REVIEW

The vascular contribution to Alzheimer's disease

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ABSTRACT

AD (Alzheimer's disease) is a progressive neurodegenerative disease of unknown origin. Despite questions as to the underlying cause(s) of this disease, shared risk factors for both AD and atherosclerotic cardiovascular disease indicate that vascular mechanisms may critically contribute to the development and progression of both AD and atherosclerosis. An increased risk of developing AD is linked to the presence of the apoE4 (apolipoprotein E4) allele, which is also strongly associated with increased risk of developing atherosclerotic cardiovascular disease. Recent studies also indicate that cardiovascular risk factors, including elevated blood cholesterol and triacylglycerol (triglyceride), increase the likelihood of AD and vascular dementia. Lipids and lipoproteins in the circulation interact intimately with the cerebrovasculature, and may have important effects on its constituent brain microvascular endothelial cells and the adjoining astrocytes, which are components of the neurovascular unit. The present review will examine the potential mechanisms for understanding the contributions of vascular factors, including lipids, lipoproteins and cerebrovascular Aβ (amyloid β), to AD, and suggest therapeutic strategies for the attenuation of this devastating disease process. Specifically, we will focus on the actions of apoE, TGRLs (triacylglycerol-rich lipoproteins) and TGRL lipolysis products on injury of the neurovascular unit and increases in blood–brain barrier permeability.

INTRODUCTION

Vascular dysfunction and endothelial injury have come to be recognized as key mediators in the development of ASCVD (atherosclerotic cardiovascular disease). ASCVD is defined as a thickening of arterial walls due to accumulation of fatty material and macrophages. Atherosclerosis affects medium-large arteries and similar disease processes may also affect the smaller arteries of the brain. Although cerebrovascular disease is a major cause of morbidity and mortality, research into the fundamental mechanisms underlying this problem has been relatively slow coming, compared with the emphasis that has been placed on atherosclerosis research in the last several decades.

Despite the apparent differences between the peripheral vasculature and the cerebrovasculature, many of the same mechanisms, or slight variants thereof, may also contribute to endothelial injury in the brain. Vascular dysfunction in the brain has long been recognized as a contributing factor to the development of stroke

Key words: Alzheimer's disease, apolipoprotein E (apoE), astrocyte, endothelial cell, lipoprotein, triacylglycerol-rich lipoprotein (TGRL), vascular system.

Abbreviations: ABC, ATP-binding-cassette; AD, Alzheimer's disease; APP, amyloid precursor protein; apoE, apolipoprotein E; ASCVD, atherosclerotic cardiovascular disease; Aβ, amyloid β; Aβ42, Aβ-(1–42); BBB, blood–brain barrier; CAA, cerebral amyloid angiopathy; CI, confidence interval; DHA, docosahexaenoic acid; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; 13-HODE, (13*S*)-hydroxyoctadeca-(9*Z*,11*E*)-dienoic acid; HR, hazard ratio; LDL, low-density lipoprotein; LDLR, LDL receptor; LpL, lipoprotein lipase; hLpL, human LpL; LXR, liver X receptor; NEFA, non-esterified ('free') fatty acid; ROS, reactive oxygen species; SFA, saturated fatty acid; TGRL, triacylglycerol (triglyceride)-rich lipoprotein; TLR, Toll-like receptor; TNF, tumour necrosis factor; VLDL, very-low-density lipoprotein; ZO-1, zonula occludens-1.

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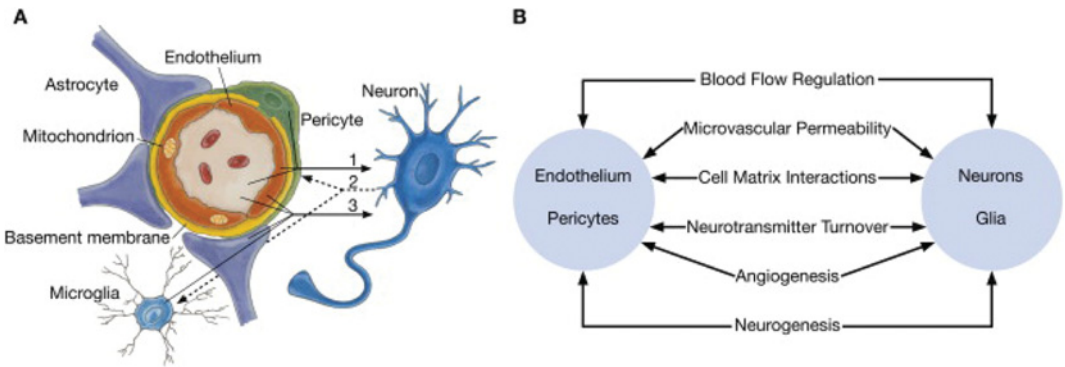

