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Review

Primary Cerebral Blood Flow Deficiency and Alzheimer's Disease: Shadows and Lights

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Abstract. Alzheimer's disease (AD) is a degenerative disorder characterized by a decreased regional cerebral blood flow (CBF). It is most likely that a reduction in CBF could displace a pathway leading to AD genesis, in so far neuron death explains a sustained reduction in the supply of oxygen, glucose, and nutrients. Nevertheless, the concept of secondary CBF deficiency cannot explain the critical stages of early memory loss while, on the other hand, the picture of progressive ischemia due to primary CBF decline sheds light on the course of AD in a most persuasive manner. The concept of primary CBF deficiency is even more strengthened by the lack of correlation between degree of dementia and amount of CBF. Vascular abnormalities, frequently observed to co-occur with AD, might play a critical role in the initiation and aggravation of AD pathology given that the elimination of amyloid-β (Aβ) through a vascular route is an important brain Aβ clearance mechanism and its failure leads to formation of vascular amyloidosis and dense-core plaques. The goal of this review is to provide scientists comprehensive knowledge of the state-of the art influence vascular damage and reduced perfusion have on the final development of AD and to hopefully stimulate more research in this area of neuroscience.

Keywords: Alzheimer's disease, amyloid-β, blood brain barrier, cerebral blood flow, nitric oxide, reactive oxygen species

INTRODUCTION

During the last 10 years, a lot of progress has been made in unraveling the pathogenic cascade leading to Alzheimer's disease (AD). However, some important aspects of the disease mechanism are not yet fully understood. In particular, there is no consensus as yet on whether the disease acts through a loss or a gain of function mechanism [1].

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AD and cerebrovascular dementia are two common causes of dementia and, by present diagnostic criteria, are mutually exclusive using vascular pathology as an arbitrary demarcation in differential diagnosis. However, evidence from epidemiological, neuropathological, clinical, pharmacological, and functional studies suggest considerable overlap in risk factors and pathological changes suggesting shared common pathogenic mechanisms between these two diseases such that vascular factors play a vital role in the pathogenesis of AD [2, 3].

It seems likely nonetheless that cerebral blood flow (CBF) deficiency could be associated with AD and converge to cause neuron dysfunction and death of some nerve cells. This view has been critically re-

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examined and AD has been re-evaluated by some researchers as a disorder caused by primary, and not secondary, CBF deficiency. In fact, some experimental evidence indicates that dysfunction of the neurovascular unit may be an early event in AD and could provide a potential link between this disorder and cerebral ischemia [4]. This approach opens new possibilities for treatment and prevention [5].

DIFFERENTIAL DIAGNOSIS

In the diagnosis of AD, it is very important to separate it from other types of dementia (e.g., frontotemporal, Pick, Lewy body type, etc.) and, above all, from the dementias associated with cerebrovascular disorder (multi-infarct dementia). Whenever a patient with suspected AD has a history of high blood pressure, coronary disease or myocardial infarction, and any type of stroke, the associated dementia will unlikely be of the AD type. Similarly nicotinism with subsequent cardiac, cerebral, and peripheral arterial effects is hardly compatible with AD [6]. Vascular dementia (VaD), recently termed vascular cognitive disorder, is characterized by multifocal and/or diffuse lesions, ranging from lacunes and microinfarcts, often involving subcortical and strategically important brain areas (thalamus, frontobasal, limbic system), white matter lesions and hippocampal sclerosis to multi-infarct encephalopathy and diffuse post-ischemic lesions [7]. They result from systemic, cardiac, and local large and small vessel disease. Vascular lesions often coexist with AD and other pathologies. Minor vascular lesions hardly contribute to cognitive decline in full-blown AD, while both mild AD pathology and small vessel disease interact synergistically. AD pathology is less severe in the presence of vascular lesions [7].

In old people, there is a progressive reshape of cerebral blood flow autoregulation from a sigmoid curve to a straight line. This implies that any abrupt change in blood pressure will result in a rapid and significant change in CBF. Hypertension has been observed to be a risk factor for VaD and sometimes, although not always, for AD [8]. Indeed, high blood pressure may accelerate cerebral white matter lesions, but white matter lesions have been found to be facilitated by excessive fall in blood pressure, including orthostatic dysregulation and postprandial hypotension. Some researchers speculate that blood pressure reduction might be an early change of the dementing process [9].

IMPAIRMENTS IN THE CEREBROVASCULAR SYSTEM IN DEMENTIA

In recent years, accumulating evidence has suggested that vascular risk factors contribute to AD. VaD had been traditionally considered secondary to stroke and vascular disease, and is distinguished from AD, considered to be a purely neurodegenerative form of dementia. However, in light of more recent literature, it appears that there is a spectrum: ranging from patients with pure VaD to patients with pure AD and including a large majority of patients with contributions from both AD and vascular pathologies [10]. The structural and functional integrity of the brain depends on the delicate balance between substrate delivery through blood flow and energy demands imposed by neural activity. Neurovascular factors represent the theoretical basis underlying the hypothesis of primary CBF deficiency. Complex cerebrovascular control mechanisms ensure that active brain regions receive an adequate amount of blood. A growing body of literature has highlighted the important contribution of the mechanisms (Table 1) by which vascular factors increase the risk of AD or accelerate cognitive deterioration among patients with AD but are not yet fully elucidated. The important question is no longer whether vascular factors contribute to dementia, but to determine their relative weight in contribution to all types of dementia in the general population. There is strong evidence to suggest that there is a spectrum: on one end, those with relatively pure dementia of vascular type, on the other end, those with relatively pure AD, and in between there is a contribution from both AD and vascular pathologies, most likely representing the largest group [10, 21–23].

