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REVIEW ARTICLE

Pharmacological modulation of dietary lipid-induced cerebral capillary dysfunction: Considerations for reducing risk for Alzheimer's disease*

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Abstract

An increasing body of evidence suggests that cerebrovascular dysfunction and microvessel disease precede the evolution of hallmark pathological features that characterise Alzheimer's disease (AD), consistent with a causal association for onset or progression. Recent studies, principally in genetically unmanipulated animal models, suggest that chronic ingestion of diets enriched in saturated fats and cholesterol may compromise blood–brain barrier (BBB) integrity resulting in inappropriate blood-to-brain extravasation of plasma proteins, including lipid macromolecules that may be enriched in amyloid-β (Aβ). Brain parenchymal retention of blood proteins and lipoprotein bound Aβ is associated with heightened neurovascular inflammation, altered redox homeostasis and nitric oxide (NO) metabolism. Therefore, it is a reasonable proposition that lipid-lowering agents may positively modulate BBB integrity and by extension attenuate risk or progression of AD. In addition to their robust lipid lowering properties, reported beneficial effects of lipid-lowering agents were attributed to their pleiotropic properties via modulation of inflammation, oxidative stress, NO and Aβ metabolism. The review is a contemporary consideration of a complex body of literature intended to synthesise focussed consideration of mechanisms central to regulation of BBB function and integrity. Emphasis is given to dietary fat driven significant epidemiological evidence consistent with heightened risk amongst populations consuming greater amounts of saturated fats and cholesterol. In addition, potential neurovascular benefits associated with the use of hypolipidemic statins, probucol and fenofibrate are also presented in the context of lipid-lowering and pleiotropic properties.

Abbreviations: AD: Alzheimer's disease; **Aβ**: amyloid-β; **APP**: amyloid precursor protein; **Apo B**: apolipoprotein B; **Apo E**: apolipoprotein E; **BBB**: blood–brain barrier; **CD**: cluster of differentiation; **CNS**: central nervous system; **CRP**: C-reactive protein; **CYP**: cytochrome P450; **DNA**: deoxyribonucleic acid; **eNOS**: endothelial nitric oxide synthase; **GI**: gastrointestinal; **HBMEC**: human brain microvessel endothelial cells; **HDL**: high-density lipoprotein; **IgG**: Immunoglobulin G; **iNOS**: inducible nitric oxide synthase; **IDE**: insulin degradation enzyme; **ICAM-1**: intercellular adhesion molecule-1; **IL**: interleukin; **LF**: low-fat; **LDL**: low-density lipoprotein; **MMP**: matrix metalloproteinases; **mRNA**: messenger ribonucleic acid; **MCP-1**: monocyte chemoattractant protein-1; **NADPH**: nicotinamide adenine dinucleotide phosphate; **NO**: nitric oxide; **NOS**: nitric oxide synthase; **NF-κB**: nuclear factor-κB; **PPARα**: peroxisome proliferator-activated receptor-α; **ROS**: reactive oxygen species; **SFA**: saturated fatty acid; **TNF-α**: tumour necrosis factor-α; **VCAM-1**: vascular cell adhesion molecule-1; **VaD**: vascular dementia; **ZO**: zonula occludens

Keywords

Atherogenic fats, blood–brain barrier, neurovascular inflammation, capillary vasodilation, redox homeostasis, beta-amyloid, lipid-lowering agents

History

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Introduction

Dementia is caused as a result of neurodegeneration and characterised by the progressive decline of cognitive function[1]. Among the subtypes of dementia, the most common are late-onset Alzheimer's disease (AD) and vascular dementia (VaD) representing nearly 70% and 10–20% of all cases, respectively[2]. However, marked geographical differences in AD prevalence exist, suggesting interactive effects of genes

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with environment and lifestyle. In 2010, dementia prevalence was higher in Europe and North America and lower in African populations[3]. However by 2040, the greatest rate increase in dementia prevalence is expected in developing regions including India, China, South Asia and Western Pacific nations[4]. Presently, AD is estimated to affect 40 million individuals worldwide, and the global prevalence is expected to triple by 2050[1]. However, current therapeutic interventions for AD have been largely ineffective in slowing disease progression[5]. Clearly, identifying strategies to reduce AD risk, or delay the onset and progression is increasingly a global health priority.