Figure 1 Schematic representation of the neurovascular unit

(A) Endothelial cells and pericytes are separated by the basement membrane. Pericyte processes sheathe most of the outer side of the basement membrane. At points of contact, pericytes communicate directly with endothelial cells through the synapse-like peg-socket contacts. Astrocytic endfoot processes unsheathe the microvessel wall, which is made up of endothelial cells and pericytes. Resting microglia have a 'ramified' shape. In cases of neuronal disorders that have a primary vascular origin, circulating neurotoxins may cross the BBB to reach their neuronal targets, or pro-inflammatory signals from the vascular cells or reduced capillary blood flow may disrupt normal synaptic transmission and trigger neuronal injury (arrow 1). Microglia recruited from the blood or within the brain and the vessel wall can sense signals from neurons (arrow 2). Activated endothelium, microglia and astrocytes signal back to neurons, which in most cases aggravates the neuronal injury (arrow 3). In the case of a primary neuronal disorder, signals from neurons are sent to the vascular cells and microglia (arrow 2), which activate the vasculo–glial unit and contributes to the progression of the disease (arrow 3). (B) Co-ordinated regulation of normal neurovascular functions depends on vascular cells (endothelium and pericytes), neurons and astrocytes. Reprinted from *Neuron*, volume 57, Zlokovic, B.V., The blood–brain barrier in health and chronic neurodegenerative disorders, pp. 178–201, Copyright (2008), with permission from Elsevier (http://www.sciencedirect.com/science/journal/08966273).

and vascular dementia. More recently, evidence has accumulated that suggests that the development of AD (Alzheimer's disease) may also be strongly related to underlying vascular problems. Whether this vascular dysfunction actually causes AD or merely contributes to the development of the disease or worsens the disease processes once they are underway, it is worthwhile to investigate how the vasculature and its related blood lipids, lipoproteins and vascular Aβ (amyloid β) promote AD. The present review will focus on the actions of apoE (apolipoprotein E), TGRLs [triacylglycerol (triglyceride)-rich lipoproteins] and TGRL lipolysis products on injury of the neurovascular unit and increases in BBB (blood–brain barrier) permeability.

PATHOPHYSIOLOGY OF AD

Dementia is the progressive decline in cognitive function due to damage or disease of the brain, and is distinct from the slowing of cognitive function that is expected with normal aging. The two most common causes of dementia are AD and vascular dementia [1–4]. For the more common form of late-onset AD, only one susceptibility allele has so far been identified, ε4 (E4) of the *apoE* gene [5]. In AD, progressive brain atrophy is observed, principally in the temporoparietal cortex, together with an inflammatory response of neurons and astrocytes, as well as deposition of amyloid plaques and neurofibrillary tangles. Astrocytes are a subtype of glial cells in the brain that are 'star shaped' and are key cells in the maintenance of the BBB, as their endfeet surround endothelial cells (Figure 1) [6–11]. In addition, the many arm-like processes of astrocytes envelop neurons. Astrocytes are associated with senile plaques in the brain and inflammation of microvascular endothelial cells, and astrocytes are common features of AD [12–22].

The neurovascular unit, including brain microvascular endothelial cells and astrocytes, regulates BBB permeability. In a study examining human subjects with mild-to-moderate AD, the BBB was found to be a significant modifier of AD progression over 1 year [23]. Increased BBB permeability plays an important role in the promotion of AD by allowing potentially neurotoxic substances, such as pro-inflammatory cytokines and lipids, access to the CNS (central nervous system) [24–28].

CEREBROVASCULAR Aβ

The physiology and pathophysiology of the neurovascular unit in AD may well be influenced by interactions with cerebrovascular Aβ. Aβ results from the proteolytic processing of APP (amyloid precursor protein), which is found in various cell types throughout the body, including cells of the brain. Proteolytic cleavage of APP by β-secretase and γ-secretase results in two forms of Aβ: Aβ40 [Aβ-(1–40)] and Aβ42 [Aβ-(1–42)] [29]. Although Aβ is a physiological component of plasma, the exact origin of plasma Aβ remains unknown. Peripheral sources, such as blood platelets, may prove to be important sources of plasma Aβ [30]. It has been suggested that, regardless of the primary origin of plasma

Aβ, it may play an important role in the cerebrovascular pathology associated with AD. Higher levels of plasma Aβ42 were found in AD patients and in those subjects who would eventually develop AD compared with those who did not develop AD [31–33]. Additionally, mutations associated with early-onset familial AD result in elevated levels of extracellular Aβ42 [33].

The neuropathological characteristics of AD usually include sporadic CAA (cerebral amyloid angiopathy), even in the absence of underlying ASCVD, with some studies reporting up to 80 % of AD patients exhibiting CAA to at least a minor degree [34,35]. Studies suggest that CAA severity increases with progressing AD [36]. The Honolulu-Asia Aging Study demonstrated that men with both CAA and AD had greater cognitive impairment than those individuals with either CAA or AD [37]. Numerous pathological, cell culture and animal model studies have demonstrated the deleterious effects of Aβ peptides and CAA on cerebral microvessels [38]. This damage includes histological and ultrastructural abnormalities of cerebrovascular walls in CAA [39]. Reduced adhesion of vascular smooth muscle cells in response to treatment with Aβ [40] and impaired function of vascular smooth muscle cells in transgenic mouse models of CAA [41] were also observed. Additional *in vitro* studies demonstrated that wild-type and mutant forms of Aβ have anti-angiogenic and vasoactive properties [42–44]. CAA-related vascular abnormalities in both transgenic mouse models and AD patients may also contribute to capillary occlusion and altered blood flow [45,46].