Neurovascular dysfunction plays an important role in neurodegeneration and cognitive decline of AD [24–26]. Circulating angiogenic cells, such as endothelial progenitor cells, participate in the maintenance of the endothelium by acting as a cellular reservoir for the replacement of dysfunctional endothelial cells [27], or by releasing angiogenic growth factors [28]. The number of endothelial progenitor cells is a surrogate marker of vascular function, and low endothelial progenitor cell counts are associated with higher cardiovascular risk [26, 29, 30].

In a recent study, Lee et al. investigated the involvement of circulating angiogenic cells in AD pathogenesis [26]. The patients with AD had significantly lower endothelial progenitor cells colony-forming units than the risk factor controls. In the patients with AD, lower levels of endothelial progenitor cells colony-forming

Table 1
The relationship between local neural activity and subsequent changes in CBF

Dysfunction of cells of the neurovascular unit in disease states	References
Morphological alterations in cerebral capillaries and lesions in the white matter surrounding the cerebral ventricles resembles ischaemic infarcts	[4, 11, 12]
Imaging studies have reported reductions in CBF and glucose utilization in patients with AD	[4, 13–15]
AD patients have severe atherosclerosis in large cerebral arteries at the base of the brain (circle of Willis), these lesions produce severe vascular narrowing that limits cerebral blood supply	[16, 17]
Aβ has powerful effects on neurons, but a growing body of evidence indicates that Aβ also has profound effects on systemic and cerebral blood vessels	[4, 18]
Neuronal death and synaptic loss reduce the synaptic processing that drives the CBF increase, resulting in a reduced haemodynamic response to activation	[4]
Progressive amyloid deposition in cerebral arterioles impairs the ability of smooth muscle cells to relax and creates a mechanical obstacle to vasodilation	[19]
Atherosclerosis in the circle of Willis and conduit cerebral arteries reduces CBF globally and further impairs the ability of neural stimuli to increase CBF	[17]
Reduction of resting CBF through impaired protein synthesis could alter memory formation and cortical plasticity which are required for normal cognition	[4]
The gene that encodes the cAMP-degrading enzyme phosphodiesterase 4D, present in endothelial and smooth muscle cells, is a risk factor for ischaemic stroke highlights the crucial role that vascular signaling has in preserving the structural integrity of the brain	[4, 20]

units were independently associated with either a lower Mini-Mental State Examination score or a higher Clinical Dementia Rating scale score, indicating a greater reduction in endothelial progenitor cells colony-forming units in advanced AD. Patients with non-AD neurodegenerative diseases did not show a significant decrease in endothelial progenitor cells colony-forming unit levels [26]. These results indicate that an abnormal capacity to regenerate endothelium is associated with AD. The abnormal activity of endothelial progenitor cells in patients with AD along with the continuing cerebral endothelial damage probably accelerates the progression of AD. In addition, these results suggest that interventions aimed at reconstituting the abnormal endothelial progenitor cells counts and thereby enhancing amyloid-β (Aβ) clearance through the blood brain barrier (BBB) may improve AD symptoms [26]. A diminished endothelial progenitor cells colony-forming unit count reflects severe coronary artery disease and is a surrogate marker for various aspects of vascular dysfunction [29, 31]. Accordingly, Lee et al. suggest that patients with AD have a reduced ability to regenerate endothelium. The number of $CD34^+$, KDR^+ and $CD133^+$ cells do not appear to be directly correlated with endothelial progenitor cells colony-forming units [26, 32].

A new study investigated what changes in the brain cause dementia Erten-Lyons et al. compared the brains of patients with AD to another group that had plaques and neurofibrillary tangles under the microscope but had normal thinking and memory [33, 34]. The authors' idea was that plaques and tangles might be necessary to cause AD, but that there might be some important reasons why some patients did not get AD. They thought that patients with healthy brains might be able to lose some brain function but have enough reserve that these changes did not result in dementia [33]. However, the groups were different when the size of some brain areas was compared. Those people with plaques and tangles who did not show thinking and memory problems had larger overall brain size than the group that had dementia. In addition, the brain structure that is important for new learning and memory, the hippocampus, was also larger in the healthy group [33].