Epidemiological studies have identified a positive association of late-onset AD prevalence with the consumption of diets enriched in saturated fatty acids (SFAs) and cholesterol[6,7]. However, the mechanisms for the dietary lipid/AD risk axis are not equivocal. Population and clinical studies suggest an association of mid-life hypercholesterolemia with AD[8] and it is established that plasma cholesterol is positively associated with ingestion of SFA/cholesterol[9]. Furthermore, many lines of evidence support the contention that dietary SFA/cholesterol, independent of plasma lipid homeostasis, may directly modulate cerebrovascular integrity, neurovascular inflammation or influence the propensity to form potentially toxic protein oligomers within the central nervous system (CNS) that compromise neuronal integrity[6,7,10,11].

In AD, cerebrovascular disturbances that may in part be indicative of chronic dietary fat intake are widely evident and generally precede the evolution of hallmark neuropathophysiological features that characterise the disease, such as amyloid plaque formation or Tau protein hyperphosporylation[12–14]. Excluding extraordinary vascular disturbances such as stroke, common cerebrovascular aberrations may include capillary dysfunction [blood–brain barrier (BBB) disturbances], altered brain perfusion, arteriosclerosis/atherosclerosis, lipohyalinosis of cerebral small vessels and amyloid-β (Aβ) deposition in cerebral blood vessels (cerebral amyloid angiopathy)[15]. Indirect support of a lipid/vascular axis for AD risk in some intervention studies with lipid-lowering agents demonstrated stabilisation in cognitive deterioration[16]. However, pleiotropic effects that influence different elements of the complex AD cascade may explain paradoxical and inconsistent findings on cognitive function of pharmacological agents that lower plasma lipids[17,18]. With the present uncertainties in aetiology of late-onset AD, disease risk associated with the ingestion of dietary fats and the putative benefits of lipid-lowering agents in attenuating AD progression, this review presents a contemporary consideration of how dietary fats, specifically SFA/cholesterol, and lipid-lowering agents modulate neurovascular inflammation, redox homeostasis and the Aβ toxicological pathway.

Cerebrovasculature in AD

The BBB describes hallmark features of brain capillary vessels with endothelial cells that are tightly apposed via abundant expression of tight junction and adherence-junction proteins that are pivotal for maintaining brain parenchymal homeostasis. The multicellular architecture and biophysical properties of capillary vessels essentially protect the brain from systemically derived potentially harmful neurotoxic and pro-inflammatory proteins and macromolecules[19], whilst allowing diffusion of small gaseous molecules (O_2 and CO_2) and the active transport of essential nutrients (glucose, amino acids and vitamins) via specific transporters[20]. The normal adult human brain constitutes an extraordinary capillary interface with an estimated 30 m^2 surface area[21]. Clearly, it is a reasonable proposition that even subtle disturbances in capillary function may have significant neurovascular sequelae.

Morphological abnormalities of cerebral capillaries and deficient cerebral circulation have been reported in several neurodegenerative and inflammation-related diseases, in particular AD and VaD[22]. Vascular based disturbances in cognition takes into consideration the consequence of a variety of cerebrovascular lesions and/or impaired brain perfusion[12,14]. Characterised by longer survival, subcortical ischemic VaD is the most significant subtype, involving substantial small vessel disease[23]. In comparison, in AD vascular lesions coexist with proteinaceous deposits[12]. Nonetheless, even in prospectively assessed AD subjects, entirely pure neurodegenerative pathology is infrequent. Rather, autopsied brains of AD subjects typically show cerebrovascular degenerative microangiopathy and cerebral infarcts concomitant with cerebral amyloid angiopathy[13,24].

Accumulating evidence suggests that capillary dysfunction precedes amyloidosis and neurodegeneration[7,25]. A compromised BBB would allow neuronal cells to become vulnerable to exposure to circulating potentially pro-inflammatory macromolecules. The latter is supported by findings where capillary leakage of several plasma proteins such as prothrombin, immunoglobulin G (IgG), albumin and lipoproteins were detected in AD brains[26–28]. Moreover, disrupted capillaries can also facilitate blood-to-brain delivery of circulating Aβ, exacerbating inflammatory processes potentially contributing to cerebral amyloid load[26,29].

Several post-mortem human and animal experiments have demonstrated significant structural changes of the cerebrovascular microanatomy commonly associated with neuroinflammation in AD[25]. The BBB breakdown coincided with substantial endothelial cell necrosis[30]. In addition, loss of tight junction proteins such as occludin, claudin and zonula occludens (ZO)-1, and adheren junction proteins has also been reported[26,31]. Subsequently, increased basement membrane thickening concomitant with fibrosis[32], significant collagen accumulation[30] and altered brain perfusion may occur[25]. The latter is supported by clinical imaging studies that demonstrated substantial cerebral hypoperfusion and hypometabolism preceding onset of dementia[25]. Similarly, dynamic contrast-enhanced magnetic resonance imaging demonstrated increased hippocampal capillary permeability in subjects with mild-cognitive impairment compared to age-matched controls[33]. Alterations in cerebrovascular function co-exist with a heightened state of cerebral inflammation and with the activation of microglia and astrocytes, resulting in enhanced secretion of neurotoxic and inflammatory mediators[31]. Early expression of inflammatory triggers in AD by non-neuronal cells, including endothelial cells, is likely to lead to the development of disease[25].