The detrimental effects of plasma Aβ and amyloid angiopathy on components of the cerebrovasculature suggest that cerebrovascular Aβ may be intimately related to the progression and development of AD through vascular pathways. The combined influences of cerebrovascular Aβ, plasma lipoproteins and apoE may form a constellation of negative interactions that lead directly to vascular dysfunction. Although conflicting studies debate the usefulness of plasma Aβ as a biomarker predictive of AD [32], the potential contribution of cerebrovascular Aβ to the vascular pathologies associated with AD merits continued attention.

APOE STRUCTURE AND FUNCTION

Although the underlying cause of AD remains unknown, an increased risk of developing the disease is linked to the presence of the apoE4 allele. ApoE is a 34 kDa glycoprotein that has many functions, including assembly, processing and removal of plasma lipoproteins [47], neuronal repair, dendritic growth and anti-inflammatory properties [48]. It is a component apolipoprotein of VLDLs (very-low-density lipoproteins), IDLs (intermediate-density lipoproteins), chylomicrons, HDLs (high-density lipoproteins) [49] and LDLs (low-density lipoproteins) [50]. ApoE serves as a ligand for LDLRs (LDL receptors) and, through its interaction with these receptors, participates in the distribution of cholesterol and other lipids among various cells of the body [51]. In humans, there are three common isoforms of apoE: apoE2, apoE3 and apoE4, with apoE3 being the most common isoform [52–60].

ApoE contains a 22-kDa N-terminal domain (residues 1–191) and a 10-kDa C-terminal domain (residues 222–299) connected by a protease-sensitive loop [61]. The N-terminal domain contains the LDLR-binding region (residues 136–150 in helix 4) and the C-terminal domain has a high affinity for lipid and is responsible for lipoprotein-lipid binding [62]. ApoE4 differs from apoE3 by the presence of an arginine residue at position 112, rather than a cysteine residue at the same position in apoE3 [63]. ApoE in the blood is generated by the liver, intestine and macrophages, whereas apoE in the brain is generated by glial cells, including astrocytes and microglia [64].

Among the human isoforms, apoE4 shows a unique domain interaction where the arginine residue at the 112 position induces an interaction of Arg^{61} in the N-terminal domain with Glu^{255} in the C-terminal domain, a feature thought to be responsible for the preferential association of apoE4 with VLDLs in blood [65,66]. Approx. 40–65 % of individuals with AD have at least one copy of the E4 allele. The E4 allele is present in approx. 25 % of the U.S. population [67–69] and is strongly linked to an increased risk of the development of AD and atherosclerosis complications [70–72]. ApoE4 is reported to have effects that promote amyloid deposition, neurotoxicity, oxidative stress and neurofibrillary tangle formation [48], all of which are pathophysiologically linked to AD. Clinical trials also suggest that apoE4 plays key causative roles in AD. In a postmortem study, brains from patients with advanced AD exhibited plasma proteins, such as prothrombin, in the microvessels, and suggested that increased permeability of the BBB may be more common in patients with at least one E4 allele [73]. These findings indicate that the E4 allele is an important determinate of AD.

APOE AND MODULATION OF NEURAL AND VASCULAR TISSUE RESPONSE TO INJURY

ApoE4 is associated with increased brain inflammation. Previous studies have shown that apoE4 can undergo proteolysis and cause mitochondrial damage [74], increase brain inflammation found in apoE4-expressing mice in response to LPS (lipopolysaccharide) [75] and facilitate the deposition of oligomeric Aβ as amyloid to a greater extent than apoE3 [76]. Our previous study showed that apoE4 increased, and apoE3 decreased, TNF (tumour necrosis factor)-α-induced human aortic endothelial cell injury [77]. These studies indicate that, in addition to

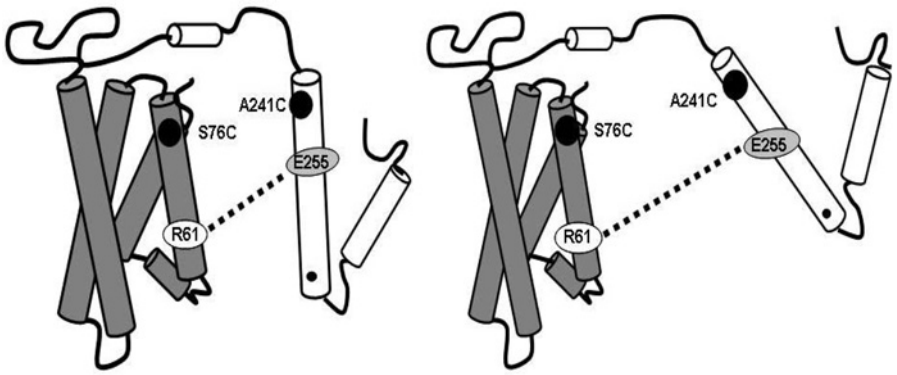

Figure 2 Schematic representation of apoE4 before and after a moderately high-fat meal

An apoE4 mutant was employed to study the domain interaction of the apoE4 mutant using EPR (electron paramagnetic resonance) spectroscopy. The dotted line represents a salt bridge between Arg^{61} (R61) and Glu^{255} (E255) of apoE4 showing a domain interaction. In this mutant, the serine residue at position 76 and the alanine residue at position 241 were mutated to cysteine and subsequently labelled with a nitroxyl spin label. The left-hand panel represents the structural conformation of apoE4 during the fasting state, and the right-hand panel represents the conformation in the postprandial state. ApoE4 had a reduced domain interaction during the postprandial state, implying a more linear protein [82]. The left-hand Figure was reproduced with permission from [82]. Copyright (2006) American Society for Biochemistry and Molecular Biology. The right-hand Figure was reproduced with permission from [222]. Copyright (2010) American Society for Biochemistry and Molecular Biology.

being a marker of increased risk for AD and ASCVD, apoE4 could directly generate microvascular and neural injury.

