate deficiency, depression, and traumatic brain injury – synergistically promote diverse pathological mechanisms including cerebral hypoperfusion and glucose hypometabolism. These risk factors trigger neuroinflammation and oxidative-nitrosative stress that in turn decrease nitric oxide, and enhance endothelin, Amyloid beta deposition, cerebral amyloid angiopathy, and blood-brain-barrier disruption. Proinflammatory cytokines, endothelin-1, and oxidative-nitrosative stress trigger several pathological feed-forward and feed-back loops. The above upstream factors persist in the brain for decades upregulating amyloid and tau, before the cognitive decline. The above cascades lead to neuronal Ca^{2+} increase, neurodegeneration, cognitive/memory decline, and AD. However, strategies are available to attenuate cerebral hypoperfusion and glucose hypometabolism and ameliorate cognitive decline.



Abstract

Alzheimer's disease (AD) is the leading cause of dementia among the elderly. There is significant evidence that pathways involving inflammation and oxidative-nitrosative stress (ONS) play a key pathophysiological role in promoting cognitive dysfunction. Several comorbid conditions including aging, hypoxia/OSA, hypertension, obesity, vitamin B12/folate deficiency, diabetes, depression, and traumatic brain injury – promote diverse pathological mechanisms. These include inflammation, ONS, hypoperfusion, and hypometabolism in the brain. In AD, chronic cerebral hypoperfusion and glucose hypometabolism precede decades before the cognitive decline. The above comorbid disease conditions may share and synergistically activate the above pathophysiological pathways. Inflammation upregulates cerebrovascular pathology through proinflammatory cytokines, endothelin-1, and nitric oxide (NO). Inflammation-triggered ONS promotes long-term damage involving fatty acids, proteins, DNA, and mitochondria; these amplify and perpetuate several feed-forward and feedback pathological loops. The latter includes dysfunctional energy metabolism (compromised mitochondrial ATP production), amyloid beta generation, endothelial dysfunction, and blood-brain-barrier disruption. These lead to decreased cerebral blood flow and chronic cerebral hypoperfusion- that would modulate metabolic dysfunction and neurodegeneration. In essence, hypoperfusion deprives the brain with its two paramount trophic substances, *viz.* Oxygen and nutrients. Consequently, the brain suffers from synaptic dysfunction and neuronal degeneration/loss leading to both gray and white matter atrophy, cognitive dysfunction, and AD. This paper underscores the importance of treating the above mentioned comorbid disease conditions to attenuate inflammation and ONS and ameliorate decreased cerebral blood flow and hypometabolism. Additionally, several strategies are described here to control chronic hypoperfusion of the brain and enhance cognition.

Accepted

1. Introduction

Alzheimer's disease (AD) is a sporadic late-onset disease; its prevalence increases with the age of 65 years onwards. Since we are living longer, there is a stark shift in the epidemiology of age-related diseases including an escalating prevalence of AD and vascular dementia (VaD) (Whitehouse et al., 1997). Approximately 5.2 million Americans have late-onset AD, and about 200,000 people younger than 65 years suffer from the early-onset AD (Alzheimer's Association, 2014). As per projections, the AD risk may double every five years (Takeda et al., 2008), and by mid-century, the number of AD patients in the United States may grow to about 9 million. AD adds a massive financial burden, and \$214 billion are estimated to be the health care cost in 2014 (Alzheimer's Association, 2014).

AD patients suffer from the progressive and gradual decline in memory and cognitive functions. While the etiology of the late-onset AD is largely unknown, familial early-onset AD is associated with gene mutations. It has been emphasized in recent years that environmental factors and epigenetic alterations may play a significant role in the neuropathogenesis of AD (Daulatzai, 2013b; 2014; 2015a; 2015b). Indeed, aging is an important risk factor for upregulation of gene expression related to inflammation and apoptosis in several age-related diseases. Mitochondrial dysfunction with resulting reactive oxygen species (ROS) generation is known to accompany aging (Daiber et al., 2015; Wu et al., 2015). Moreover, aging correlates with genetic and epigenetic perturbations and telomere attrition (Aviv et al., 2002; Blackburn et al., 2015).

Progressive atrophy, degeneration, and loss of neurons (referred here as neurodegeneration) are characteristic features of several neurodegenerative diseases. These include AD, Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Creutzfeldt-Jakob disease, and Huntington disease. The most salient risk factor for developing neurodegenerative diseases, in general, and late-onset AD, in particular, is aging. The characteristic visible neuropathological lesions in AD are 1. senile plaques (SPs) formed by amyloid beta ($A\beta$) and located outside neurons, and 2. neurofibrillary tangles (NFT) comprised of hyperphosphorylated tau (i.e. phospho-tau) are located within neurons (Su et al., 1996; Zhao et al., 2010). According to the amyloid cascade hypothesis, $A\beta$ is the noxious agent that triggers angiopathy, synaptopathy, glial (including microglial and astrocytic) activation-related inflammatory and reactive oxidative stress (ROS) responses, tau hyperphosphorylation (owing to altered activities of relevant kinases and phosphatases), and neuronal death (De Felice et al., 2007).

According to Tau hypothesis, phospho-tau accumulation, and the neurofibrillary degeneration occurs in neurons. The paired helical filaments in NFTs induce abnormal cellular metabolism and cause neuronal death. NFTs, therefore, are intimately associated with memory and cognitive dysfunctions (Goedert, 1993; Wes et al., 2014).

The intracellular endoplasmic reticulum (ER) is a reticular membrane network (Baumann and Walz, 2001) that performs several vital functions. These include: (i) protein folding, (ii) maintenance of cellular calcium, (iii) synthesis of lipids and sterols, and (iv) regulation of cellular homeostasis (Baumann and Walz, 2001; Gorchach et al., 2006; Schroder and Kaufman, 2005; Bernales et al., 2006; Ron and Walter, 2007; Kim et al., 2008).

According to ER stress hypothesis, ER stress and activated unfolded protein response (UPR) signaling are present in AD (Hoozemans et al., 2009) as well as other chronic neurodegenerative conditions (Lindholm et al., 2006; Paschen and Mengesdorf, 2005; Matus et al., 2008; Kanekura et al., 2009; Scheper and Hoozemans, 2009). Importantly, diverse conditions such as cerebral ischemia and viral infections can also induce ER stress and trigger the UPR signaling (Hoozemans et al., 2009; DeGracia and Montie, 2004; Williams and Lipkin, 2009). Indeed, ER stress of neurons is linked to the inflammatory activation that may promote AD pathogenesis (Salminen et al., 2009).

Data from the brains of those with advanced age and AD have consistently shown damage or abnormalities in basal forebrain projections to the cortex; this correlates with cognitive decline. Hence, the "cholinergic hypothesis" postulates that a loss of cholinergic function in the brain contributes to the cognitive decline associated with advanced age and AD (Bartus, 2000; Schliebs and Arendt, 2011; Shen and WU, 2015). Therefore, to date, the mainstay of preventive treatment of AD is acetylcholinesterase inhibitors (Hosoi et al., 2015).

Brain's viability and its myriad of functions critically rely on the continuous supply of energy substrates and oxygen via blood flow. During functional activation – when there is an increased energy demand, regional cerebral blood flow (rCBF) is locally adjusted in the brain to meet this demand. This is achieved by regulating microvessel diameter and concomitant dilatation of upstream arteries and arterioles (that supply blood to the capillary bed). This physiological neurovascular coupling is essential regarding rCBF changes being linked to neuronal activity, temporally and spatially (Feuerstein et al., 2014; Vanzetta et al., 2008). Any sustained reduction in rCBF, therefore, may reduce tissue function and cause regional cerebral damage. 2-[18F]fluoro-2-Deoxy-D-glucose (FDG) positron emission tomography (PET) (FDG-PET) is used to measure the cerebral metabolic rate of glucose (CMRglc) as a surrogate for neuronal activity. FDG-PET shows in vivo cerebral glucose utilization (CGU) and changes in brain metabolism. The term upstream refers to arterial branches the blood flows through before reaching the metabolite exchange (glucose, O₂/CO₂) site. Under pathologic conditions, the upstream blood supply limitation could be the proximal (involving arterioles or pial arteries) or distal (involving the carotid artery and heart).

Cortical spreading depolarizations (CSD - a self-propagating wave of membrane/tissue depolarization) is associated with significant changes in tissue metabolism and blood flow (Ayata et al., 2006, Feuerstein et al., 2010, Lauritzen, 1987; Piilgaard et al., 2009). CSD can arise in the normal brain; it can also arise after brain injury (Kumagai et al., 2010, Shin et al., 2006; Strong et al., 2007) and clinically (Dohmen et al., 2008, Fabricius et al., 2006, Hartings et al., 2011; Lauritzen et al., 2011). As such, CSD is a phenomenon that correlates with the normal or reduced rCBF response (via upstream blood supply) to energy needs in health and disease. The close regional coupling of rCBF, therefore, involves both cerebral metabolic rate of oxygen (CMRO₂) and CMRglc (Powers et al., 2011). Neurovascular coupling (i.e. functional hyperemia) involves communication between neurons, astrocytes and cerebral vessels and this neurovascular unit adjusts blood supply for energy and oxygen needs of activated neurons (Lecrux and Hamel, 2011). Astrocytes cover the surface of intraparenchymal capillaries through their processes, suggesting that they may participate in glucose uptake. Other astrocytic processes wrap around synapses – the sites for receptors and reuptake of

neurotransmitters. There are specific glutamate transporters on the astrocytes, and glutamate stimulates glucose uptake into these cells (Magistretti and Pellerin, 1999).

A growing body of evidence emphasizes an association between vascular risk factors and Cognitive decline (Dickstein et al., 2010, Murray et al., 2011; Wang et al., 2014). Further, sex/gender is considered to play a pivotal role in the susceptibility for developing dementia induced by cardiovascular risk factors (Azad et al., 2007; Rosvall et al. 2009; Dufouil et al., 2014; Chêne et al., 2015). This interrelationship is important in understanding etio-pathophysiological mechanisms and the impact of vascular pathology in promoting neuropathology (*i.e.* plaque and tangle pathology) (Yarchoan et al., 2012). The underlying neuropathology may persist for decades before clinical diagnosis of AD. This paper is focused on the significance of chronic hypoperfusion-related pathophysiological signaling. The latter may upregulate several pathological mechanisms including endothelial dysfunction, glucose dyshomeostasis, inflammation, oxidative stress, and neurotoxicity. These trigger memory and cognitive dysfunction - before frank AD. This paper underscores significant evidence relevant to AD and emphasizes a link between the two major upstream pathogenetic factors and neuronal dysfunction and degeneration. The triggering of cognitive/memory dysfunction and AD, therefore, is posited to be a function of chronic hypoperfusion and glucose hypometabolism. Readers may find some early reviews on hypoperfusion, oxidative stress, and neuroinflammation interesting (de la Torre, 2012; Kim et al., 2012; Liu and Zhang, 2012).

2. Conditions That Promote Hypoperfusion

Various factors including older age, hypertension, hypercholesterolemia, diabetes, obesity, atherosclerosis, and cardiac diseases have been shown to enhance vascular risk and facilitate onset and progression of cognitive impairment (Debette et al., 2011, Kalaria, 2010, Murray et al., 2011; Rodrigue, 2013; see Table 1). Hence, identification and attenuation of these vascular risk factors in midlife must encompass an essential strategy to thwart the onset and progression of cognitive decline in advanced age.