The findings are interesting and suggest that there is not a direct link between the presence of plaques and tangles and dementia. It has been long suspected that it is possible to survive into old age without developing dementia, even with many plaques and tangles in the brain. The results raise the important possibility that healthy brain aging requires healthy brain cells and a high number of brain cell connections [34]. This is consistent with the cognitive reserve idea, which suggests that larger brain size and greater cognitive abilities beginning early in life may be important for later protection against dementia. Whether or not this idea is true, the findings indicate that brain size measurements may show if someone is at risk of developing dementia. Studies like this may point the way toward better prevention of dementia [34].

Defining the exact role of vascular risk factors on all dementias including AD is particularly important from the perspective of defining a robust strategy for prevention. Because the most common forms of dementia affect the old or very old, even a modest delay in

the appearance or worsening of cognitive deterioration could translate into a large reduction of the incidence of disease as these subjects would die from other causes before entering an overt stage of dementia. Indeed it is estimated that among the 106 million cases of AD expected globally by the year 2050, about 23 million could be avoided completely if it was possible to delay the start of disease by 2 years starting in the year 2010 [10, 35]. According to Viswanathan et al. [10], it is important that clinicians should take into account the respective influences of both vascular risk factors and neurodegenerative pathologies. For instance, if vascular risk factors are present in a patient with probable AD, clinicians should identify these factors to patients and caregivers and emphasize their relative contribution to the patient's cognitive impairment. In the absence of an etiology-based therapy for dementia, an important therapeutic goal is to maximize the cognitive capacity of the patient and increase the period of dementia-free living. Aggressively treating vascular risk factors such as elevated blood pressure or poorly controlled diabetes could potentially avoid cognitive deterioration and its major consequences for patient autonomy, dignity, as well as caregiver and societal burden [10].

Differences between Alzheimer's disease and vascular dementia: comparing metabolic and hemodynamic parameters

VaD due to multiple small infarction constitutes a small, but significant, part of mental deterioration in the elderly, as compared to AD, which is the most common cause. In many cases, AD and VaD share behavioral and neuropsychological manifestations, and furthermore the ischemic vascular lesions in VaD patients often coexists with pathological characteristic features of AD in postmortem studies. Accordingly, in clinical practice many difficulties may exist in the differential diagnosis between AD and VaD. Structural neuroimaging techniques, such as X-ray computerized tomography and magnetic resonance (MR) imaging, have been used in the detection of organic changes including large or small lacunar infarcts and leukoaraiosis. However, mild ischemia may cause partial neuronal loss and consequently result in undetectable structural changes on such neuroimagings [36]. Functional neuroimaging techniques, including single photon emission computerized tomography (SPECT) and positron emission tomography (PET), provide quantitative measures of brain function; the pattern of hypoperfusion and hypometabolism in AD is assumed to be different from that of VaD [36].

The previous studies with PET and SPECT demonstrated characteristic hypoperfusion and hypometabolism patterns in AD patients. The reduction of CBF and energy metabolism was more pronounced in the parietotemporal associated neocortical areas and correlated with the distribution of neuropathological features such as senile plaques, neurofibrillary tangles, vascular amyloid deposits, and neuronal cell loss, whereas the primary sensorimotor and visual neocortical areas, basal ganglia, thalamus, and cerebellum are relatively preserved in AD [37, 38].

In VaD patients, functional imaging revealed even more heterogeneous patterns of hypoperfusion or hypometabolism. The reduction was observed in frontal, temporal, and parietal lobes, which are within the territory of the middle cerebral artery and/or basal ganglionic areas, irrespective of localization of small infarcts or white matter lesions, and correlated with the degree of neuropsychological deficit [38, 39]. The occipital cortex was relatively spared in the majority of VaD patients. Thus, the typical cases of dementia due to either pathology can be readily distinguished by the patterns of hypoperfusion and/or hypometabolism visualized on PET or SPECT images [36]. PET studies with oxygen-15 compounds also provide important information concerning vascular and metabolic reserve, including the balance between blood flow and energy metabolism of the brain. In patients with VaD, reduction of blood flow may theoretically first occur because of occlusive vascular lesions or hypotension, and the depression of energy metabolism follows subsequently [37, 40]. In contrast, in dementia due to the degenerative process such as in AD, fallout of neuronal cells can primarily be caused by energy failure.

Some researches have studied hemodynamic parameters in patients affected by probable AD, and, in VaD patents, they have found a mildly increased oxygen extraction fraction (OEF) [36]. Tohgi et al. conducted PET studies based on patients with senile dementia of the Alzheimer's type and those with diffuse white-matter lesions on MR images [41]. The authors speculated that the increase of the OEF seen in patients with senile dementia of the Alzheimer's type might be associated with the reduction in CBF resulting from the impaired cholinergic vasodilatory function, whereas the increased OEF observed in the demented patients with diffuse white matter lesions was caused by the relative preservation of oxidative metabolism as compared to decreased perfusion; they have

not tested vascular reactivity in their patient groups [41].