In contrast, apoE3 is associated with reduced brain inflammation [78,79]. Microglial activation by APP was reduced by apoE3 [80]. In addition, apoE3 interacts with Aβ via an apoE-receptor-mediated process to inhibit neurotoxicity and neuroinflammation, a process possibly related to binding and clearance of apoE3–Aβ oligomer complexes. Our findings suggest a role for apoE3 to prevent inflammation and balance the intracellular redox state in injured human aortic endothelial cells [77]. Thus these results suggest that apoE3 protects against and apoE4 promotes AD and ASCVD.

LIPIDS AND APOE CONFORMATION

Our studies indicate that the postprandial state, and specifically TGRL lipolysis products, can have a profound effect on apoE4 conformation to increase formation of a more linear species of apoE4 [82], which may potentially have an impact on the pathogenesis of AD (Figure 2) [82]. Regardless of the plasma triacylglycerol levels, consistent conformational changes were observed as a result of interactions between TGRL lipolysis products and apoE4. In contrast, TGRL lipolysis products did not cause linear conformation changes in apoE3. Using thrombin-accessibility assays, other studies have shown that binding of high triacylglycerol-containing VLDLs to macrophages was related to differences in the conformation of apoE [83–86], although the specific conformational change was not known. These studies, among others [72,75,82,87,88], indicate that lipids can have dramatic effects on apoE4 conformation and binding to cells. In the presence of varying plasma lipid levels, similar apoE4 conformational and cell interaction effects were observed, which suggests that comparable mechanisms at the level of the lipoprotein may be important in apoE4 individuals irrespective of their overall lipid levels.

It is unknown whether increased VLDL particle fluidity and linearization of apoE4 resulting from VLDL lipolysis products acts to increase apoE4 binding and injury to brain microvascular endothelial cells. This potential mechanism of injury to endothelial cells may increase BBB permeability, enabling TGRL lipolysis products to have increased access to the brain, where they may promote astrocyte and neuronal injury that could initiate and perpetuate AD.

Other studies have indicated that Aβ clearance and degradation mechanisms in the brain are dramatically affected by the lipidation state of apoE [89–94]. Using real-time *in situ* microdialysis methods in mice, Bell et al. [95] showed that Aβ clearance across the BBB is decreased when Aβ associates with poorly lipidated apoE3, and is almost completely blocked when Aβ associates with lipidated apoE3. Following the same experimental methods, Deane et al. [96] showed that lipidation of the apoE2, apoE3 or apoE4 isoform significantly reduced the transport of apoE–Aβ complexes across the BBB. The extent of this effect was dependent on the specific isoform, where apoE4–Aβ transport was most significantly disrupted, compared with apoE3–Aβ or apoE2–Aβ complexes [96]. Interestingly, lipidation of apoE appears to have opposing effects on Aβ degradation in the brain. Additional studies have shown that strategies to increase apoE lipidation reduce amyloid burden in animal models. Overexpression