2.1. Aging

Aging is an important risk factor for several age-related diseases and upregulation of gene expression related to inflammation and apoptosis. Aging is also correlated with genetic and epigenetic perturbations, telomere attrition (see above), mitochondrial dysfunction, and ROS increase (see below). An interrelationship has been emphasized between unhealthy diet, dysfunctional breathing, sleep restriction, and excess consumption of alcohol - and neuropathogenesis of cognitive dysfunction (Daulatzai, 2015b). AD, therefore, is recognized to arise from multifocal and multi-factorial mechanisms (Fig. 1.). The latter promote potentially deleterious downstream factors including amyloid and tau increase, mitochondrial dysfunction, synaptic injury/loss, and eventual neuronal degeneration and loss (Daulatzai, 2015a-2015d).

Two important indices of healthy brain aging are rCBF and CMRO₂. A PET study (in 66 healthy volunteers aged 21 to 81 years) found that the magnitudes of CBF and CMRO₂ declines in large areas of the cerebral cortex (Aanerud et al., 2012). Recently, perfusion deficit in the brain of cognitively normal older adults has been documented in the inferior parietal lobules (Okonkwo et al., 2014). Some possible reasons may be that aging is inevitably accompanied by vascular pathology (Bouras et al., 2006; Jeynes and Provias, 2006). The

latter may include cortical microinfarcts (Kövari et al., 2004; 2007), gray matter lacunes (Gold et al., 2005), and irreversible endothelial dysfunction (Hallam et al., 2010; Thal et al., 2009). Vascular pathological burden as hypoperfusion and neurodegeneration both precedes and parallels cognitive decline (Giannakopoulos et al., 2007; Jellinger, 2002; Kalara et al., 1993; Koike et al., 2011). NFT were common in tau-positive neurons in the hippocampus from non-demented elderly persons (Takayama et al., 2002). In the elderly without dementia but memory dysfunction, cerebral circulatory/vascular abnormalities, and deleterious metabolic and functional impact may contribute to mild cognitive impairment (MCI) (Beckmann et al., 2003, Bennett et al., 2005; Okonkwo et al., 2014).

2.2 Intermittent Hypoxia/Obstructive Sleep Apnea

There are marked changes in cerebrovascular control during sleep disordered breathing notably Obstructive Sleep Apnea (OSA); this suggests that the cerebral circulation may be vulnerable to intermittent hypoxia (fig. 1.). Changes in CBF velocity (CBFV) and vascular compliance were evaluated (using transcranial Doppler sonography and cerebral pulse transit time) in patients with severe OSA. CBFV reactivity was significantly diminished in dysfunctional respiratory periods. CBF hyporeactivity was evident as a loss of vasoreactivity and increased arterial stiffness (Foster et al., 2007; Furtner et al., 2009). Further, a reduction in CBF occurs during Non-REM sleep despite a relative hypercapnia state (Baril et al., 2015; Corfield and Meadows, 2006). Patients with severe OSA (compared to controls) showed reduced CBF in the left parietal lobules, precentral gyrus, bilateral postcentral gyri, and right precuneus (Baril et al., 2015). Hence, vascular impairment in these AD-related important brain areas could result in neurodegenerative processes, neuronal dysfunction, and cognitive deficits (Fig.1.).

There is a close correlation between mean arterial pressure and CBFV. Thus, cerebral perfusion pressure prevents cerebral ischemia. Cerebrovascular autoregulation counteracts physiological fluctuations and maintains perfusion pressure. However, cerebral hypoperfusion may occur when there are a systemic hemodynamic failure and chronic dysfunctional cerebrovascular autoregulation. However, cerebral autoregulation is inadequate from rapid pressure changes in OSA (Bålfors and Franklin, 1994), and is, therefore, unable to protect the brain. Nocturnal apneas are associated with profound changes in CBF. Normally, vaso-neuronal coupling occurs owing to CBFV variations during neuronal stimulation (Daffertshofer and Hennerici, 1995). However, there is significant neuronal dysfunction in OSA patients (Daulatzai, 2015d; also see below) rendering vaso-neuronal coupling sub-optimal and CBFV insufficient. OSA patients develop decreased CBF velocity and delayed cerebrovascular compensatory response owing to sustained alterations in blood pressure. The above-mentioned increase the risk of cerebral ischemia during OSA (Daulatzai, 2013a; 2015b; Urbano et al., 2008). Apnea-induced hypoxemia in conjunction with reduced CBF (nocturnal and awake) would sustain cerebral hypoperfusion in OSA patients (Daulatzai, 2012; 2013a; 2013b; 2015a; 2015b; Foster et al., 2007).

2.3. Hypertension

Various epidemiological studies link Hypertension to AD. Hypertension leads to changes in blood vessel wall in the brain; this may upregulate hypoperfusion and ischemia thus promoting AD neuropathogenesis (Hughes et al., 2015). There are epidemiological data that show a relationship between high blood pressure (BP) and cognitive dysfunction and dementia. The relationship between hypertension and the prevalence of AD/dementia

have been shown in cross-sectional studies; indeed, longitudinal studies have suggested that high BP in midlife is associated with a higher incidence of AD in later life (Launer et al., 2000). A recent arterial spin labeling study has documented that individuals with hypertension have reduced temporal and occipital brain perfusion as well as decreased total and regional cortical thickness (compared with controls without hypertension) (Alosco et al., 2014). The meta-analysis also found that high BP leads to brain volume reduction, including the hippocampus (Beauchet et al., 2013). The synergistic effect of high BP and type 2 diabetes mellitus (T2DM) has a significant impact on hypoperfusion and cortical thickness (CThk). The latter was evident in the right lingual gyrus, posterior cingulate, precuneus, superior and middle frontal, and middle and inferior temporal regions (Tchistiakova et al., 2014). The above pathology and cognitive decline are inter-linked (Alosco et al., 2013).

Arterial spin-labeling MR imaging studies in the MCI patients (relative to controls) showed significant regional hypoperfusion in the right inferior parietal lobe. Further, the AD patients (relative to controls) showed significant regional hypoperfusion in several regions including right and left inferior parietal cortex extending, bilateral posterior cingulate gyri, and bilateral superior and middle frontal gyri (Johnson et al., 2005). After accounting for underlying cortical gray matter atrophy, the hypoperfusion persisted in the right inferior parietal lobe, bilateral posterior cingulate gyri, and right and left middle frontal gyri (Johnson et al., 2005).

Two important pathologies *i.e.* atherosclerosis and impaired cerebrovascular autoregulation are caused by chronic hypertension (Duron and Hanon, 2008; Kennelly et al., 2009; Qiu et al., 2005). In the Honolulu-Asia Aging study, 3605 Japanese-American men were followed prospectively over 26 years (1965-1991). The study found that high Systolic BP in midlife has a stronger adverse effect on cognitive function in APOE- positive persons (Peila et al., 2001). This particular study also found that elevated BP in midlife was associated with brain atrophy and greater numbers of amyloid plaques in both neocortex and hippocampus. However, elevated diastolic BP was associated with extensive NFT in the hippocampus (Petrovitch et al., 2000). Further, the A β -related pathological risk, *e.g.* of cerebral amyloid angiopathy (CAA), was found to be higher when BP was higher (Shah et al., 2012). This indicated that hypertension compromises vascular integrity, leads to CAA, and impairs A β clearance from the brain (Shah et al., 2012).

Functional MRI (fMRI) was performed in 541 women and men with mean age 50.4 years. Cerebrovascular reactivity (CVR) was quantified as the percentage change in blood-oxygen level dependent (BOLD) signal. Mean CVR was calculated for brain regions associated with the default-mode network (DMN) - a network implicated in AD (Haight et al., 2015). The study found that reduced CVR may represent diminished vascular functionality for the DMN for individuals with prehypertension/hypertension in mid-life (Haight et al., 2015). In a recent study on elderly patients with hypertension, a quantitative analysis of FDG-PET was conducted in the brain with an aim to characterize any MCI-like hypometabolic pattern. The study, although on a small number of patients, did find an MCI-like hypometabolic pattern in elderly hypertensives (Van Der Gucht et al., 2015). Indeed, hypertension was significantly associated with subjective memory impairment in older adults (Chen et al., 2014).

The relationship between severe OSA and the possible development of systemic hypertension (see below) is well established (Foster et al., 2009, Morrell et al. 2000, Nieto et al. 2000, Peppard et al. 2000). Indeed, patients with severe OSA may have increased the incidence of cardiovascular and cerebrovascular disease, and evidence

of structural cerebral lesions (Almendros et al., 2011; Foster et al., 2009). Epidemiologically, patients with severe OSA may have the risk of stroke (Arzt et al. 2005; Foster et al., 2009; Yaggi et al. 2005). Further, hypertension is a risk factor for MI, CVD, stroke, ischemic white matter hyperintensities (WMH), and silent infarcts. Indeed, there would be synergistic vascular insults (Kerber et al., 2006) since hypertension is linked to other risk factors such as T2DM, obesity, and hypercholesterolemia (Allan et al., 2015, Firkbank et al., 2007, Kovacic and Fuster, 2012; Skoog and Gustafson, 2003; 2006). These risk factors mentioned above have been related to AD, and an extensive literature exists on this. It is noteworthy that hypotension in late-life is also associated with an increased risk of AD (Mehrabian et al., 2010; Sambati et al., 2014). A recent experimental study on a mouse model of AD (TgSwDI) induced chronic hypertension and studied its effects after six months. Chronic hypertension promoted 1. vascular inflammation, 2. microvascular A β deposition, 3. BBB disruption, 4. pericyte loss, and 5. cognitive deficits (Kruger et al., 2015). The Aged hypertensive mice (25 months old) (compared to 3 months old younger mice) showed increases in the APP-binding proteins in the hippocampus (Csiszar et al., 2013).

2.4. Obesity/ Metabolic Syndrome

About a third of U.S. adults have the metabolic syndrome (MetS) - and about one-sixth of 60 and older have MetS. Indeed, the incidence of MetS increases in the older adults (Ford et al., 2002). Several risk factors constitute MetS; these include abdominal obesity, hypertension, dyslipidemia, and glucose/insulin dysregulation. MetS is linked to diabetes, cardiovascular disease (CVD), and dementia. 65 years old obese patients without a clinical history of cognitive impairment showed high levels of tau and A β precursor protein expression, in some cases comparable to AD. AD-type changes in the obese (Compared to non-obese) may be due to comorbid diseases *viz.* Congestive heart failure, OSA, and hyperlipidemia (Mark, 2009). Mean gray matter CBF is about 15% lower in MetS (compared to controls); this may mediate the lower memory function noted in MetS (Birdsill et al., 2013). A significant increase in plasma Intercellular adhesion molecule 1 (ICAM-1), IL-8, and neutrophils occurs in the obese (relative to healthy subjects) (Carpagnano et al., 2010). MetS patients have significant inflammation, and this impacts cognition and memory. Indeed, individuals having both MetS and high inflammation possess a higher probability of memory and cognitive decline (Dik et al., 2007; Misiak et al., 2012; Yaffe et al., 2004). An Italian Longitudinal Study on Aging followed MCI patients with MetS (over 3.5 years) - an increased incidence of dementia was found in this population (Solfrizzi et al., 2011). Obesity per se is a recognized cause of cardiovascular pathologies (Alpert, 2001; Kalogeropoulos et al., 2010; Massie, 2002). Synergistic action of cerebral hypoperfusion and obesity is implicated in cognitive dysfunction in persons with heart pathology (Alosco et al., 2012; 2014). Indeed, this is further enhanced in individuals with, MetS, T2DM, and pathological heart issues, reflected in their lower volume of the cortical brain and cognitive test functioning (Alosco et al., 2013).