The increase of the OEF due to the disproportionate fall of blood flow to oxygen metabolism is known as a misery perfusion syndrome [42], and is usually regarded as a compensatory phase of recent cerebral ischemia. From observation in ischemic stroke patients, the misery perfusion syndrome mostly appears immediately after the insult and can be sometimes observed in the chronic stage [42]. In cases with chronic ischemia due to occlusive vascular lesions, vascular reactivity (VR) was significantly depressed and the increase of the OEF correlates with the prolongation of vascular transit time [43]. A change in VR to vasodilating agents such as CO_2 is assumed to be mediated at the level of the arteriole, which is known as a vascular resistance vessel. Depletion of VR is assumed to be caused by either the maximal dilatation by exposure to ischemia or the impaired arteriolar vasculature due to advanced arteriosclerosis, as seen in VaD patients [44, 45]. Because VR was well preserved in AD patients, the angioarchitectural integrity of the arteriole is considered to remain normal in the AD brain. This evidence may suggest a cerebrovascular involvement underlying AD, possibly at the level of capillary and the BBB, not at the level of arteriole [36].

Together with the larger cerebral vessels comprising penetrating arteries and arterioles with degenerative smooth muscle [44, 46], recent ultrastructural studies demonstrate characteristic angioarchitecural abnormalities in the capillaries and sites of the BBB [47, 48]. It was also speculated that the structural alterations of microvasculature can initiate interference with the fluid dynamics, hemorrhagic compromise resulting in the increased resistance, the increased blood viscosity, and changes in shear stress [49, 50]. Extensive abnormalities in the capillaries and BBB may cause hemorrhagic and hemodynamic changes that will alter the delivery of energy nutrients to the brain [36].

Vascular involvement in Alzheimer's disease progression

The clinical manifestations of AD are pleiotropic. Although core symptoms are present in nearly all cases, there often is heterogeneity in mode of presentation, rate of presentation, and expression of associated features such as age at onset, family history of dementia, behavioral and motor complications. Some clinical features may be present at one stage of the illness but not another. In spite of its rich and varied phenomenology, a general picture of probable AD in mild, moderate, and severe stages can be described. The progression of AD is identified by three stages [51]. The first stage is characterized by memory defects at an extent that clearly exceeds the usual memory loss of normal aging. Under mild ischemic condition of incipient AD, cerebral regions of relatively poor blood supply are naturally the first ones to feel the lack of blood supply, particularly the hippocampus, which has a prominent role in processing and retrieving of memory data. The cortex of the posterior temporal region and adjacent portions of the parietal and occipital lobes are next in line. The explanation of this is the fact that ischemic process targets "watershed regions", areas in the borderzone between two major arterial territories [5]. In this first stage, all cerebral efferent/afferent systems are still normal, and only a little portion of the associative systems have been involved. Forgetfulness is the typical presenting symptom. Common examples of memory deficits in this stage are the repetition of questions or statements and the misplacement of items without independent retrieval. Impaired acquisition of new information is manifested by inability to recall recent conversations or events, whereas highly learned material from years gone by may be remembered with seeming clarity. Minor geographic and temporal disorientation also may be early symptoms; the patient may need directions to find even familiar locations or ask for frequent reminders as to the date. Poor judgment and impaired problem solving occur as part of the dysexecutive syndrome wherein patients lack insight, have poor attention and experience uncharacteristic difficulty in completing tasks that involve sequencing of information. Word-finding difficulty or dysnomia may occur as an early feature of probable AD and is associated with hesitancy of speech and reduced verbal output. Passivity, disinterest, withdrawal, and other personality changes are common symptoms even in the mild stages of dementia and occasionally may be presenting features. The mildly demented patient usually performs self-care activities without problem and may still be engaged in many other activities of daily living, including cooking, driving, voting, and socializing with friends and family, although function in these activities usually is impaired relative to previous levels of performance. Many patients in the mild stage of probable AD appear normal to causal observers.

Progressive decline of further association cortex will lead to stages 2 and 3 when the cerebral disturbance becomes increasingly diffuse along with pronounced

slowing of EEG activity and changes in MRI and PET scan. Progressive decline in all cognitive domains is the rule as the patient advances to the moderate stages. Memory for recent events is severely compromised and confusion about relationships and identifies of relatives may occur. Accomplishing even simple tasks, such as making change or washing dishes with acceptable cleanliness, becomes difficult. Driving and other complex activities typically are relinquished by this stage and basic care often requires at least supervision by others. Language skills deteriorate further with incomplete sentences, paraphasic errors and impaired comprehension of both written and spoken language. The moderate stage of probable AD may be complicated by troublesome behaviors. Agitation, restlessness, day-night disorentiation, suspiciousness, verbal or occasionally physical aggression, delusions, visual or auditory hallucinations occur with increasing dementia severity.

The severe stage of probable AD is characterized by total or near-total dependence on caregivers for even basic functions. Only fragments of memory remain; even the spouse and children may not be recognized appropriately. Verbal output is restricted to short phrases or single words. First urinary and then fecal incontinence develop. Terminal-stage AD consists of a bedridden, uncomprehending, vegetative state. Weight loss and dysphagia are nearly universal. Death usually results from aspiration, inanition, pulmonary embolus, or infection. The total duration of the clinical course of AD can range from a few years to 20 years or longer, but the average time from onset to death is in the range of 8 to 10 years.