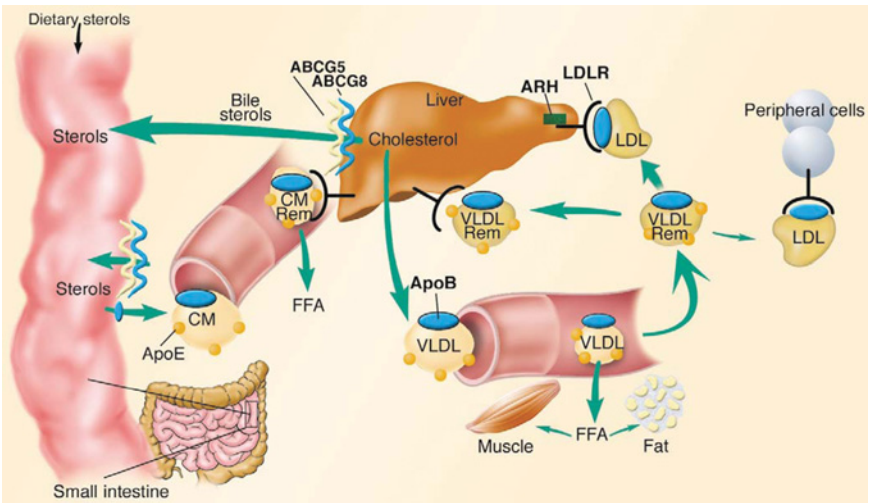

Figure 3 Overview of LDL metabolism in humans

Dietary cholesterol and triacylglycerols are packaged with apolipoproteins in the enterocytes of the small intestine and secreted into the lymphatic system as chylomicrons (CM). As chylomicrons circulate, the core triacylglycerols are hydrolysed by LpL, resulting in the formation of chylomicron remnants (CM Rem), which are rapidly removed by the liver. Dietary cholesterol has four possible fates once it reaches the liver: it can be (i) esterified and stored as cholesteryl esters in hepatocytes; (ii) packaged into VLDL particles and secreted into the plasma; (iii) secreted directly into the bile; or (iv) converted into bile acids and secreted into the bile. VLDL particles secreted into the plasma undergo lipolysis to form VLDL remnants (VLDL Rem). Approx. 50 % of VLDL remnants are removed by the liver via the LDLR and the remainder mature into LDL, the major cholesterol transport particle in the blood. An estimated 70 % of circulating LDL is cleared by LDLR in the liver. ABCG5 and ABCG8 (ABC family G, members 5 and 8 respectively) are located predominantly in the enterocytes of the duodenum and jejunum, the sites of uptake of dietary sterols, and in hepatocytes, where they participate in sterol trafficking into bile. ApoB, apolipoprotein B; ARH, autosomal recessive hypercholesterolaemia protein; FFA, non-esterified ('free') fatty acid. *Journal of Clinical Investigation*. Online by Rader, D.J., Cohen, J. and Hobbs, H.H. Copyright 2003 by American Society for Clinical Investigation. Reproduced with permission of American Society for Clinical Investigation in the format Journal via Copyright Clearance Center.

of ABCA1 [ABC (ATP-binding-cassette) family A1] in the brain promotes the formation of lipidated apoE and reduces the formation of amyloid plaques [97,98]. LXR (liver X receptor) agonists have also been shown to have a beneficial effect on amyloid burden in the brain. LXRs are involved with the removal of cholesterol by ABC transporters and the transfer of this cholesterol to apolipoproteins such as apoE and apoAI (apolipoprotein AI). Stimulation of these receptors by LXR agonists resulted in reduced Aβ levels and enhanced apoE lipidation [92,99–101]. Furthermore, the molten globule form of apoE4, which is a partially unfolded reactive intermediate, has been associated with increased pathogenicity [74,102]. These studies indicate that the lipidation state and conformation of the apoE isoforms are important determinants of Aβ homoeostasis in the brain; however, the exact mechanisms by which this occurs are not well understood.

LIPOPROTEINS AND THE DEVELOPMENT OF AD

Lipoproteins are heterogeneous lipid and protein complexes. The principal function of lipoproteins is to transport lipids as fuel for cells throughout the body. Typically, a lipoprotein particle consists of a monolayer surface shell of phospholipids, cholesterol and apolipoproteins surrounding a hydrophobic core of triacylglycerols and cholesterol esters [103–105]. The apolipoproteins are integrated into the lipid environment through amphipathic helices, which contain hydrophobic and hydrophilic domains. Following food intake, energy distribution occurs largely through generation of TGRLs, either chylomicrons or VLDLs, which are synthesized from exogenous and endogenous lipids respectively (Figure 3) [106]. The elevation of triacylglycerol in the blood after consumption of a meal, postprandial lipaemia, is the result of contributions from both of these pathways. Once in the blood, the triacylglycerols in TGRLs are hydrolysed by LpL (lipoprotein lipase), an enzyme anchored to endothelial cells [107–111]. Hydrolysis results in the successive formation of smaller TGRLs, called lipoprotein remnant particles, as well as other lipolysis products, such as fatty acids, phospholipids, monoacylglycerols and diacylglycerols. Furthermore, lipolysis of VLDL remnant particles yields LDL. The composition and size distribution of TGRLs have been shown to be important in ASCVD [56]. For example, VLDLs and chylomicron remnant lipoprotein particles are known to penetrate arterial walls and become trapped in the artery wall, thus participating in the early stages of atherosclerosis.

However, VLDL and chylomicron remnant particles are unlikely to penetrate brain microvascular endothelium because of the reduced permeability of the BBB.

Previous studies have indicated that cardiovascular risk factors, including elevated blood cholesterol and triacylglycerol, increase the likelihood of AD and dementia [112–118]. Most, but not all, previous studies have shown that elevations in mid-life cholesterol levels in the blood are associated with the development of AD [115,116,119–124]. However, definitive randomized control trials have yet to show that HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors (statins) reduce the incidence of AD [59,120,125–127]. Despite the lack of conclusive evidence that cholesterol interventions have a preventative effect on AD, a substantial body of data supports the notion that mid-life blood cholesterol and triacylglycerol levels are associated with the development of AD.

TRIACYLGLYCEROLS, FATTY ACIDS AND THE INITIATION AND PROGRESSION OF AD

Most, but not all, previous studies in humans have shown an association between AD and elevated fasting triacylglycerols in the blood and also an association of AD with the metabolic syndrome. In one human study, the only significant relationship of lipids/lipoproteins with AD was elevated triacylglycerols [128]. The Three Cities Study showed that a high plasma triacylglycerol level was the only component of the metabolic syndrome that was significantly associated with the incidence of all-cause {HR (hazard ratio) 1.45, [95 % CI (confidence interval), 1.05–2.00]; $P = 0.02$} and vascular [HR, 2.27 (95 % CI, 1.16–4.42); $P = 0.02$] dementia, even after adjustment for the apoE genotype [129]. In another study, elevated total cholesterol, LDLs and triacylglycerol, with normal HDLs and total cholesterol/HDL ratio characterize the lipid profile in AD, which overlaps with the ASCVD risk profile [130]. Additionally, patients with AD had a significantly larger mean waist circumference, higher mean plasma concentrations of triacylglycerols and glucose, and a lower mean plasma concentration of HDL-cholesterol compared with controls [131]. Thus most previous human clinical studies have shown an association of serum triacylglycerols and AD or vascular dementia.