Those with mid-life obesity may run the risk of cognitive dysfunction/AD in later life. Cerebrovascular (CV) dysfunction showed a direct relationship with the duration of high-fat diet intake. The resulting hyperlipidemia disrupts CBF regulation and disrupts endothelial and smooth muscle function (Ayata et al., 2013). Obesity decreases CBF; it decreases the level of endothelium-derived nitric oxide (NO) (Toda et al., 2014). Obesity-enhances endothelial dysfunction while a decrease in CBF enhances A β production – the latter, in turn, impairs

endothelial function; this vicious pathological cycle promotes cognitive dysfunction (de la Torre et al., 2003; Toda et al., 2014).

In a recent interesting study on high-fat-diet-induced memory impairment in triple-transgenic Alzheimer's mice (3xTgAD), it was found that high-fat diet has rapid and sustained negative impact on memory (in control as well as in 3xTgAD mice) – this was ascribed to neuroinflammation in the AD mice. However, 3xTgAD mice at 3-4 months of age (compared to 15-16 months) have microglial activation, when fed with high-fat (Knight et al., 2014). The obese Zucker rat (OZR) represents a model of T2DM exhibiting increased arterial hypertension, vasoconstriction in the cerebral vasculature, and oxidative stress (Osmond et al., 2009). There is a significant increase in the astrocytic number in the OZR brain (in the frontal and parietal cortex, and in the hippocampus) (Tomassoni et al., 2013). Further, feeding saturated fat induces the hippocampal pathology and impaired cognitive function (Kanoski and Davidson, 2011). Higher BMI has been shown to induce the stroke at a significantly younger age (Dehlendorff et al., 2014).

2.5. Vitamin B12/Folate Deficiency

Vitamin B12/Folate intake has an impact on mental and physical health. A large number of elderly, even in the industrialized nations, consume less than recommended optimum amount of dietary nutrients. Up to 60%, elderly may be vitamin B12-deficient and about 29% folate-deficient. Poor cobalamin intake may cause atrophic gastritis resulting in lower gastric acid and pepsinogen secretion, and hence decreased absorption of B vitamins. B-vitamin deficiency may induce vascular disease (Hofmann et al., 2001; Huo et al., 2015; Kolb and Petrie, 2013; Shiran et al., 2015; Sudduth et al., 2013).

Homocysteine metabolism requires B vitamin cofactors. However, nutritional deficiencies in folic acid, vitamin B6 (pyridoxal phosphate), and B12 (methylcobalamin) enhance hyperhomocysteinemia (Hhcy). Vitamin B12/folate deficiency induces atherosclerotic lesions and neurocognitive decline. Folate deficiency is correlated with reduced cellular proliferation (17%) and increased apoptosis (16%) (Akchiche et al., 2012). In folic acid deficiency, homocysteine upregulates proatherogenic pathways including ROS and fibrin synthesis. However, folic acid (0.5-5 mg/d) supplementation significantly decreases homocysteine level (up to 25%) (Wolters et al., 2004).

In older adults, Hhcy increases CVD that may cause cognitive decline leading to AD. Older hypertensive individuals with Hhcy may undergo brain atrophy (Narayan et al., 2011) (see below). C57BL6/J mice were fed the vitamin B-deficient diet for ten weeks to induce Hhcy. This caused a significant pathology of hippocampal microvasculature and decreased spatial learning and memory (Throen et al., 2008). Chronic Hhcy increased pro-inflammatory TNF- α , IL-1 β and IL-6, chemokine CCL(2) and prostaglandin E(2) in the Wistar rats' hippocampus and serum (da Cunha et al., 2012). Hhcy may stimulate the vascular and cerebrovascular dysfunction in homocystinuria patients (da Cunha et al., 2012).

The frequency of the TT MTHFR genotype is quite high among individuals with B12 deficiency. This TT polymorphism in B12 deficiency correlated with endothelial dysfunction, and may be associated with potential vascular abnormalities that upregulate cardiovascular risk (Shiran et al., 2015). A model of VaD has been developed that induces Hhcy in mice. These mice develop neuroinflammation (determined by TNF- α , IL-1 β ,

and IL-6) and brain microhemorrhages. Increases in the matrix metalloproteinase 2 (MMP2) and MMP9 activity found in these animals are implicated in their cerebral hemorrhage pathology (Sudduth et al., 2013). Hhcy induced in mice by a methionine-rich diet increased atherosclerosis; it also enhanced RAGE (receptor for advanced glycation end products), VCAM-1, tissue factor, and MMP-9 in the vasculature (Hofmann et al., 2001). The above pathologies were significantly suppressed by feeding folate and vitamins B6/B12. Hhcy is a recognized factor that decreases gray matter thickness in bilateral frontal, parietal, occipital, and right temporal regions and lower gray matter volumes in left frontal, parietal, temporal, and occipital regions (Madsen et al., 2015). The above mentioned increases the risk for AD.

2.6. Diabetes

About 8% of the adult population suffers from T2DM. A direct association between glycemia and dementia has been shown in older persons (≥ 60 years old) with or without diabetes (Crane et al., 2013; Logue et al., 2011). Also, the correlation also exists between poor glucose metabolism (high fasting blood glucose) and lower executive function (Karlman et al., 2014), hippocampal atrophy, and lower memory, in older adults even without diabetes (Cherbuin et al., 2012; Kerti et al., 2013). Association also exists between insulin resistance and brain atrophy in those aged ≤ 60 years (Willette et al., 2013). It is known that cardiovascular risk factors, higher blood glucose, and memory decline are correlated in non-diabetic mid-life males (Anstey et al., 2015; Mortby et al., 2013). Further, in midlife adults, studies have reported: i) An elevated risk of vascular disease (Petrea et al., 2009), ii) Higher white matter pathology (Sachdev et al., 2004), iii) Enhanced glycaemia, and iv) Insulin resistance (Xu et al., 2013). After adjustment for hypertension, BMI, and smoking, only insulin sensitivity and C-reactive protein (CRP) were associated with a cognitive decrease in prediabetic stage (Anstey et al., 2015; Biessels et al., 2014).

Blood flow velocities (BFVs) were measured in the middle cerebral arteries of T2DM patients (and control). BFVs were negatively associated with HbA(1c) (A1C), and inflammatory markers. These data showed that reduced cerebral BFVs is related to increased resistance in middle cerebral arteries (Novak et al., 2006). Regional cerebral hypoperfusion and vasoreactivity, as well as cortical and subcortical atrophy, have been documented in the brain of T2DM patients. Patients with uncontrolled diabetes, therefore, may have enhanced hypoperfusion and brain atrophy. The resulting metabolic dysfunction in frontal and temporal regions from the effects mentioned above may impact negatively on cognition (Last et al., 2007). Indeed, cerebral perfusion is extensively compromised in the diabetic patients suffering from hypertension (Efimova et al., 2007; Last et al., 2007; ten Dam et al., 2007). CBF is significantly decreased in patients suffering from diabetic ketoacidosis (Yuen et al., 2008). T2DM is a vascular risk factor that may increase dementia risk. Neuronal cell death has been shown to increase in the hippocampus of the hypoperfused T2DM rats (Fukazawa et al., 2013; Kwon et al., 2015). This reflects that diabetes can enhance vascular-triggered cognitive dysfunction and promote dementia owing to cerebral hypoperfusion, inflammatory component, and neuronal degeneration (Kalaria et al., 2012; Rosenberg, 2009).

T2DM shares several risk factors with AD. While A β is deposited in AD brain, amyloid polypeptide APP called amylin accumulates within pancreatic beta-cells in T2DM. An increase in plasma glucose increases insulin levels even in subjects free of insulin resistance. This status has been shown to reduce 18F-FDG uptake in

precuneus/posterior cingulate, lateral parietal cortex, and frontal cortex – the AD-related regions (Ishibashi et al., 2015). Several studies have emphasized that T2DM may develop and persist in up to 30% of OSA patients (Kent et al., 2014; Pamidi and Tasali, 2012; Punjabi et al., 2004). Synergistically, they may modulate neuronal degeneration, and promote cognitive decline and AD (Daulatzai, 2013a; 2015b; 2015d). High stable glucose measures in younger individuals (25-59 YO; Compared to older persons) were associated with cognitive decline (after 12 years) (Anstey et al., 2015). A recent study evaluated the cognitive status of about 1000 diabetics and controls. The results showed that the occurrence of all-cause dementia, AD, and VaD was much higher in diabetics (4.8%, 2.7%, 1.4% respectively) compared to non-diabetics (2.2%, 1.2%, 0.4% respectively) (Zhao et al., 2012). The incidence of dementia and AD was significantly higher in T2DM patients carrying APOE ϵ 4 carriers (diabetics: 9.2%, non-diabetics: 3.3%) than APOE ϵ 4 non-carriers (diabetics: 6.3%, non-diabetics: 2.35%) (Zhao et al., 2012).

2.7. Depression

Significant research shows the relationships between depression, brain structural changes and cognitive decline, in older adults. 34 males (average age. 73.9) were studied with “multi-channel Near-infrared spectroscopy” (Uemura et al., 2014). rCBF was lower in the depressive subjects (compared with controls - the non-depressed) in the PFC. Further, there was less PFC activation in older depressed adults thus accounting for executive function decline (Uemura et al., 2014).

Single photon emission computed tomography (SPECT) was used to evaluate rCBF patterns in major depressive disorder (MDD) (Périco et al., 2005). An inverse relationship was present between severity of depressive mood and rCBF in the brain (notably amygdala, lentiform nucleus, and parahippocampal gyrus). A direct correlation with rCBF was, however, found in the right postero-lateral parietal cortex. Interestingly, specific rCBF patterns existed in variable MDD symptoms. For example, the severity of 1. Insomnia correlated inversely with rCBF in parts of anterior cingulate, insula and claustrum; 2. Anxiety correlated directly with rCBF in the right orbitofrontal cortex. Regions of orbitofrontal cortex and the left lentiform nucleus showed CBF that directly correlated with Cognitive performance (Périco et al., 2005; Bench et al., 1993). Another SPECT study on depression patients showed reduced rCBF in the PFC, left temporal lobe, and bilateral occipital lobes (Nagafusa et al., 2012). This work further showed that different specific symptoms may be associated with differing regional functional deficits in MDD, yet they are unaffected by age. As per a recent SPECT study, treatment-resistant depressed patients possess significantly low CBF in frontotemporal (bilateral), insular, anterior cingulate, and the caudate (left) regions (Richieri et al., 2015). rCBF was studied in MDD patients (compared with healthy controls) utilizing MRI with the arterial spin labeling method (which does not require radioisotopes) (Ota et al., 2014). Significant rCBF reductions were present in the prefrontal cortex (right inferior) and anterior cingulate in the MDD patients. The above results document a range of hypoperfusion and significant change in gray matter blood flow in major depression. The Pulsatility Index (PI) values and rCBFV parameters were also decreased in the cerebral arteries in depressive participants (Wang et al., 2014).

A meta-analysis of 23 studies identified conjoint decreases in rCBF and regional homogeneity in the insula and superior temporal gyrus in medication-free MDD patients. Also, altered rCBF was documented in the precuneus

and the frontal-limbic-thalamic-striatal neural circuit; the analysis showed altered regional homogeneity in the uncus and parahippocampal gyrus (Chen et al., 2015). A recent work has shown frontotemporal gray matter reduction in MDD patients and reduced rCBF in the anterior cingulate and parahippocampal region (bilateral). Interestingly, frontoparietal and striatal areas showed CBF increase (Vasic *et al.*, 2015).