The concept of secondary CBF deficiency cannot explain the critical stages of early memory loss, while the theory of progressive ischemia due to primary CBF decline fully explains the course and progression of AD [5]. The progressive cerebral ischemia due to primary decline of CBF derives from the insufficient distribution of blood in healthy vessels. Etiologically, this concept is presumed to be related to the human upright gait along with individual predisposition. In such perspective the shutdown of cholinergic activity makes sense as an energy saving measure under the threat of progressive ischemic starvation [5].

Ischemic blood-brain barrier and development of Alzheimer's disease

The structural and functional integrity of the central nervous system depends on the coupling between neural activity and CBF and the regulation of transport across the BBB. These two critical functions require the coordinated activity of a neurovascular unit that includes perivascular neurons, astrocytes, endothelial cells, and vascular smooth muscle cells. Dysfunction of the neurovascular unit may be an early event in AD and could provide a potential link between this disorder and cerebral ischemia [25]. In this perspective the neuropathogenesis of AD involves an initial ischemic neuronal alterations leading to enhanced neuronal vulnerability to Aβ peptide and the ischemic breakdown of the BBB with leakage of serum borne Aβ peptide into brain parenchyma, activation of Aβ peptide-dependent toxicity culminating in the formation of amyloid plaques, and finally, full-blown AD [52]. So we can describe combined mechanisms of ischemia processes, ischemic and chronic BBB dysfunction, and Aβ peptide-dependent injury in pathology of neurodegeneration that is observed in AD. Cerebral vasculature is continuously modified during aging and it is possible that senescence of the microcirculatory system after ischemia with insufficient angiogenesis severely influence response of endothelial cells to physiologic and pathologic conditions, which in turn could affect BBB function. Neuronal cells are primary targets affected by repeated and silent ischemic-reperfusion episodes and chronic ischemic BBB dysfunction is leading to enhanced neuronal vulnerability to ischemia. Chronic ischemic BBB dysfunction can cause microvascular pathology, angiopathy in pial and intracerebral arteries, vascular senescence and neuroinflammatory response which all occur in AD brain [52]. On the other hand, pathologic permeability and faulty clearance of Aβ across the ischemic BBB could act as seeds for the process that is responsible for amyloid accumulation and maturation in AD neurodegeneration progression. It has been found that Aβ peptides in plasma and cerebrospinal fluid exist in equilibrium, regulated at the BBB by influx and efflux receptors. Aβ produced in the brain might be cleared through the BBB by efflux receptors to be metabolized in the liver instead of being deposited in senile plaques. Furthermore, the transcytosis of plasma-derived Aβ across the BBB might be suppresed through inhibition of influx receptors [53].

A study by Bowman et al. [54] showed that BBB impairment is a stable characteristic over 1 year and present in an important subgroup of patients with mild to moderate AD patients. The Rotterdam Study [55], conducted on 1,730 participants with transcranial Doppler, suggested that cerebral hypoperfusion

precedes and possibly contributes to onset of clinical dementia.

Qi et al. [56] have investigated the expression and distribution of $A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$, and apolipoprotein E (ApoE) in human hippocampus after cerebral ischemia to determine the role of cerebral ischemia in AD. This study demonstrated that the accumulation of both $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ were increased dramatically and consistently after cerebral ischemia. Neuronal ApoE immunoreactivity was also significantly increased in all ischemic groups compared with controls. These results may partly explain the contribution of cerebral ischemia to the pathogenesis of AD.

Studies on transgenic mice overexpressing amyloid-β protein precursor (AβPP) indicate that functional hyperemia is impaired in this model of AD even before development of amyloid plaques or vascular amyloid [4]. Soluble Aβ oligomers elicit vasoconstriction and attenuate endothelium-mediated vasodilation, leading to a reduction of regional CBF. In addition to its effect on CBF autoregultion, Aβ has toxic effects on endothelial cells, both via direct mechanims and by inducing local inflammatory responses [57].

Vascular oxidative stress in Alzheimer's disease

There is accumulating evidence that vascular oxidative stress leads to profound alterations in cerebrovascular regulation [58]. Hypertension, AD, and cerebral ischemia are associated with evidence of oxidative stress in cerebral blood vessels [59–61]. Thus it is likely that vascular oxidative stress is responsible for the cerebrovascular alterations observed in these conditions. Many studies implicate metabolic defects in AD, and a reduced brain metabolism is one of the best documented abnormalities in the disease. Notably, since endothelial reactive oxygen species (ROS) such as nitric oxide (NO) act as vasodilators at low concentrations, increased production coupled with elevated ROS scavenging of NO, can lead to reduced bioavailability of NO and increased oxidative stress that damage sensitive vascular cells. The high nitroxidative stress can initiate a cascade of redox reactions which can trigger apoptosis and evoke cytotoxic effects on neurons and endothelial cells [62]. Some researchers have demonstrated that oxidative stress is one of the earliest pathological changes in the brain of AD patients and plays a critical role in the vascular abnormalities underlying metabolic defects in AD [2]. The vascular endothelium, which regulates the passage of macromolecules and circulating cells from blood to tissue, is a major target of oxidant stress, playing a critical role in the pathophysiology of several vascular diseases. It is well-demonstrated that there are increased regional levels of oxidative stress in the AD brain [63–65].