However, the clinical measurement of the mass of triacylglycerols in blood may not reveal the true pathogenicity of TGRLs, and specifically TGRL lipolysis products. Chylomicrons and VLDL particles, which carry most triacylglycerols in blood, are not strongly associated with ASCVD or AD, perhaps because they are large particles and do not easily enter the artery wall and do not cross the BBB.

Mouse models and cell culture models also have suggested a role for triacylglycerols and fatty acids in AD pathogenesis. Elevated triacylglycerol levels were found in the brain of a mouse model of AD [132]. In another study, elevated blood triacylglycerol levels preceded amyloid deposition in mouse brain [133]. It has been shown that fatty acids can cause generation of presenilin-1, an important determinate of γ-secretase activity necessary for generation of Aβ in neuroblastoma cells [134]. Furthermore, palmitic and stearic fatty acids [SFAs (saturated fatty acids)] induce AD-like hyperphosphorylation of Tau in primary rat cortical neurons [135]. These results establish a central role for NEFAs [non-esterified ('free') fatty acids] in causing hyperphosphorylation of Tau through astroglia-mediated oxidative stress. Accumulating evidence from human, mouse and cell culture models suggests triacylglycerols and fatty acids are related to the development of AD (Figure 4) [136,137].

The literature also contains substantial data that specific fatty acids can either prevent or promote cognitive decline [119,138–141]. For example, eating fish or consuming increased long-chain omega-3 fatty acids in the diet had a beneficial effect on cognitive decline [139,142,143]. Oxidized linoleic acid, otherwise known as 13-HODE [(13*S*)-hydroxyoctadeca-(9*Z*,11*E*)-dienoic acid], is the most prevalent oxidized lipid in oxidized LDLs, a known mediator of vascular injury and atherosclerosis. A recent study has shown that 13-HODE is the most prevalent oxylipid present in VLDL lipolysis products in normal young adults [144], raising concern about life-long implications of 13-HODE elevations at the blood–endothelial cell interface where lipolysis occurs. Further study is needed to unravel the relationship between long-chain fatty acids, stroke and AD, and to examine the potential beneficial effects of omega-3 long-chain PUFAs (polyunsaturated fatty acids), such as DHA (docosahexaenoic acid) [145].

Previous studies also indicate that the fat composition and fat quantity of the diet is important in the promotion or prevention of AD, vascular dementia and ASCVD [52,53,60,146–157]. For example, a Mediterranean diet confers protection against AD, as compared with a Western diet [121,158–164]. In addition, DHA is an abundant fatty acid in the brain, and increased plasma levels of DHA were associated with reduction in AD in the Framingham Heart Study [165]. Understanding how lipids/lipoproteins influence AD pathophysiology could have a substantial impact on primary prevention of this devastating disease.

TGRL LIPOLYSIS PRODUCTS AND VASCULAR INFLAMMATION

Triacylglycerols in blood are contained in the core of TGRLs (chylomicrons, VLDLs and their remnant particles) and are not in direct contact with endothelium. LpL is anchored to brain microvascular

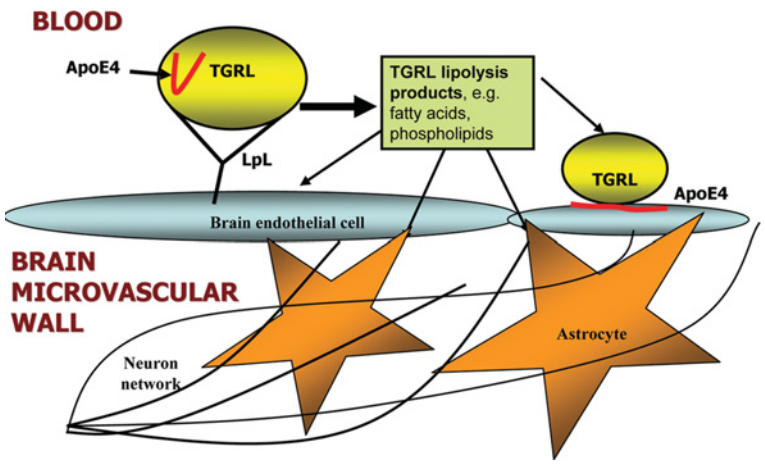

Figure 4 Vascular disease model illustrating how TGRL lipolysis products and apoE4 may interact with brain microvascular endothelial cells and astrocytes

Hydrolysis of TGRLs by LpL present in the circulation results in the release of lipolysis products, including TGRL remnant particles, mono-, di- and tri-acylglycerols, phospholipids and NEFAs. Lipolysis products may influence the inflammatory environment of the brain through two pathways: (i) direct injury to brain microvascular endothelial cells or astrocytes, or (ii) indirect injury to glial cells and neurons through cascades that begin with damaged endothelial cells. In addition, apoE4 associated with TGRL undergoes a conformational change to a more linear species in the presence of TGRL lipolysis products. This conformational change may influence the binding of apoE4 to brain microvascular endothelial cells. Negative effects to the endothelial cells due to the altered apoE4 conformation may disrupt the barrier function of the cerebrovasculature and allow TGRL lipolysis products to access the brain parenchyma, causing damage to neurons and glial cells.