2.8. Traumatic Brain Injury

Traumatic brain injury (TBI) is a major cause of disability and death. Initial management of TBI concentrates on prevention of subsequent secondary insults and cerebral hypoperfusion (Stein et al., 2011). TBI may cause memory impairment even after long-term following the insult (Stulemeijer et al., 2010; Dean and Sterr, 2013).

Indeed, a substantial single or repeated TBI may lead to a chronic traumatic encephalopathy and dementia (Walker and Tesco, 2013). Neuropathological findings after TBI may be similar to those found in AD. TBI may up-regulate axonal damage and A β 42 production, and down-regulate LTP (Walker and Tesco, 2013; Fakhran et al., 2013). Indeed, brain injury and ischemia could contribute to AD pathogenesis owing to cerebral circulatory and other abnormalities (Beckman et al., 2003).

There is evidence of significant pathology and altered metabolic milieu after TBI including edema, excitotoxicity, loss of neuronal and glial integrity, dysfunctional mitochondrial bioenergetics, oxidative stress, inflammation, and cell membrane disruption (Golding et al., 1999; Van Putten et al., 2005; Harris et al., 2012).

A substantial CBF reduction occurs in frontal and occipital cortices following sub-acute mild TBI (Lin et al., 2016). Consequently, a cascade of pathophysiological mechanisms is linked to vascular impairment-decreased CBF, brain hypoperfusion, glucose hypometabolism, and diminished energy supply (Olesen et al., 1981; Golding et al., 1999; Ayata et al., 2004; Parkin et al., 2005; Lauritzen et al., 2011; Romero et al., 2014).

TBI causes changes to brain's glucose uptake and its metabolism. Early after TBI, two deleterious features include: (1) regional cerebral oxygen tension and consumption decrease significantly in the cortex; and (2) at the same time point, glucose uptake is significantly reduced globally (Gajavelli et al., 2015; Jalloh et al., 2015). TBI affects brain glucose metabolism during sleep also and significantly lowers rCMR_{glc} in the amygdala, hippocampus, parahippocampal gyrus, thalamus, insula, uncus, culmen, visual association cortices, and midline medial frontal cortices (Stocker et al., 2014). The dysfunctional cerebral glucose metabolism contributes to secondary brain damage (Clausen et al., 2011). However, systemic administration of beta-hydroxybutyrate (a ketone body) in TBI can effectively reduce ROS production in several cortical regions including the hippocampus and prevent neuronal death (Julio-Amilpas et al. 2015).

3. Framework Highlighting Pathological Ramifications and Cognitive Vulnerability Owing to Chronic Hypoperfusion and Glucose Hypometabolism

3.1 Diverse Comorbid Conditions Trigger Vascular Pathology

About 40% of AD patients may suffer from comorbid VaD. MRI, CBF and mean CThk were compared between patients with mild AD and MCI converters to AD (MCI-c) after two years of clinical follow-up (Lacalle-Aurioles et al., 2014). A significant hypoperfusion was noted in the parietal lobes of the MCI-c patients. This study indicated that rCBF deficits are already present in the MCI stage, emphasizing that CBF is a more sensitive parameter in MCI-c patients (Lacalle-Aurioles et al., 2014).

Cerebral hypoperfusion and metabolic dysfunctions are crucial features of AD that precede significant neuropathology. We need to unravel upstream factors/mechanisms that trigger the AD pathogenesis. *Prima facie*, vascular dysfunction causes reduced rCBF, and vascular pathology contributes to inflammation and oxidative stress causing vicious cycles. NADPH oxidase generates vasoactive superoxide in vascular pathology. The role of hypoperfusion and glucose metabolic dysfunction described in aging, diabetes, dyslipidemia, hypertension, and other comorbid risk conditions (delineated above) are potentially potent in upregulating vascular inflammatory and ROS-related pathological damage (Murray et al., 2011). Oxidative stress and activation of proinflammatory factors e.g. Hhcy are deemed causal in promoting atherosclerosis that in turn enhances hypoperfusion (Zhou and Austin, 2009).

There is a documented decrease in glucose metabolism with age in several brain areas. A recent FDG-PET study was done on 70-year-old normal individuals. There were statistically significant declines in FDG ratio in most cortical and subcortical regions, as a function of age (Knopman et al., 2014). 31.3% had elevated Pittsburgh compound B (PIB); however, no interaction was found between PIB status and Apolipoprotein E4 (APOE ϵ 4) genotype regarding glucose metabolism (Knopman et al., 2014). This study made other important observations. Carrying an APOE ϵ 4 allele was associated with reductions in FDG ratio in the posterior cingulate, precuneus, and lateral parietal regions. However, there was no interaction between “age and APOE ϵ 4 status”. They concluded that the above regions possess an inherently unique vulnerability to reductions in glucose metabolic rate in aging and carrying an APOE ϵ 4 allele (Knopman et al., 2014). There is another study of note, although on a single patient, with posterior cortical atrophy. Both amyloid and tau were studied with their specific tracers viz. PIB and [(18) F]AV-1451, respectively. While amyloid was found throughout association neocortex, “[18) F]AV-1451 was selectively retained in clinically affected posterior brain regions that also showed a significant reduction in [(18) F]FDG uptake (Ossenkoppele et al., 2015).

A voxel-based analytical work showed significant hypometabolism but not atrophy in cognitively normal A β -positive subjects in comparison with cognitively normal A β -negative subjects (Kljajevic et al., 2014). This is in contrast to another recent study that found cognitively normal older adults with higher amyloid deposition are relatively hypermetabolic in some brain areas, e.g. frontal and parietal (Oh et al., 2014). A 9-year longitudinal study was conducted on MCI patients employing serial brain imaging with PIB (Knopman et al., 2015). It was found that the patients positive for amyloid and neurodegenerative changes showed volumetric and metabolic worsening in their temporal and parietal association areas (Knopman et al., 2015). Thus, clearly more extensive work is needed to evaluate both amyloid deposition and NFT concurrently - since many studies do not carry out the simultaneous evaluation of tau status in A β -positive or negative subjects.

Current evidence shows age-related cerebral microvascular pathologies. These include tortuous blood vessels/capillaries, venous collagenosis, low vascular density, and microembolic brain injury that lead to compromised blood supply. A decrease in cerebrovascular angiogenesis may impact recovery from ongoing OSA/hypoxia-related factors. Most lipid microemboli from the heart may remain for weeks in the brain (Brown and Thore, 2011). Consequently, there is a functional failure of the aging microvasculature; this is also noted in AD brain emphasizing the possible role of the compromised brain microcirculation and decreased cerebral metabolism in AD pathogenesis (Farkas and Luiten, 2001; Hunter et al., 2012). These factors may impact drainage of A β along perivascular elimination pathways in aging artery walls (Weller *et al.*, 2009) (see below).

Recent work has shown that Hhcy is an important independent risk factor that induces arterial pathology. Also, endothelial injury and inhibition of insulin sensitivity are promoted by Hhcy (Liu et al., 2014). The arterial endothelial dysfunction occurs in OSA, hypertension, Hhcy, and insulin resistance (Liu et al., 2014). A significant number of elderly suffer from the above-combined stigmata that may induce arterial stiffness and a decrease in rCBF; the ensuing hypoperfusion would increase cerebrovascular damage (Chung et al., 2010). Mice fed a diet depleted of folate and vitamins B6 and B12 showed an increase in atherosclerotic lesion. The vasculature of these mice showed an enhanced expression of the receptor for advanced glycation end products (RAGE), VCAM-1, tissue factor, and the MMP9. However, the above effects decreased significantly following reintroduction of folate and vitamins B6 and B12 in the diet (Hofmann et al., 2001). Similarly, vascular dyshomeostasis and endothelial dysfunction occur in obese individuals with prehypertension, prediabetes, hyperinsulinemia, and insulin resistance (Gupta et al., 2012). Hence, chronic cerebral hypoperfusion would lead to neural injury and cognitive impairment (see below).

VaD patients are known to develop several vascular lesions (confirmed by MRI and histology) including microhemorrhages, hemorrhagic infarcts, or ischemic infarcts. Mice subjected to hyperhomocysteinemia develop neuroinflammation reflected by elevated TNF- α , IL-1 β , and IL-6, (Sudduth et al., 2013). An earlier study on diet-induced Hhcy in mice (Hofmann et al., 2001) found higher levels of the MMP2 and MMP9. The latter is implicated in the development of cerebral hemorrhage. Hhcy induced spatial memory deficit (radial-arm water maze test) in the mice. There are growing data that low Vitamin B12 is directly associated with AD. A combination of high Hcy and low vitamin B12/folate levels are found in AD (Chen et al., 2015). A recent meta-analysis also corroborated that the above factors may increase AD risk (Shen and Ji, 2015). Vascular risk factors underlie AD or vaD (Fig. 1.). Ethanol abuse and hypercholesterolemia also underlie pathologies that are similar to AD (Ullrich et al., 2010). Long-term ethanol treatment in adult Sprague-Dawley rats spatial memory dysfunction; this was owing to decreased cortical acetylcholine, elevated cortical monocyte chemoattractant protein-1 and tissue-type plasminogen activator, microglia increase, reduced number of choline acetyltransferase- and p75 neurotrophin receptor-positive neurons in the nucleus basalis of Meynert. Further, the ethanol-treated rats displayed BBB leakage. Thus, ethanol and cholesterol may be causative in cognitive dysfunction in AD and vaD (Ehrlich et al., 2012).

3.2 Cerebral Amyloid Angiopathy (CAA)

The CAA increases with age; almost 100% elderly 80 years and over have CAA. In CAA, A β peptide is deposited within the walls of the blood vessels and capillaries. CAA and hypoperfusion enhance deposition of leptomeningeal A β . CAA may originate from neurons. According to drainage hypothesis, neuronally-produced A β crosses the blood-brain barrier (BBB) (Burgermeister et al., 2000). Another theory suggests that A β originates in the circulating bloodstream. A β may also be generated by vascular smooth muscle cells, and pericytes (Revesz et al., 2002). Regardless of its origins, A β is deposited and builds up on the walls of the blood vessel due to its increased accumulation and decreased clearance (deficiency in the A β transport) (Segare et al., 2013). This would cause narrowing of the lumen and induce vascular pathology. CAA induces the degeneration and death of endothelial cells (Ferrer et al., 2004).

ROS-mediated vascular/endothelial and BBB dysfunction (Ferrer and Keller, 2012 and Freeman et al., 2012) due to A β may induce inflammatory responses causing migration of leukocytes across blood vessels (Sutton et al., 1999; Thomas et al., 1997). Further, A β mediates production of TNF- α and IL-1 β that in turn mediate inflammatory response and vascular pathology (Sutton et al., 1999). Hence, while CAA increases cerebral hypoperfusion, conversely hypoperfusion accelerates CAA (Okamoto et al., 2012). Besides, A β may disrupt Blood–CSF barrier integrity (Brkic et al., 2015).

The rat brain capillary endothelial cells (RBE4), deprived of oxygen and glucose generated 250% increase in A β 42 production. The mechanism has been shown to be time-dependent and involves the HIF1-mediated β -secretase (BACE1) and APP gene up-regulation. This work clearly showed that oxygen and glucose deprivation has a direct impact on endothelial cells of the brain to upregulate the intra-endothelial cell deposition of A β 42 (Bulbarelli et al., 2012).