Several observations demonstrate that vascular wall cells, especially their mitochondria, appear to be a central target for oxidative stress-induced damage before the development of AD pathology. Notably, long-term ischemia/reperfusion leads to disintegration of mitochondria ultrastructure and apoptosis of degenerating neurons occurs in association with the accumulation of perikaryal abnormal mitochondria and oxidative damage to the nucleus. This same pattern of mitochondria lesions is observed in human AD brain biopsy samples [66]. As outlined by Zhu et al. [2], it is probably that chronic vascular hypoperfusion is a central initiating factor for vascular alterations by inducing mitochondrial dysfunction, increasing ROS production, reducing NO bioavailability via ROS scavenging, and damaging vascular functions as well as severely affecting regional CBF which ultimately leads to cognitive decline and the disease.

Elderly patients with AD show several hemorheological abnormalities compared to age-matched healthy controls: increase of blood viscosity, plasma viscosity, and blood viscoelasticity, decrease in erythrocyte deformability, and increase in blood flow resistance despite the lack of any significant difference in erythrocyte rigidity. These hemorheological abnormalities found in AD patients may be explained by the parallel findings of oxidative damage on erythrocyte membranes that could result in a decrease of erythrocyte deformability. Furthermore, the oxidative stress-induced elevation of fibrinogen concentration could lead to accelerated erythrocyte aggregation as a consequence of a rise in blood viscosity and blood viscoelasticity. Taken together, these factors may impair the oxygen transport efficiency of blood in AD patients [67].

A study by Sun et al. [68] has identified a functional hypoxia-responsive element in the BACE 1 (β-site amyloid-β protein precursor cleavage enzyme 1) gene promoter. Hypoxia upregulated β-secretase cleavage of AβPP and Aβ peptide production by increasing BACE 1 gene transcription and expression both *in vitro* and *in vivo*. Hypoxia treatment markedly increased Aβ peptide deposition and neuritic plaque formation and potentiated the memory deficit in Swedish mutant AβPP transgenic mice. These results demonstrate that hypoxia can facilitate AD pathogenesis and provide a molecular mechanism linking vascular factors to AD.

CURRENT MEDICAL MANAGEMENT OF ALZHEIMER'S DISEASE

To treat cognitive symptoms, the US Food and Drug Administration (FDA) has approved five drugs that affect the activities of two chemical neurotransmitter systems: acetylcholine and glutamate (Table 2). Acetylcholine (ACh) is a neurotransmitter centrally involved in learning, memory, judgment, attention, and concentration. Normally, ACh is transiently released at the presynaptic terminal, stimulates receptors on the postsynaptic terminal, and is then rapidly broken down by the enzyme cholinesterase to terminate the synaptic signal [72, 75]. Areas of the brain that depend predominantly on cholinergic circuitry are generally the first and most severely damaged by AD [69]. The mechanism involved in cholinesterase inhibitor drugs involves blocking breakdown of ACh, thus elevating ACh levels at the cholinergic synapses and (in theory) compensating for loss of cholinergic circuits [76]. However, in clinical trials and practice, cognitive benefits of CI drugs are minimal; more than half the subjects show no measurable improvement. Furthermore, the window of efficacy averages six months to one year; benefits fade as brain deterioration worsens [72].

Glutamate is another prevalent brain neurotransmitter. When released presynaptically, glutamate is essential to learning and memory via facilitation of n-methyl-d-aspartate (NMDA) receptors that allow small influxes of calcium into stimulated nerve cells [75].

NUTRIENTS FOR ALZHEIMER'S DISEASE: THERAPEUTIC APPROACHES

In 1968, two-time Nobel laureate, Linus Pauling, conceived of the treatment of disease or the correction of metabolic imbalances by substances naturally part of human biochemistry: molecules orthodox to the body, orthomolecules [77]. Direct validation at the biochemical level came with the report by Ames et al. [78]; now it is possible to assess orthomolecules that would be effective and safe for long-term use because of intrinsic biochemical value and evolutionary intimacy with living systems (Table 3).

Many endogenous and exogenous AD risk factors have been documented, herein termed Alzheimer's risk factors (ARF). Other adverse factors likely contribute to AD risk but are not yet fully supported by evidence, termed Alzheimer's contributory factors (ACF). Multiple factors undoubtedly work synergistically and additively to increase AD risk. Depending on which risk factors are involved, AD risk would not be predictable but might wax and wane as adverse factors interact [72]. While some risk factors are not modifiable, most can be modified, especially when patients are motivated and have help from knowledgeable professionals [112, 113] (Table 4).