endothelium, where it hydrolyses TGRLs to smaller lipolysis products, such as fatty acids and phospholipids. These lipolysis products are generated in very high concentrations immediately adjacent to brain microvascular endothelial cells. Potentially, lipolysis products generated at the luminal surface of the vascular endothelium can directly injure the endothelium and increase permeability and/or cross the BBB and injure astrocytes (Figure 4). Our studies have shown that TGRL particles, including chylomicrons and VLDLs, have relatively little effect on a variety of endothelial cell types in comparison with the dramatic effects on endothelial cell injury that we have observed with TGRL lipolysis products [107,166–169]. Thus, with regard to the brain microvasculature, TGRL lipolysis products, rather than plasma triacylglycerols, may be the most meaningful lipids to study in terms of the pathogenesis of AD.

Previous investigations have shown that TGRL lipolysis products have both pro- and anti-inflammatory effects on endothelium [170–173]. Sub-physiological concentrations of lipolysis products (5–10 μg of VLDL + 200 units/ml LpL) in endothelial cell culture prevented endothelial cell injury through generation of PPAR (peroxisome-proliferator-activated receptor) ligands in response to cytokine stimulation with TNF-α [174,175]. Similar studies using human aortic endothelial cells in culture generated comparable results. However, as VLDL triacylglycerol concentrations approached physiological concentrations (50 mg/dl triacylglycerol) in the human aortic endothelial cell culture system, endothelial cell injury predominated when TGRLs were treated with LpL. Thus TGRL lipolysis products at high physiological-to-pathophysiological concentrations appear to have a predominately pro-inflammatory effect.

The products of TGRL lipolysis, especially the fatty acid fraction, and treatment with individual fatty acids, such as palmitic acid, in moderate-to-high physiological concentrations also injure endothelial cells. These experiments strongly indicate that it is the enzymatic function of LpL that is an important factor in generating endothelial cell injury [166]. As shown by Eiselein et al. [166] in Figure 5, the permeability of human aortic endothelial cell monolayers in culture is radically affected by exposure to TGRL lipolysis products. ZO-1 (zonula occludens-1) is an integral member of structurally sound tight junctions between adjacent endothelial cells and helps to regulate the paracellular permeability of endothelial monolayers. Exposure to TGRL lipolysis products resulted in a transition from smooth continuous ZO-1 staining to a fragmented discontinuous appearance. The disruption of the structural integrity of the tight junctions between cells suggests that the monolayer's ability to regulate its permeability was negatively affected. Additional experiments using TEER (transendothelial electrical resistance) measurements showed that the resistance of the monolayer decreased following treatment with TGRL lipolysis products [166]. Recent studies in mice overexpressing hLpL (human LpL) have shown that excess vascular wall LpL augments vascular dysfunction

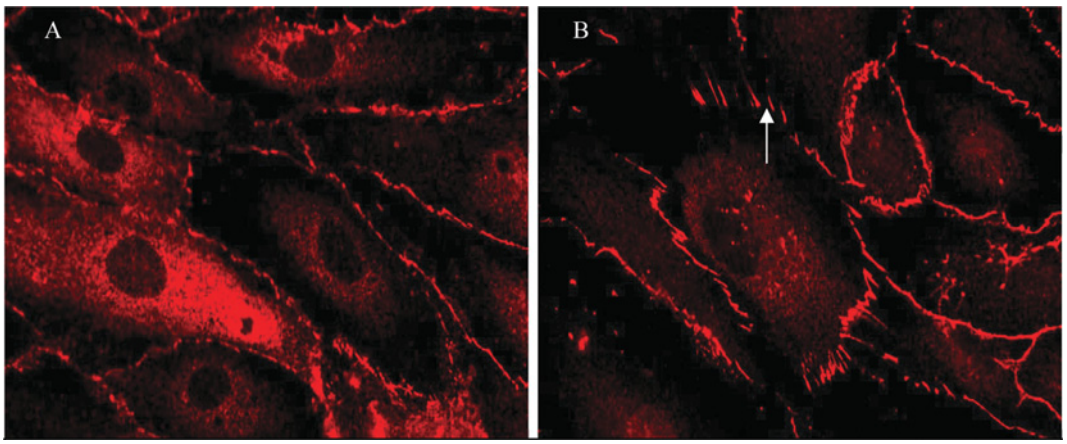

Figure 5 ZO-1 immunofluorescence before and after treatment with TGRL lipolysis products

Images of human aortic endothelial cell monolayers showing (A) continuous ZO-1 staining with treatment with TGRL (150 mg/dl triacylglycerol), and (B) discontinuity and radial rearrangement of ZO-1 (arrow) during exposure to lipolysis products generated from co-incubation of TGRL (150 mg/dl) + LpL (2 units/ml), causing increased endothelial layer permeability. This Figure was reproduced from [166] and is used with permission. Copyright (2007) American Physiological Society.

in the setting of inflammation [176,177]. Furthermore, in transgenic mice expressing hLpL, agonist-induced contraction of smooth muscle cells was increased when compared with that of wild-type mice [178]. These studies strongly indicate that TGRL lipolysis products in high-physiological and supra-physiological concentrations injure endothelium and smooth muscle cells. The aforementioned experiments that observed similar results using varying concentrations of LpL in both cell culture and animal models suggest that the physiological action of normal LpL levels is sufficient to generate injurious levels of TGRL lipolysis products at the vascular wall.