In AD, CAA has been shown to range from 70% to 97.6% (Attems, 2005). CAA may cause microscopic bleeding in the neocortex making it an important AD pathology (Jellinger, 2007). This has been corroborated recently (De Reuck et al., 2013; Samuraki et al., 2015). CAA-related microbleeds were located (in 158 AD patients) mainly in cortex and subcortex, but in the occipital lobe also. Patients with CAA-related microbleeds showed glucose hypometabolism and gray matter atrophy in the temporal lobe and cerebellum. Consequently, it was concluded that CAA-related microbleeds are causative regarding gray matter atrophy and glucose hypometabolism in AD (Samuraki et al., 2015). Sustained cerebral hypoperfusion through microinfarcts, hemorrhage, and white matter disruption produced glio-vascular alterations and cognitive deficits (Holland et al., 2015).

In Tg2576 mice, human apoE4 expression caused substantial CAA at 15 months of age (Fryer et al., 2005). When microvessels are pathological, they may contribute to neuronal injury and death by releasing toxic factors that directly injure neurons (Grammas, 2000). Microvessels isolated from AD brain release higher levels of monocyte chemoattractant protein (MCP-1), TNF- α , IL-1 β , and IL-6, compared to microvessels from non-AD brain (Grammas and Ovasé, 2001). The AD microvessels secrete a high level of neurotoxic inflammatory mediators including protease thrombin and the inflammation-associated proteins IL-8, α V β 3, and α V β 5 integrins (Grammas et al., 2006). These neurotoxic agents upregulate the “pathologic activation of cerebral microvasculature” and dysfunctional endothelial cells may lead to neuronal injury/loss in AD brain (Grammas et al., 2002).

The transgenic A/T mice (APP(Swe, Ind)) overexpress a mutated form of the APP and transforming growth factor- β 1 (TGF- β 1). In these aged mice, chronic inflammation triggers a cascade leading to several AD-like pathophysiological features - encompassing cerebrovascular amyloidosis, microvascular fibrosis and degeneration, hypoperfusion, and cerebrovascular amyloid angiopathy. These lead to significant alterations in metabolic activity in different brain regions implicated in learning and memory processes (Wyss-Coray et al., 2000; Buckwalter et al., 2002). Further, these mice displayed deficient neurovascular and neurometabolic coupling to whisker stimulation, and memory performance (Ongali et al., 2010). At nine months of age, these mice had degenerative alterations in endothelial cells and pericytes, associated with decreased regional cerebral glucose utilization (Wyss-Coray et al., 2000; Hamel, 2015). Further, they showed a decline in NO activity in

vessel walls and cerebrovascular function with dilatory deficits thus causing decreased vessel tone (Papadopoulos et al., 2014; Tong and Hamel, 2015). Hence, endothelium-mediated vascular dysfunction may be an important component in AD pathogenesis (Di Marco et al., 2015).

3.3 Blood–Brain Barrier (BBB) Dysfunction

The neurovascular unit is comprised of brain microvascular endothelial cells and astrocytes that regulate BBB permeability. This interface *viz.* the BBB protects the brain from any noxious molecules in peripheral circulation. BBB is an important component of the vascular hypothesis (Rocchi et al., 2009; Valenti et al., 2014; Canobbio et al., 2015; Janota et al., 2015; Rius-Pérez et al., 2015; Di Marco et al., 2015). Indeed, hypoperfusion, hypoxia and neuroinflammation due to various factors may lead to BBB leakiness and apoptosis in AD (Biron et al., 2011; Hartz et al., 2012; Heye et al., 2014; Yang et al., 2015; Michael et al., 2015; Banks et al., 2015; Nathoo et al., 2016). In mild-to-moderate AD, the BBB undergoes significant disruption during the disease progression (Bowman et al., 2007). In AD progression, the BBB permeability is crucial in letting the neurotoxic substances such as pro-inflammatory cytokines enter the CNS (Bell et al., 2009; Desai et al., 2002; Lashuel, 2005; Persidsky et al., 2006; Simionescu and Antohe, 2006).

Aging reduces BBB integrity, and this is linked to AD (Altman and Rutledge, 2010; Deane and Zlokovic, 2007). Also, a high-saturated-fat and cholesterol (HFHC) diet contributes to BBB breakdown. Activated microglial cells play a significant role in altering the BBB integrity (Hawkins and Davis, 2005). Increase in microglial activation was shown in aged rats receiving the HFHC diet (Freeman and Granholm 2012). The lipopolysaccharide-stimulated inflammation enhances BBB disruption, activated microglial cells, and damaged endothelial cells causing their death (Kacimi et al., 2011). Rats with hypoperfusion (after transient middle cerebral artery occlusion) underwent both microglial activation and neuronal loss (Emmrich et al., 2015).

Chronic sleep restriction (CSR) may also induce BBB dysregulation. The latter may occur via inhibition of endothelial and inducible nitric oxide synthase (eNOS and iNOS, respectively), endothelin1 upregulation, and decreased 2-deoxy-glucose uptake. As little as six days of CSR was enough to impair BBB dysfunction - decreasing several tight junction proteins, and increasing BBB permeability. Interestingly, following just 24 h of recovery sleep, the BBB permeability became normal (He et al., 2014).

3.3.1 Disruption of Glucose Uptake Impairs BBB Integrity

There is hypometabolism of differing severity in different regions of the AD brain. Cerebral hypometabolism reflected by a reduction in glucose utilization begins decades before any AD symptoms or histopathologic changes. The increase in plasma glucose levels reduces 18F-FDG uptake in precuneus/posterior cingulate, lateral parietal cortex, and frontal cortex in AD-related regions. The potency of this phenomenon is such that it can occur even in normal individuals without insulin resistance (Ishibashi et al., 2015).

90% of brain energy is supplied by glucose metabolism (Handa et al., 2000). The blood glucose concentration and transporter protein are the rate-limiting factors for its transport into the brain. Any disruption of BBB integrity interferes with glucose uptake. Chronic ethanol abuse impairs glucose tolerance and causes inability to maintain plasma insulin levels (Wilkes and Nagy, 1996). Recent work measured the glucose metabolism in different brain regions of the chronic alcoholics by FDG-PET (Volkow et al., 2006), and found a decline in

glucose metabolism in the frontal cortex. Additionally, alcohol consumption enhances monocytes migrating across the BBB, and ROS-mediated BBB disruption (Haorah et al. 2005b; 2007a; 2007b). Several other mechanisms are implicated in the alcohol-induced BBB disruption; these include activation of myosin light chain kinase (Haorah et al. 2005a), inositol 1,4,5-triphosphate-gated intracellular Ca²⁺ release (Haorah et al. 2007a; 2007b), and protein tyrosine kinase-mediated matrix metalloproteinase signaling pathways (Haorah et al., 2008a; 2008b).

3.3.2 BBB Disruption Promotes Neuronal Loss

In cultures of neuron and astrocyte (human stem cell-derived), treatment with A β 42 induces hypometabolism.

The A β -exposed cultures displayed decreases in glucose uptake and its utilization (Tarczyluk et al., 2015). The latter has been shown to disrupt the energy-redox axis reflected by changes in NAD⁺/NADH, ATP, and glutathione levels (Tarczyluk et al., 2015). The pyruvate uptake, (an important energy source in the brain mitochondria) was lower after A β 42 treatment of the cultures; this, however, decreased ATP but increased Ca²⁺ and ROS levels. Consequently, unlike astrocytes, the neurons succumbed to death (Tarczyluk et al., 2015).

Alcohol negatively interferes glucose metabolism in the brain (Handa et al. 2000; Volkow et al. 2006). The BBB dysfunction would adversely affect the uptake and utilization of glucose by neurons and glial cells. This would impact their survival as well. Indeed, this has been confirmed in that attenuation of glucose uptake causes neuronal degeneration (Abdul Muneer et al., 2011a; 2011b). Alcohol significantly inhibited the uptake and transport of glucose across the BBB; this was validated by both *in vitro* and *in vivo* findings.

Decreases in glucose transport across the BBB (*e.g.* due to alcohol) and glucose uptake in cells correlated with reduction of GLUT1 protein (due to defective mRNA biosynthesis of GLUT1) expression in cell culture and brain microvessels (Abdul Muneer et al., 2011a). The above mentioned causes further breakdown of BBB integrity (Abdul Muneer et al., 2011a). Consequently, cerebral glucose hypometabolism may lead to neurotoxicity and neuronal degeneration (Fig. 1.).

3.3.3 Hypoperfusion and Neuronal Death

The mechanisms underlying neuronal death due to chronic cerebral hypoperfusion has been extensively studied (Martin et al., 2000). Ultrastructurally and immunocytochemically, degenerating hippocampal CA1 pyramidal neurons and cerebellar Purkinje cells undergo necrosis, while degenerating granule neurons show both necrotic and apoptotic processes. Indeed, the vulnerable neurons undergoing degeneration after hypoperfusion/ischemia are mediated by the apoptosis-necrosis continuum (MacManus et al., 1995; Martin et al., 2000; and Portera-Cailliau et al., 1997a; 1997b). Neurodegeneration due to hypoperfusion involves intracellular Ca²⁺ dyshomeostasis and excitotoxic activation of neuronal glutamate receptors (GluRs) (Diemer et al., 1993).

Several other deleterious changes occur in neurons after hypoperfusion; these may include damage to the plasma membrane and cytoplasmic organelles. In neuronal degeneration (Laiho et al., 1971; Laiho and Trump, 1975; Martin et al., 2000) mitochondrial dysfunction causes a decrease in ATP synthesis (Laiho and Trump, 1975). Indeed, as early as 6 hours after cerebral ischemia, total protein synthesis is severely reduced particularly in vulnerable neurons (Araki et al., 1990; Furuta et al., 1993; Johansen and Diemer, 1990; Thilmann et al., 1986) followed by a lack of restoration of biosynthetic function. Early after hypoperfusion, cytoskeletal disintegration

occurs in dendrites, before degeneration of neuronal cell bodies (Kitagawa et al., 1989; Yamamoto et al., 1990). The above pathophysiological abnormalities persist during the process of neurodegeneration (Kirino, 1982; Kirino and Sano, 1984; Kirino et al., 1984; Martin et al., 1998). Of note, CNS ischemia has a deleterious impact on non-neuronal cells also - astrocytes, oligodendrocytes, inflammatory cells, and vascular cells die apoptotically (Martin et al., 1997a; 1997b; 1998). Signaling pathway mediated by the HIF is an important compensatory protective mechanism; it is triggered by pathophysiological conditions including hypoxia and ischemia. Hypoxia-inducible factor 1-alpha (HIF-1 α) activation was studied in the animal model of chronic cerebral hypoperfusion. HIF-1 α increased as early as 12 h after hypoperfusion and continued increasing for 56 days. Importantly, there is the sustained increase of HIF-1 α during chronic cerebral hypoperfusion - but without any protective effect (Yang et al., 2013).

3.4 Cerebral Hypometabolism

There is evidence that AD patients suffer from abnormal forward glucose transport in the cortical brain regions (Jagust et al., 1991; Piert et al., 1996). The impaired glucose metabolism is said to be the basis for neuronal/synaptic dysfunction and cognitive decline. The functional biomarker CMRglc in conjunction with changes in the brain volumes is valuable to gain information about disease progression and drug treatment outcome. A CMRglc study in the aging-associated cognitive decline identifies patients with metabolic alterations, and who may develop aMCI (Hunt et al., 2007); it may also predict those aMCI patients who may subsequently convert to AD (Herholz et al., 2007). MCI converters to AD possess a much lower CMRglc in the right cingulate, left inferior parietal and left temporal gyrus, and most of their brain areas undergo significantly decreased CMRglc during AD progression (Ishii et al., 2009).