Dietary fats, cerebrovascular integrity and the risk of AD

Dietary lipids are a vital source of energy, essential for maintaining several biological functions. Saturated, trans, monounsaturated and polyunsaturated fatty acids are major dietary fatty acids with differential biochemical properties and can be sourced from vegetable oils, grains, dairy, meat, fish and fish oils[34,35]. They are characterised by structural differences in length, the hydrogen atom arrangement surrounding the carbon double or triple bonds, and the position of unsaturation[35]. SFAs are synthesised in the body, however, the essential $n-3$ and $n-$ s6 polyunsaturated fatty acids must be consumed by diet[35,36]. In populations that consume Western diets enriched in SFAs and cholesterol, the plasma cholesterol levels are primarily influenced by the fatty acid composition[35,37]. Cholesterol consumption is considered unnecessary as it is synthesised in the body and is heavily regulated[37]. In contrast to SFA and cholesterol, the composition of trans fatty acids in diets has declined in the past few decades due to growing public awareness and improved legislation upon recognition of the associated cardiovascular health risks[35]. Furthermore, the global mean consumption level of SFA is substantially higher than that of trans fat, with regional variation[38]. Trans fat intake is generally higher at younger ages, whereas cholesterol intake increases in adults[38]. Therefore, this review will focus on the detrimental effects of SFA and cholesterol.

Consumption of high-fat diets is an established risk factor for AD and VaD. Increased AD risk was associated with SFA and cholesterol, whereas diets rich in poly- and mono-unsaturated fatty acid consumption were associated with a decreased risk of AD[6,35]. Consistent beneficial effects on cognitive function with ageing are indicated based on the Mediterranean diet[39–41]. Epidemiological studies reported that SFA and cholesterol are also related with mild cognitive impairment, a poorer Mini Mental State Examination score and global cognitive decline[7,10,11,35]. Although the underlying mechanisms for dietary fat-mediated AD risk are uncertain, several lines of evidence are consistent with the hypothesis that dietary SFAs and cholesterol influence the risk of AD/VaD through compromised cerebrovascular integrity.

Effect of dietary saturated fat and cholesterol on cerebrovascular structure and function

Recent findings suggest that dietary lipids and metabolic dyslipidemia are associated with cerebrovascular dysfunction. A population study found both atherogenic and metabolic dyslipidemia more prevalent in AD subjects with BBB disturbances than in subjects without BBB impairment[42]. A significant association was observed between plasma triglyceride and cerebrospinal fluid albumin levels[42], the latter being a marker of increased cerebral capillary permeability. In addition, increased cerebrovascular dysfunction associated with significant loss of tight junction proteins and increase in reactive astrocytes and microglia in response to chronic SFA and cholesterol consumption were demonstrated in rodent models[29,43–49]. Freeman and Granholm[48] evaluated long-term effects of a diet rich in SFA and cholesterol in a rat model. They observed that chronic feeding compromised capillary integrity with increased microgliosis in the hippocampus and loss of the vascular tight junction protein occludin. Similarly, findings made in our laboratory demonstrated that a well-tolerated and physiologically relevant Western-styled diet modestly enriched in SFA resulted in BBB dysfunction and significant delivery into the brain of plasma proteins[29]. Others indicated BBB permeability with the loss of cortical cholinergic neurons[46], decline in spatial memory[46] and impaired hippocampal-dependent cognitive functions[50,51]. However, changes in plasma lipid levels in these animal models were paradoxical. Franciosi et al.[44] observed an increase in the diameter of cerebral capillariesin mice with a null mutation in the low-density lipoprotein (LDL) receptor and in wild-type (C57BL/6 J) mice fed a high-cholesterol diet. Both mouse models exhibited degeneration of segments of the vasculature and significant thickening of the micro-vascular basement membrane. The high-cholesterol diet significantly increased plasma cholesterol in the mutant LDL receptor mice; however, the observed capillary dysfunction in wild-type mice was independent of significant changes in plasma lipid profile[44]. The latter suggests that alternative pathways to hypercholesterolemia induced by dietary cholesterol may contribute to cerebrovascular dysfunction.