Lipotoxicity is the term commonly used to describe cell dysfunction and death induced by lipid accumulation in non-adipose tissue [179]. Most lipotoxicity has been associated with SFA-induced lipotoxicity [180–182]. Furthermore, lipotoxicity has been related to ER (endoplasmic reticulum) stress [181,183,184], apoptosis [182], mitochondrial dysfunction [185–188], lysosomal pathways and potentially autophagy [189,190]. Neurovascular lipotoxicity may play an important role in TGRL lipolysis-induced brain microvascular endothelial cell and astrocyte injury.

TGRL LIPOLYSIS PRODUCTS, ROS (REACTIVE OXYGEN SPECIES) AND AD

Oxidative stress, in which ROS overwhelm antioxidant mechanisms, is hypothesized to be important in neurodegeneration [191–193]. Previous studies have shown ROS to be important in AD [2,12,14,21,194–197], although whether ROS are causes or consequences of AD has yet to be defined. For example, lipoprotein oxidizability (as indicated by the accumulation of lipid hydroperoxides from the aggregate lipoproteins under oxidizing conditions) was measured in cerebrospinal fluid and plasma from 29 AD patients and was found to be significantly increased in comparison with 29 controls without dementia [198]. ROS can directly oxidize and damage DNA, proteins and lipids [199], and induce stress-response genes. In addition, astrocyte NADPH oxidase may be a key enzyme in the production of ROS in AD [12]. Some studies have indicated that ROS can be reduced by HMG-CoA reductase inhibitors (statins) [88]. One potential mechanism by which statins could reduce astrocyte injury is by down-regulation of NADPH oxidase, leading to a reduction in ROS production [200,201]. In addition, ROS can mediate apoptosis by mitochondrial apoptotic pathways [202]. VLDL lipolysis products generate ROS in human aortic endothelial cells [144,203], suggesting that VLDL lipolysis product-induced ROS generation in human microvascular endothelial cells and astrocytes may be an important mechanism of oxidative injury in these cells.

TLRs (Toll-like receptors) are a class of proteins that play a key role in the innate immune system. Recent work has shown that TLRs may be important in the pathophysiology of AD and may specifically mediate astrocyte injury and apoptosis [204,205]. SFAs modulate TLR4 through regulation of receptor dimerization and incorporation of TLR4 into lipid rafts in a ROS-dependent manner [206]. High concentrations of SFAs induced by lipolysis of VLDLs may injure astrocytes by generation of ROS and activation of TLR4.

BRAIN LIPIDS AND AD

The brain contains more lipid than any other single organ in the body. Both extra- and intra-cellular lipids,

as well as lipids within the plasma membrane, are essential to normal brain function, but also have the capacity to induce injury, apoptosis and cell death of the brain [207–218]. DHA, phospholipid oxidation products, neurotrophin receptors, lipoprotein receptors, neural membrane glycerophospholipid and sphingolipid mediators, and small-molecule oxidation products that trigger disease-associated protein misfolding have all been associated with either the promotion or prevention of AD. Montine et al. [219] demonstrated that measurements of F_2-isoprostanes in cerebrospinal fluid, which are indicative of free radical damage to brain lipids, correlate well with the degree of neurodegeneration in AD patients and may be a promising biomarker for AD. Preliminary studies also suggest that resolvins, compounds that are derived from the omega-3 fatty acids EPA (eicosapentaenoic acid) and DHA [220,221], may be important in AD for their anti-inflammatory properties. Further research is needed to unravel the intricate web of connections between specific lipids, their locations and functions within the brain, and the pathology of AD.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Current treatment strategies for AD revolve around attempts to slow the progression of the disease, maintain cognitive ability and reduce the negative behavioural consequences of the disease. However, there are no known treatments to prevent or cure AD. As the underlying causative factors for AD are still unknown, targeted treatments that effectively combat the development of the disease have proven to be elusive. An increasing number of studies suggest that, whether or not lifestyle factors are the primary cause of AD, they have a significant effect on the course of the disease. As such, these lifestyle factors represent an important avenue of approach to help slow or prevent the progression of AD. In particular, lipids derived from the diet, such as fatty acids, provide an appealing target, given the abundance of current research that suggests potentially detrimental effects of these lipids on cellular components of the cerebrovasculature.

Our present review shows considerable overlap of the risk factors associated with AD and the risk factors associated with ASCVD, such as dyslipidaemia and the presence of the apoE4 allele. Furthermore, dyslipidaemia, hypertension and diabetes are believed to be causative for ASCVD. It is reasonable to speculate that these same risk factors could initiate or promote AD, although these areas are relatively understudied in AD. Given this background information, aggressive treatment of 'cardiovascular risk factors' for the prevention and attenuation of AD appears warranted and should be vigorously pursued.

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