12 weeks of hypoperfusion decreases CBF by 26% in CAA mice (compared to wild-type mice), indicates perivascular A β accumulation and impaired microvascular function. This study also documented that cortical microinfarcts in AD brains are mainly located close to CAA afflicted vessels (Okamoto et al., 2012).

FDG-PET studies have highlighted CMRglc abnormalities in preclinical individuals in their 40's (Reiman et al., 2004). CMRglc reductions in the Hippocampus during normal aging is considered to predict cognitive decline much earlier than the clinical diagnosis (Mosconi et al., 2008). The dysfunctional entorhinal cortex (EC) connection has been implicated in cortical hypometabolism. Assessment with FDG-PET pointed out CMRglc reductions in the EC and the ipsilateral temporooccipital cortex (Mosconi et al., 2004). Importantly, Presymptomatic familial early-onset AD individuals have an absence of brain atrophy but show significant widespread MRglc reductions (Mosconi et al., 2006). Reduced CMRglc was found only in posterior cingulate cortex (PCC) in aMCI patients; however, low CMRglc was present in AD in several areas including frontal, parietal, temporal, and occipital cortex (O'Brian et al., 1992). Other studies on AD have also documented CMRglc reductions in the PCC, precuneus, temporoparietal and frontal multimodal association regions (Del Sole et al., 2008; Herholz et al., 2007). Worth noting is the fact that aging-associated cognitive decline patients (who later converted to AD) showed the metabolic decline in more extensive regions, viz. frontal and temporal cortices, right cingulate gyrus, right thalamus, and bilateral precuneus (Hunt et al., 2007). However, in

subcortical vascular dementia patients, the glucose hypometabolism was more severe in the thalamus, brainstem, and cerebellum (Seo et al., 2009).

When AD patients were studied with FDG-PET after one year (from the baseline), they had a significant decline in glucose metabolism in frontal, parietal, temporal, and posterior cingulate cortices (Alexander et al. 2002). In another study, 16 AD patients were followed up for two years, and interval change in amyloid deposition and CMRglc studied. Relative PIB retention in cortical regions differed by 3-7%; in contrast, CMRglc decreased by 20%. Interestingly, this follow-up study showed a significant negative correlation between CMRglc and PIB retention in the parietal cortex. (Engler et al., 2006). An interesting study in AD patients has documented that hypometabolism in parietal and precuneus regions is negatively correlated with PIB retention in AD patients (Cohen et al., 2009). However, others have found a positive correlation between PIB and CMRglc in all cortical regions studied but particularly in the posterior cingulate and parietal cortices (Forsberg et al., 2012). The reasons for the above discrepancy is not known. Finally, an elegant study in baboons has highlighted the interrelationship between rhinal cortex pathology and the CMRglc decline in the inferior parietal, posterior temporal, posterior cingulate, and the posterior hippocampal regions (Meguro et al., 1999). Importantly, as much as 49.9% decrease of CMRglc may occur in the parietal cortex of the AD patients (Piert et al., 1996).

Neuronal damage and dysfunction in the rhinal cortices may cause glucose hypometabolism in several brain areas; this is said to play a significant role in the pathogenesis of AD (Meguro et al., 1999; Millien et al., 2004; Daulatzai, 2015b). FDG PET studies suggest that normal anatomico-physiological connections with the EC are important to maintain cortical glucose metabolism. Conversely, decreases in the CMRglc in the temporoparietal and hippocampal areas noted in AD may be due to their disconnection with the rhinal cortex (Meguro et al., 1999; Millien et al., 2004; Mosconi et al., 2004; Daulatzai, 2013a; 2013b; 2014; 2015b; 2015c).

3.5 Brain Atrophy: A Defining Impairment in Multiple Risk Factors

3.5.1 Aging

Aging is associated with cognitive decline in some (but not all) aged persons. Owing to susceptibility, the vulnerable persons begin to decline from their 40s onwards. Significant pathology may continue to accumulate at the time they are in their 50s and 60s. Age-related cognitive decline correlates with decreases - in regional brain volume (Allen et al., 2005; Fotenos et al., 2005; Sowell et al., 2003), cortical thickness (Magnotta et al., 1999; Salat et al., 2004), and white matter (Pfefferbaum et al., 2006; Salat et al., 2005). There is an ongoing accumulation of NFT (Del Tredici and Braak, 2008) and A β (Beckmann et al., 2003; Bennett et al., 2005; Okamoto et al., 2012; Okonkwo et al., 2014).

Healthy aging is associated with widespread age-related neuroanatomical volume change. The brain volume loss of 0.2% per year occurs after age 35 years. This is followed by a decrease in brain volume loss of 0.5% annually at age 60. However, in over 60 years old, the volume loss is more than 0.5% in the brain (Hedman et al., 2012). With older age, gray matter (GM) volume was lower in the sensorimotor, frontal, temporal, occipital, and parietal lobes, as well as in the cerebellum, posterior hippocampus, thalamus, and middle cingulate gyrus (Raji et al., 2009; Walhovd et al., 2011). In the presymptomatic stage with no cognitive decline, hypertension and AD are additive in enhancing gray matter damage (Glodzik et al., 2012). Interestingly, in *Aplysia californica*, the

neurons express genes related to apoptosis and AD; however, these are expressed differentially in older animals. This was inter-related to (i) changes in histones, (ii) DNA methylation, and (iii) regional relocation of RNAs; these alterations are thought to underlie age-related changes in neuronal functions and synaptic plasticity (Moroz and Kohn, 2010). Importantly, normal aging has little effect on medial temporal lobe volume loss (Dickerson et al., 2009; Salat et al., 2004).

3.5.2 Obesity

Obesity is a risk factor for AD (Kivipelto et al., 2005). Higher cortisol secretion may decrease brain volume (Bjorntorp, 2001; Simmons et al., 2000). Several studies have emphasized the brain volume decline as a function of obesity (Gustafson et al., 2004; Pannacciulli et al., 2006; Ward et al., 2005). In one study over a 6-year period, BMI was shown to influence gray matter volume (Taki et al., 2011). OSA is one of the risk factors for obesity. Data show that OSA patients undergo a reduction in their gray matter (compared with non-apnoeic controls) (Morrell et al., 2010). Indeed, gray matter volume decreases have been confirmed in the left hippocampus, EC, left PCC, and right superior frontal gyrus (Canessa et al., 2011). After CPAP treatment, memory, attention, and executive functioning were significantly improved; concomitantly gray matter volume increased in the hippocampus and frontal cortex (Canessa et al., 2011). Using tensor-based morphometry (TBM) and computational analysis, the study showed that increase in body's adipose tissue (hence greater BMI) correlates with lower brain volumes in the hippocampus, orbital frontal cortex, and parietal lobes in cognitively normal elderly adults (Raji et al., 2010). Recent proton magnetic resonance spectroscopy (MRS) studies also showed that higher BMI lowers neuronal viability in the brain regions including, frontal, parietal, and temporal lobes (Gazdzinski et al., 2009). In effect, every unit increase in BMI was associated with a 0.5%–1.5% average brain tissue reduction in MCI and AD patients studied (after controlling for age, sex, and education) (Ho et al., 2010; Verstynen et al., 2012). The BMI associated brain atrophy is predominantly in the white matter (Gregoire et al., 2011; Verstynen et al., 2012).

3.5.3 Homocysteine

Homocysteine is an agonist at N-methyl-D-aspartate (NMDA) receptor (the glutamate binding site), but as a partial antagonist at the glycine receptor site. It mediates excitation at the Schaffer collateral-CA1 synapses (at NMDA receptors) in the hippocampus (Ito et al., 1991). Under physiological conditions, modest Hhcy may contribute neurotoxicity via overstimulation of NMDA receptors (Lipton et al., 1997; Schwarz et al., 1990). Excessive stimulation of these receptors mediates brain damage (Lipton and Rosenberg, 1994; Simon et al., 1984).

Elevated homocysteine enhances brain atrophy rates in older hypertensives (Narayan et al., 2011). Hhcy correlates with white matter atrophy and hippocampal atrophy (Firbank et al., 2010; Choe et al., 2014). Recent multiple linear regression analyses have confirmed that plasma total homocysteine level has a significant impact on hippocampal volume (after controlling for the amyloid beta deposition, vascular burden, age, gender, education, and ApoE4 genotype). Indeed, homocysteine has a direct adverse impact on the hippocampus, not mediated by A β (Choe et al., 2014). However, B-vitamin treatment decreases (7 fold) the gray matter atrophy in the medial temporal lobe (Douaud et al., 2013).

Under pathological conditions, the neuronal damage is a function of excessive Ca^{2+} influx and higher ROS. ROS can be generated extracellularly by homocysteine (Stamler et al., 1993) causing excessive NMDA receptor stimulation, cytochrome c release, neurotoxicity, and apoptosis (Baydas et al., 2005; Ho et al., 2001; Lafon-Cazal et al., 1993; Lipton et al., 1997). Importantly, superoxide dismutase and catalase may offer protection from neuronal damage (Truelove et al., 1994). Overstimulation of NMDA receptors leads to increased level of cytoplasmic Ca^{2+} by L-glutamate, and mitochondrial pathology (Kim et al., 1999; Wang et al., 1999). 14-3-3 brain protein suppresses apoptosis mainly through sequestration of Bad, a pro-apoptotic protein (Brunelle et al., 2009; Dougherty et al., 2004; Yacoubian et al., 2010). However, the level of 14-3-3 ϵ is significantly reduced after reducing homocysteine (Wang et al., 2012).

3.5.4 Sleep Deprivation

Chronic sleep deprivation (CSD) may compromise neuronal stability and induce cell death (Daulatzai, 2013a; 2015b; 2015d). A recent study has shown significantly reduced hippocampal volume in sleep-restricted animals (Novati et al., 2011). The hippocampus of young and aged animals subjected to CSD showed apoptosis and cell death (de Souza et al., 2012). This was ascribed to Ca^{2+} signaling dysregulation (de Souza et al., 2012). CSD produces unhealthy physiological consequences. Indeed, healthy adults subjected to CSD manifest adverse effects on endocrine, metabolic and inflammatory functions. Furthermore, the CSD-induced increase in brain TNF- α and IL-1 β and decrease in hippocampal BDNF might contribute to neurocognitive decline (Zielinski et al., 2014). Finally, synapses are affected by sleep. Excitatory synapses change their efficacy; they grow or shrink – as a function of sleep. Sleep deprivation affects the synaptic function of LTP (long-term potentiation) (Cirelli, 2013). Consequently, sleep restriction has a potent impact on neurobehavioral, memory, and cognitive functions.

3.5.5 Chronic Alcohol Abuse

Chronic alcohol abuse is one of the common reasons for neurodegeneration. Excessive consumption of alcohol is associated with neurodegeneration and cognitive dysfunction, as well as microglial activation (Zhao et al., 2013). Cerebral microbleeds occur in heavy drinking (Ding et al., 2015). The loss of dopaminergic and cholinergic neurons from chronic alcohol administration occurs in the hippocampus and striatum. Copious data also document that alcohol-induced neurodegeneration (AND) is related to enhanced oxidative stress, increased NF-kappaB transcription, and proinflammatory proteins – both are neurotoxic (Crews and Nixon, 2009). Ethanol disrupts synaptic signaling in the hippocampus causing spatial memory decline (Wright et al., 2003). However, blocking of oxidative stress and NF-kappaB transcription, and increasing CREB transcription may nullify the above derangements (Crews and Nixon, 2009).