The brain inherently carries a high metabolic and free radical burden and functions in delicate balance between health and ill-health [142]. As a consequence, virtually any factor adverse to the health of the body as

Table 2
Current therapies for delaying the progression of Alzheimer's disease

Neurotrasmitter system	Characteristics	Studies
Cholinesterase inhibitor (CI)	It is a drug that prevent the breakdown of ACh, thereby conserving ACh at the synaptic junctions. FDA-approved CI drugs are: tacrine, donepezil, galantamine, and rivastigmine [69].	Tacrine was the first CI drug, approved in 1993, but it is currently rarely prescribed because of liver toxicity and other major adverse effects [70]. Its immediate successor, approved for all stages of AD, donepezil, is less toxic but still has appreciable adverse effects [71]. Galantamine and rivastigmine are approved for mild-tomoderate AD [69]. Donepezil appears to be the most effective and best tolerated, although all four CI drugs have marginal clinical utility [69, 70, 72]. CI drugs seem to be well tolerated, with the exception of tacrine. When prescribed by experienced physicians under recommended guidelines, side effects can include nausea, vomiting, loss of appetite, and increased frequency of bowel movements. Combining CI drugs does not heighten efficacy and could increase adverse effects [69]. Idebenone is a synthetic, low-molecular-weight derivative of ubiquinone (coenzyme Q10). A 2002 RCT compared idebenone to tacrine in patients with mild-tomoderate probable AD [73]. The idebenone patients showed higher scores for cognitive function benefit than the tacrine patients [72].
Glutamate	FDA-approved glutamate enhancement drug is memantine, an NMDA-receptor antagonist.	Although memantine has shown no apparent benefits in mild-to-moderate AD, it is FDA approved for moderate-to-severe AD [69]. A 2007 meta-analysis found limited but statistically significant benefits for cognition, behavior, and activities of daily living over a six-month trial period [74]. Memantine's side effects include headache, constipation, confusion, and dizziness [72].

Table 3
Molecules showed as potential for AD treatment

Orthomolecules	Functions	Effects	References
Phosphatidylserine (PS)	Phospholipids are molecular building blocks for cell membranes, the dynamic sites of most life processes.	PS improves orientation, concentration, learning, and memory for names, locations, and recent events. However, it is most likely that PS benefits for motivation, socialization, and general adaptability to the environment.	[75, 79, 80]
Glycerophosphocholine (GPC, alpha-GPC, Choline Alphoscerate, Choline Alfoscerate)	A vital phospholipid orthomolecule, GPC differs from PS in being water-soluble.	GPC significantly benefits memory and other cognitive measures.	[81–84]
Acetyl-L-Carnitine (ALC)	ALC is important for energetics in the brain and other tissues.	ALC conserves NGFreceptor density in the aging rat brain, partially restoring a youthful receptor profile.	[76, 85, 86]
Omega-3 Fatty acids	Omega-3 fatty acids stimulate blood circulation, increase the breakdown of fibrin and additionally have been shown to reduce blood pressure.	Total omega-3 intake and docosahexaenoic acid intake, but not eicosapentaenoic acid intake alone, are significantly associated with decreased AD risk. More recently, the researchers noted significant improvement of agitation in ApoE4 carriers and improvement of depression in non-ApoE4 carriers.	[72, 87–93]
Vitamin E	Vitamin E is known to inhibit the activity of protein kinase C, an important cell-signaling molecule. It appears to also affect the expression and activities of molecules and enzymes in immune and inflammatory cells. Additionally, it has been shown to inhibit platelet aggregation and to enhance vasodilation.	Vitamin E at a high daily intake (2,000 IU) delays disease progression by seven months and was slightly more beneficial than selegiline. Vitamin E deficiency can have a strong impact on gene expression in the hippocampus, a key area afflicted by AD.	[72, 94]
Citicoline	Citicoline is an energy-activated form of choline, choline linked to cytidine by a diphosphate bridge. It is an intermediate in the biosynthesis of phosphatidylcholine.	Citicoline gives some benefit on memory function and behaviour.	[72, 95–97]
Folic acid	Folic acid helps the body break down, use, and create new proteins. The vitamin has the capacity to form red blood cells and helps produce DNA. Folic acid also promotes tissues grow and cells work.	Snowdon et al. found a strong association between low blood folate and severity of atrophy in the neocortex on routine blood sample.	[75, 98]
Vitamin B_{12}	Vitamin B_{12} is normally involved in the metabolism of every cell of the body, especially affecting the DNA synthesis and regulation but also fatty acid synthesis and energy production.	The Mediterranean diet, rich in vitamins B_{12}, has been linked to lowered incidence of AD.	[99–101]
Ginkgo Biloba Extracts (GBE)	Ginkgo Biloba can increase brain function, including memory. It also has the capacity to increase the oxygen content of the blood. GBE both increases the amount of neural transmission and increases the number of receptor sites for neural transmission.	GBE improves AD patients with mild or moderate cognitive impairment and stabilizes or retards the decline of those most severely afflicted.	[63, 72, 102–111]

Table 4
Primary prevention of Alzheimer's disease through risk factors management