Collectively, these findings suggest that consumption of SFA and/or cholesterol enriched diets may compromise cerebral capillary integrity in a manner that compromises neuronal function and subsequently cognitive performance. The following content and Figure 1 summarises the putative mechanism of BBB endothelial dysfunction mediated by dietary SFA and cholesterol.

Putative mechanisms involved in dietary saturated fat and cholesterol induced cerebral capillary dysfunction

Inflammation and oxidative stress-mediated peripheral vascular dysfunction

It is well established that pro-inflammatory properties of high-fat diets enriched in SFA and cholesterol increase risk of cardiovascular disease and negatively influence peripheral vascular function[52,53]. An early study by Shi et al.[52] showed a marked increase in circulating pro-inflammatory cytokines associated with endothelial dysfunction in femoral arteries of baboons fed a diet enriched in saturated fat and cholesterol. They observed that interleukin (IL)-6 and tumour necrosis factor-α (TNF-α) levels were only elevated at 3 weeks, however, IL-8 and monocyte chemoattractant protein-1 (MCP-1) concentrations remained elevated throughout the 7 weeks of dietary intervention. Similarly, *ex vivo* studies in endothelial cells extracted from the femoral artery of the baboons displayed significant endothelial cell dysfunction in response to high-fat, high-cholesterol diet, concomitant with heightened pro-inflammatory status[52]. There was increased expression of membrane-bound vascular cell adhesion molecule-1 (VCAM-1) and membrane-bound E-selectin, consistent with the possibility of heightened CNS leukocyte recruitment[52]. Similar observations were made in high-fat fed hyperlipidemic rabbits with significant endothelial dysfunction[53]. In addition to inflammation, others have identified high-fat induced oxidative mediators contributing to