3.6 Elderly and Cognitive Impairment

Cognitively healthy elderly having pathological biomarkers for AD may not progress to AD (Lue et al., 1999; Riudavets et al., 2007; Iacono et al., 2008; Erten-Lyons et al., 2009; Kramer et al., 2011; Bjorklund et al., 2012). Conversely, a significant proportion of elderly having cognitive and memory concerns/impairment do not necessarily convert to dementia/AD either (Marchant et al., 2013; Wirth et al., 2013; Hwamee et al., 2014; Mormino et al., 2014; Amariglio et al., 2015).

Longitudinal, observational study with serial brain imaging (conducted over 10 years) in a population-based cohort has shown that older subjects even positive for neurodegeneration can lack an AD metabolic profile and pathophysiology (Knopman et al., 2015). Indeed, older adults may possess age-related gray matter atrophy across the whole brain, regardless of A β deposition (Oh et al., 2014; Jansen et al., 2015; Foley et al., 2015). Importantly, the presence of brain amyloidosis alone is not sufficient to produce cognitive decline (Jack et al., 2008; 2009; 2015). A discussion on A β deposition and neuroimaging (PIB), and other biomarkers, in cognitively normal elderly and those with preclinical AD, is beyond the scope of this paper.

Subtle losses in cognitive function may not always be symptomatic of AD. However, among “vulnerable” elderly, about 79.5% in age group 90 years (or older) and 46.7% among those aged 71–79 transition to AD (Brookmeyer et al., 2011). The overall prevalence of MCI (in the United States) for individuals aged 71 years or older is reported to be 22% (Brookmeyer et al., 2011). Of these, the annual conversion rate in 3 years (in clinical samples) from MCI to AD is about 8-15% (Devanand et al., 2008). Estimations have shown that AD accounts for approximately 69.9% of all dementia while VaD being 17.4%. Other types of dementia including Parkinson's dementia, normal pressure hydrocephalus dementia, frontal lobe dementia, alcoholic dementia, traumatic brain injury-related dementia, and Lewy body dementia (to name a few) account for about 12.7% cases (Brookmeyer et al., 2011).

4. Cerebral Hypoperfusion: Therapeutic Approach

Several therapeutic substances have been documented that attenuate cerebral hypoperfusion. Some of the selected ones are mentioned below. The therapeutic approach is subdivided as follows into 1. Reperfusion-Rehabilitation Approach, 2. Pharmacological Approach, and 3. Nutraceutical Approach.

4.1 Reperfusion-Rehabilitation Approach

The brain reperfusion-rehabilitation therapeutic strategy has been presented recently. The effect of the brain reperfusion rehabilitation therapy (BRRT) was evaluated in 15 patients with mild AD. They underwent BRRT for 12 months with significant improvement in tissue oxygen saturation (measured with near-infrared spectroscopy), Mini-Mental State Examination (MMSE), and Rey Auditory Verbal Learning (RAVLT) tests. This indicates that the attenuation of hypoperfusion may result in improvement in verbal memory-learning and global cognitive impairment (Viola et al., 2014).

4.2 Pharmacological Approach

Minocycline

Minocycline is a tetracycline derivative that reduces inflammation and ameliorates cerebral ischemia. It controls oxidative stress and attenuates the cognitive decline in an animal model of chronic cerebral hypoperfusion (Wistar rats) (Cai et al., 2008). A decrease in the relaxant NO enhances cerebral ischemia, and minocycline down-regulates expression of iNOS but upregulates eNOS. Its beneficial effects include decreasing oxidative stress and apoptosis and protecting neural function (Cai et al., 2008).

Cilostazol

Chronic cerebral hypoperfusion was induced in T2DM rats. These rats were treated with cilostazol - a potent inhibitor of type III phosphodiesterase. Cilostazol was significantly beneficial in these hypoperfused animals; it

inhibited neuronal cell death, activated CREB phosphorylation, upregulated BDNF expression, and improved memory impairment (Kwon et al., 2015). Cilostazol also improved endothelial dysfunctions in mesenteric arteries of T2DM rats. This endothelial effect of cilostazol treatment is via improved: (a) acetylcholine-induced relaxation and (b) cyclic adenosine monophosphate (cAMP)-mediated relaxations (Matsumoto et al., 2008; Miyamoto et al., 2009). An earlier study also showed protective effects of cilostazol on focal cerebral ischemia - through decreasing TNF- α level, Bax protein level, cytochrome c release, and increasing the levels of Bcl-2 protein (Choi et al., 2002). This led to a decrease in brain ischemia, and oxidative apoptotic cell death (Choi et al., 2002). A recent study corroborated some of the above data and further documented that cilostazol upregulated p-CREB and Bcl-2, as well as increased cyclooxygenase-2 expression, and reduced microglial activation. Thus, cilostazol is brain-protective and may be potentially useful in ameliorating cognitive impairment (Watanabe et al., 2006). Several elements of the above studies have been confirmed in the rats subjected to focal transient ischemic damage (Hong et al., 2006) and chronic cerebral hypoperfusion (Lee et al., 2008).

Edaravone

Edaravone is another important therapeutic candidate for consideration in treating cerebral hypoperfusion. Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a potent free radical scavenger; its antioxidant function inhibits lipid peroxidation. It is used clinically for the treatment of acute cerebral ischemia. In a rat model of chronic hypoperfusion, edaravone protected axonal damage, and provided protection against white matter lesions; the mechanisms for these included endothelial protection and free radical scavenging (Ueno et al., 2009). In a rat model of transient global cerebral ischemia, the beneficial effect of edaravone in the hippocampus included: increased number of neural stem/progenitor cells and newly generated neurons in the subgranular zone, decreased apoptosis of neural stem/progenitor cells, decreased ROS generation, and inhibition of HIF-1 α and caspase-3 expression (Lei et al., 2014). Edaravone's benefit in hypoxic-ischemic injuries in the brain (Noor et al., 2005; Sun et al., 2015; Zhang et al., 2012) and other tissues (Doi et al., 2004; Taniguchi et al., 2007) is well documented.

Gallic acid

ROS-mediated damage is implicated in cerebral hypoperfusion. Gallic acid (GA) is another antioxidant therapeutic that exerts the benefit through attenuating free radical-induced neural damage in cerebral hypoperfusion. In an animal model (rat) of vascular dementia, hypoperfusion reduced total thiol and glutathione peroxidase (GPx) antioxidants but increased malondialdehyde (MDA) level - in both hippocampus and frontal cortex. There was a concomitant decrease in spatial memory. However, when GA was administered (chronically), it increased total thiol and GPx contents and decreased MDA levels. GA administration significantly enhanced the spatial memory (Korani et al., 2014; Mansouri et al., 2013).

S-nitrosoglutathione

S-nitrosoglutathione (GSNO) is the nitric oxide carrier; it decreases A β accumulation in the brain and improves cognitive function. In chronically hypoperfused rat brains, GSNO treatment decreased iNOS expression and nitro-tyrosine formation. GSNO showed protective role in iNOS/nitrosative stress mediated calpain/tau pathologies (Won et al., 2015). GSNO reduced the A β and ICAM-1/VCAM-1 levels in the rat brain following

chronic cerebral hypoperfusion. Besides, GSNO treatment induces other beneficial effects; these include decreased cytokine-induced proinflammatory response (viz. activation of NF κ B and STAT3) and expression of ICAM-1 and VCAM-1 in the endothelial cells. Furthermore, experiments in primary rat neuron cell culture confirmed that GSNO decreases A β through inhibition of the β -secretase activity (Won et al., 2013).

L-carnitine

There is impaired endothelial function in vascular diseases. The dysfunction develops owing to oxidative stress; hence, antioxidant can be of clinical advantage. The effectiveness of antioxidant L-carnitine was studied in TNF- α -stimulated human umbilical vein endothelial cells in vitro. Following antioxidant treatment, mitochondrial β -oxidation was restored; also, increased cell adhesion molecule and Nox4 expression, leukocyte adhesion, and inflammatory cytokine secretion were counteracted. Further work has shown that endothelial inflammation and oxidative stress are Nox4-induced (Scioli et al., 2014).

28 days after the induction of chronic hypoperfusion, rats were treated with (or without) L-carnitine. L-carnitine had the following beneficial effects. It reduced PTEN (phosphorylated phosphatase tensin homolog deleted on chromosome 10) and increased phosphorylated Akt and mammalian target of rapamycin (mTOR) (Ueno et al., 2015). Further, L-carnitine treatment in the hypoperfused rats reduced lipid peroxidation and oxidative DNA damage but increased myelin sheath thickness. Hence, L-carnitine has been shown to be effective in regulating the PTEN/Akt/mTOR signaling pathway, and enhancing axonal plasticity; it also ameliorates oxidative stress and increases myelination of axons (Ueno et al., 2015). This study also documented that L-carnitine ameliorates white matter pathology and cognitive decline in chronic hypoperfusion.

Simvastatin

It is noteworthy that simvastatin treatment of APP(Swe, Ind) mice fully restored NO activity in their vessel walls and ameliorated dilatory deficits, but not the impaired hyperemic response to whisker stimulation (Papadopoulos et al., 2014; Tong and Hamel, 2015).

L-arginine, Clazosentan, and Bosentan

L-arginine is the substrate for nitric oxide synthase. Both clazosentan and bosentan are the antagonist of endothelin-1. The administration of the above compounds can ameliorate vasoconstriction and reduce hypoperfusion (Fabricius et al., 1995; Scheckenbach et al., 2006; Schubert et al., 2008; Kreipke et al., 2011; D'haeseleer et al., 2013).

4.3 Nutraceutical Approach

Several studies have emphasized the use of multi-nutrient dietary interventions in both prevention and treatment of AD. The effectiveness of diets is based on specific nutrients provided. These diets claim to attenuate neurodegenerative and enhance neuronal maintenance/repair.

Fortasyn® Connect (FC)

Male A β PP-PS1 mice (and wild-type littermates) were fed the Fortasyn® Connect (FC) diet (that contains cofactors for membrane synthesis). FC is enriched with the omega-3 fatty acids docosahexaenoic acid (DHA),

eicosapentaenoic acid (EPA), uridine monophosphate, phospholipids, choline, folic acid, vitamins, and antioxidants. This diet is claimed to ameliorate synapse loss and synaptic dysfunction in AD. The FC diet was found to restore neurogenesis in A β PP-PS1 mice and decrease the anxiety-related behavior (Jansen et al., 2013). APP^{swE}/PS1^{dE9} mice on control diet showed hypoperfusion, axonal disconnection and neuronal loss (as found in AD). However, after feeding FC diet, there was reduced water diffusivity and increased cortical CBF in the dentate gyrus and cortical regions of these mice (Zerbi et al., 2014). The beneficial effects of FC diet have been confirmed in terms of decreasing A β and amyloid plaque burden in the hippocampus of these transgenic animals (Broersen et al., 2013).

Rutin and Polyphenols

Rutin is a biologically active flavonoid; its antioxidant and anti-inflammatory properties protect the brain. Rutin has shown multi-faceted therapeutic benefits including the alleviation of cerebral hypoperfusion (Qu et al., 2014).

Polyphenols are widespread natural compounds found in vegetables, fruits, grains, bark, roots, tea, and wine.