Non-modifiable risk factors	References	Modifiable risk factors	References
Age	[114–122]	Smoking	[130, 131]
Gene mutations (early-onset AD)	[123–125]	Obesity	[132, 133]
Family history of AD	[112, 114, 115]	Hypertension and cardiovascular abnormalities	[98, 134–136]
Down syndrome	[126–128]	High homocysteine	[100, 137, 138]
ApoE status	[66, 129]	Diabetes	[118, 139–141]
		Folate or other B-vitamin deficiencies	[72]

a whole is adverse to brain health. Several known factors lack full documentation for being ACF but likely to contribute to AD risk [72] such as: mercury [143, 144], aluminum [145], C-reactive protein [146–149], hypothyroidism [72, 150–152], epilepsy [72, 150], and electromagnetic fields [72, 153].

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Production and retention of Aβ might be controlled by nutraceutical measures that decrease neuron cholesterol synthesis (policosanol or D-003), promote cholesterol export (9-cis-beta-carotene as a source of 9cRA), or that boost PPARγ activity (isohumulones from hops extract, 9-cis-beta-carotene). Since low concentrations of NO appear to have a favorable impact on AβPP processing, and since good cerebral perfusion may favorably influence AD risk in other ways, a range of nutraceutical, dietary, and lifestyle measures which promote efficient NO production by the cerebral vasculature seem likely to be protective; these include a low-salt/high-potassium diet, aerobic exercise training, fish oil (DHA), high-dose folate, flavanol-rich cocoa powder, and possibly policosanol. Good insulin sensitivity also has a favorable impact on cerebrovascular health, and efficient insulin activity in the brain itself may decrease expression of beta-secretase while promoting IDE-mediated Aβ catabolism; conversely, insulin resistance syndrome has emerged as an important risk factor for AD. Whether insulin-sensitizing nutraceuticals such as chromium picolinate and cinnamon extract can reduce cerebral Aβ deposition in the context of insulin resistance syndrome merits evaluation. High fish consumption has been linked to reduced AD risk in epidemiology, and DHA limits Aβ deposition in transgenic AD mice for reasons that are not yet clear [154].

The process of AD appears to consist of a vicious cycle in which increased production of Aβ leads to excessive activation of microglia, which in turn releases agents that further boost production of Aβ while also inducing or upregulating neural apoptosis. Thus, measures which suppress microglial activation would be expected to prevent an acceleration of Aβ production, while helping to preserve the viability of neurons. Nutraceuticals that might be helpful in this regard include vitamin D, genistein, hops extract, 9-cis-beta-carotene, policosanol, and sesamin [154].

Finally, certain nutraceutical have general neuroprotective activity, either because they boost antioxidant defenses, aid bioenergetics, or reduce glutamate release from excitatory terminals; these measures might or might not influence Aβ production, but they have the potential to retard neuron loss and thus slow progression of the clinical syndrome. Vitamin E, lipoic acid, creatine, coenzyme Q10, and caffeine are of particular interest in this regard, and have shown neuroprotective activity in animal models of various neurodegenerative disorders; with the exception of vitamin E, however, little evidence is currently available regarding their impact on animal models of AD or on the clinical syndrome, though some epidemiology suggests that high caffeine intakes may decrease risk for AD [154].

This essay has focused on nutraceutical measures, because it is presumed that such measures would be safest, most convenient, and most affordable for use in primary prevention. Further research with these agents in rodent models of AD, and, ultimately, in clinical trials, may help us to discern which of the numerous measures cited above are most likely to provide meaningful protective benefit. Ultimately, it should prove feasible to develop complex nutraceutical regimens which can provide protection from AD and other neurodegenerative disorders, while also favorably influencing vascular health, insulin sensitivity, and perhaps other health parameters. It stands to reason that addressing the AD process at numerous complementary points, rather than attempting to control it with one or two "wonder drugs", would be more likely to achieve success; it is inherently easier to effect such a strategy with nutraceuticals than with prescription drugs. Nonetheless, there clearly will be a role for drug therapy, perhaps as a complement to safe nutraceutical measures, in patients who are starting to lose intellectual function, or who are known to be at high genetic risk for early-onset AD [154].

CONCLUSIONS

In conclusion, notwithstanding the progress of scientific research, there is still no consensus as yet on whether the deficiency of CBF flow is a cause or a consequence of AD. Several data show that vascular factors play an important role in the pathogenesis of AD. Some researchers speculate that AD may be caused by silent and subletal ischemic episodes that attack and slowly steal the minds of its victims. There is a deep separating rift between the vascular and

the ischemic concept [5]. In the ischemic concept, the blood vessels (especially arteries) are structurally intact or nearly intact. In predisposed individuals the blood supply is poor and the hippocampus is the first suffering site by having the poorest blood supply of entire cerebrum especially (and noteworthy) in its Sommer sector and CA1. The association cortex (posterior temporal, parietal, anterior occipital), located along the wathershed line between middle and posterior cerebral arteries, suffers next.

Further evolution in the study of AD is important in our understanding the role of CBF in the pathogenesis of AD.

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