Most polyphenols possess antioxidant, anti-inflammatory, and anti-apoptotic properties; they also have protective effects on mitochondria, glutamate uptake, regulation of intracellular calcium levels, and ischemic injury (Panickar and Jang, 2013). Studies have documented that green tea polyphenols (GTP) reduce BBB permeability after ischemia. GTP reversed the opening of tight junction (TJ) barrier, decreased mRNA and lowered protein expression of claudin-5, occludin, and ZO-1 in microvessel fragments after hypoperfusion. Hence, GTP functions as a neuroprotective agent in cerebral ischemia (Liu et al., 2013).

Ligustilide

Ligustilide (LIG) is an interesting nutraceutical. It is a lipophilic component of Danggui – a Chinese Angelica root, *Radix Angelica sinensis*. Rats having Chronic cerebral hypoperfusion (induced surgically) were treated with LIG (80mg/kg, oral). LIG prevented dendritic damage, neuronal apoptosis, and neuronal loss in the parietal cortex and hippocampus. LIG also inhibited astrocytic proliferation following hypoperfusion. LIG, therefore, appears valuable in imparting beneficial neuroprotective effects in chronic cerebral hypoperfusion injury (Feng et al., 2012)

Souvenaid

Souvenaid® is a medical food product that has components found in Fortasyn® Connect (FC) diet, with modifications. Synaptic loss is integral to cognitive deficits in AD; therefore, Souvenaid has been developed over 12 years to affect synaptic integrity and function in AD. Two randomised, double-blind, controlled trials (duration 12 and 24 weeks) in AD patients (not treated with acetylcholinesterase inhibitors and/or memantine) have found Souvenaid® to be effective in improving episodic memory performance (de Waal et al., 2014; Pardini et al., 2015; Ritchie et al., 2014). Given the above beneficial effects, it is not unreasonable to expect Souvenaid® to be protective in cerebral hypoperfusion also.

5. Concluding Remarks

Chronic cerebral hypoperfusion noted in many medical conditions in the elderly stimulates several pathologies including glucose hypometabolism, WM Lesions, and cognitive impairment. Chronic hypoperfusion in

conjunction with inflammation, ONS, A β accumulation, and tau hyperphosphorylation promotes synaptic dysfunction and neuronal degeneration/loss – leading to gray and white matter atrophy. These pathological events eventually lead to cognitive decline in the vulnerable aged with comorbid conditions (Zhao and Gong, 2015; Zhu et al., 2007).

There is a close relationship between rCBF and metabolic activity in brain regions. Thus, rCBF is closely coupled to CMRglc, and CMRglc reflects neuronal activity (see above). Studies in normal aged humans have found age-related decreases in brain glucose metabolism. In gray and white matter areas CBF and blood volume (CBV) decrease with age approximately 0.50% per year (Leenders et al., 1990). There is age-related decline also in CMRO2 (Takada *et al.*, 1992). The decrease in CBF and CMRO2 in gray matter is about 18% and 17% respectively in aging (Pantano et al., 1984). Similarly, in the aged rhesus monkeys (roughly equivalent to 54–75 yo humans), correlated decreases occur in both CMRglc and CBF in many brain regions including frontal, temporal, and occipital cortices, and cerebellum, hippocampus, and striatum (Noda et al., 2002). Several medical conditions discussed above may synergistically upregulate hypoperfusion and hypometabolism. For example, higher peripheral insulin resistance even in cognitively normal late middle-aged (60 yo) persons was associated with lower global glucose metabolism and lower CMRglc in the frontal, parietal, and temporal lobes (Willette et al., 2005). In hypertensive individuals, cerebral microbleeds (related to CAA) may be associated with significantly reduced resting- state CBF in multiple brain regions with the highest decrease in the parietal cortex and precuneus (Gregg et al., 2015). The above mentioned pathological stigmata have been described in a diverse range of medical conditions (see above)

A β overexpression (*e.g.* in CAA) impairs CBF in critical brain regions including the entorhinal, temporal, parietal and precuneus. Chronic hypoperfusion, therefore, is contributory in inducing neuronal injury/neurodegeneration and promoting cognitive decline/AD (Daultazai; 2013a, 2013b, 2014, 2015b-d; Mattson et al., 2014). Strategies including pharmacotherapy and nutraceutical consumption described here may be neuroprotective and attenuate chronic hypoperfusion. The above discussion on the multi-faceted origin of hypoperfusion, therefore, calls for early, sustained, and aggressive intervention through exercise, lifestyle changes, pharmacotherapy, and dietary supplementation.

Finally, there are convincing and accumulating studies that cerebral hypoperfusion is correlated with cognitive impairment and neurodegenerative disease (Bennett et al., 1998; Dardiotis et al., 2012; de la Torre, 2012; Daultazai, 2013; Abete et al., 2014; Toda et al., 2014). Furthermore, data from experimental models of chronic hypoperfusion clearly corroborate an association of cerebral hypoperfusion with cognitive dysfunctions (Ni et al., 1994; Sarti et al., 2002; Farkas et al., 2007; Cechetti et al., 2010).



Figure Legend

Figure 1. Schematic representation of the pathogenesis of cognitive decline in aging and AD.

Several comorbid conditions in aging are associated with the risk of cerebral hypoperfusion and glucose hypometabolism. Thus, multifactorial modulators have the potential to trigger inflammatory and oxidative stress responses that may give rise to dysregulation of homeostasis. Cerebral microvascular pathology deposits A β in the walls of cerebral vessels which is a common cause of cerebral amyloid angiopathy (CAA). Consequently, dysfunctional neurovascular unit alters CBF regulation, promoting a secondary cascade of events. Endothelin-1 (released by the endothelium) activity - a potent vasoconstrictor is upregulated. Decreased endothelial NO (a major vasodilator) plays an important role in modulating APP and upregulating A β expression within the cerebrovasculature. The chronic activation of microglia is also associated with A β increase. Besides, dysfunctional BBB contributes to an increase in cerebral neurotoxic substances, leukocytic migration across the BBB, and the development of neurodegeneration.

CONFLICT OF INTEREST STATEMENT

The author has no conflicts of interest to declare.

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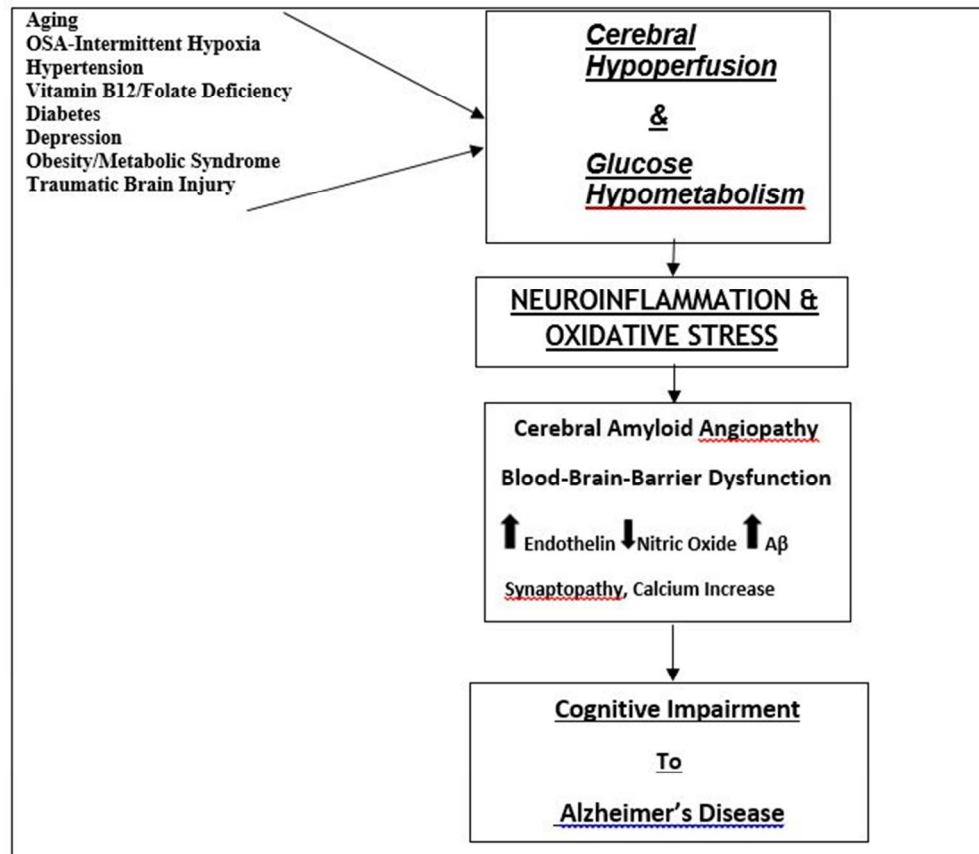
Table 1.

Conditions That Promote Cerebral Hypoperfusion and Glucose Hypometabolism:**Pathophysiological Ramification**

Risk	Factors	Implications for Vulnerability
Aging	Multi-factorial mechanisms unhealthy diet, dysfunctional breathing, sleep restriction, and excess consumption of alcohol	Vascular pathology and cortical microinfarcts (Kövari et al., 2004; 2007), gray matter lacunes (Gold et al., 2005), and irreversible endothelial dysfunction (Hallam et al., 2010; Thal et al., 2009).
Obstructive Sleep Apnea	Nocturnal apneas/hypopnea	Cerebral hypoperfusion - Decreased CBF velocity and delayed cerebrovascular compensation (Bålfors and Franklin, 1994; Baril et al., 2015; Corfield and Meadows, 2006).
Hypertension	Vascular inflammation, BBB disruption, hypoperfusion, and ischemia	Changes in blood vessel wall, hypoperfusion, and a decrease in cortical thickness; brain volume reduction (Shah et al., 2012, Beauchet et al., 2013; Alosco et al., 2013; Kruyer et al., 2015; Van Der Gucht et al., 2015).
Obesity/Metabolic Syndrome	Dyslipidemia, and glucose/insulin dysregulation, diabetes	Hyperlipidemia disrupts endothelial and smooth muscle function; vasoconstriction in the cerebral vasculature, and oxidative stress (Osmond et al., 2009). Decreased NO and CBF (Ayata et al., 2013; Toda et al., 2014).
Vitamin B12/Folate Deficiency	Hyperhomocysteinemia, microvasculature pathology	Proatherogenic, pro-inflammatory, increases CVD, increased matrix metalloproteinases, RAGE, apoptosis (Akchiche et al., 2012; Narayan et al., 2011; da Cunha et al., 2012; Shiran et al., 2015; Hofmann et al., 2001; Madsen et al., 2015)
Diabetes	Dysglycemia, insulin resistance	Increased C-reactive protein, inflammatory markers, and reduced CBF (Anstey et al., 2015; Biessels et al., 2014; Cherbuin et al., 2012; Kerti et al., 2013; Willette et al., 2013; Novak et al., 2006; Fukazawa et al., 2013; Kwon et al., 2015).
Depression	Lower CBF	Decreased arterial Pulsatility and reduced blood flow in several brain regions including PFC (Nagafusa et al., 2012; Ota et al., 2014; Uemura et al., 2014; Wang et al., 2014).
Traumatic Brain Injury	edema, excitotoxicity, loss of neuronal and glial integrity, dysfunctional mitochondrial	Upregulates axonal damage and A β 42 production, and down- regulates long-term potentiation

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	bioenergetics, oxidative stress, inflammation, and cell membrane disruption	(Walker and Tesco, 2013; Fakhran et al., 2013). Decreased CBF, brain hypoperfusion, glucose hypometabolism, and diminished energy supply (Olesen et al., 1981; Golding et al., 1999; Ayata et al., 2004; Parkin et al., 2005; Lauritzen et al., 2011; Romero et al., 2014).
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