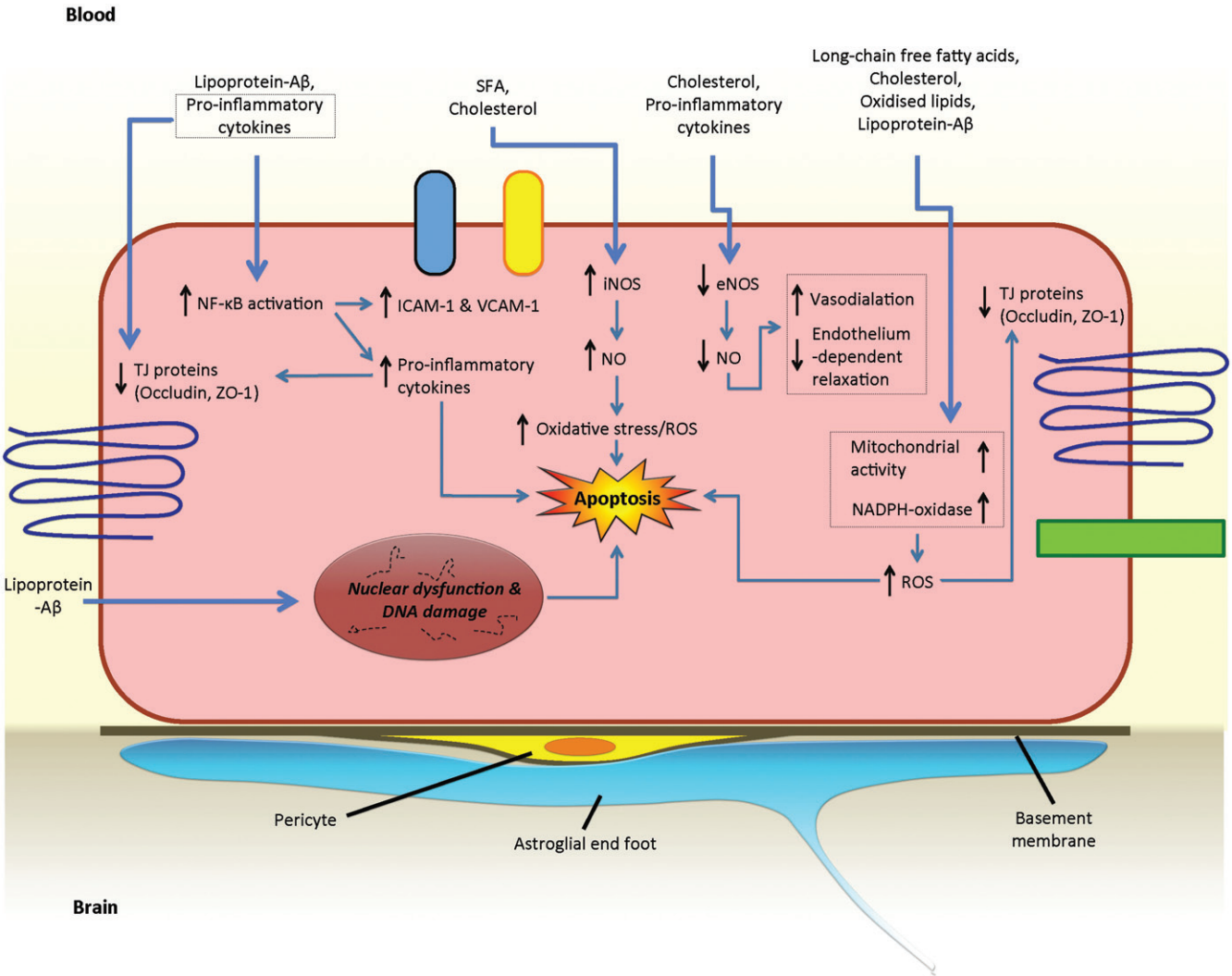

Figure 1. The image illustrates putative molecular mechanisms involved in dietary SFA and cholesterol modulated BBB endothelial dysfunction. Saturated fat and cholesterol directly modulate endothelial NO levels, mitochondrial activity and the NADPH-oxidase pathway leading to oxidative stress and vascular dysfunction. Increased peripheral oxidised lipids, pro-inflammatory cytokines and lipoprotein-Aβ in response to dietary SFA and cholesterol consumption would further influence endothelial damage via activation of intracellular inflammatory response, oxidative stress, DNA damage and attenuate the expression of endothelial tight junction proteins. Aβ, amyloid-β; DNA, deoxyribonucleic acid; eNOS, endothelial nitric oxide synthase; ICAM-1, intercellular adhesion molecule-1; iNOS, inducible nitric oxide synthase; VCAM-1, vascular cell adhesion molecule-1; NADPH-oxidsase, nicotinamide adenine dinucleotide phosphate-oxidase; NF-κB, nuclear factor-κB; NO, nitric oxide; ROS, reactive oxygen species; SFA, saturated fatty acids; TJ, tight junction; ZO-1, zonula occludens-1.

endothelial dysfunction in rodent models[54,55], healthy human subjects[56] and by Western-styled diets in wild-type mice[57].

Inflammation in cerebral capillary dysfunction

The susceptibility of the cerebrovascular endothelium to inflammatory changes has been previously explored. Several studies have demonstrated that exposure to vasoactive cytokines markedly increased cerebrovascular permeability[58] by directly acting on the endothelium[59] and promoting breakdown of the tight junction proteins[60]. However, the mechanisms underlying SFA-mediated inflammation and cerebrovascular disturbances are unclear. Nevertheless, dietary SFA-induced vascular endothelial dysfunction may be dependent on the fatty acid phenotype. Current evidence suggests that endothelial toxicity was dependent on the length and the dose of the SFAs[61,62]. The most potent palmitic (16:0) and stearic (18:0) acids significantly impacted cell growth and viability of several endothelial cell lines *in vitro* by stimulating pro-inflammatory pathways[62,63]. The role of dietary lipids on inflammation and oxidative stress-mediated vascular endothelial dysfunction was further supported by observations made by van Oostrom et al.[64]. They demonstrated that postprandial lipemia increased plasma IL-8 and hyperperoxides. The latter was associated with significant endothelial dysfunction in subjects given fat enriched high-energy diets. Furthermore, healthy subjects randomised to high-fat diets enriched in SFA had increased plasma levels of C-reactive protein (CRP), TNF-α and IL-6[65–68]. Similarly, long chain SFA triggered expression of pro-inflammatory genes in human coronary artery endothelial cells, *in vitro*[69]. Potential mechanisms for SFA-mediated pro-inflammatory cytokines on endothelial dysfunction include cellular apoptosis via activation of the nuclear factor (NF)-κB pathway[70–72]. Several *in vivo* and *in vitro* studies have demonstrated the detrimental role of NF-κB activation on

cerebral endothelial cell integrity[73–75]. The omnipresent heterodimeric NF-κB protein, upon post-translational activation in response to pathogenic stimuli, regulates transcription of cytokine and adhesion molecule genes involved in expression of leukocyte adhesion molecules and release of cytotoxic proteins resulting in cell damage[76–78].

Numerous studies have shown that consumption of cholesterol enriched diets increase peripheral pro-inflammatory mediators in several animal models concomitant with hypercholesterolemia and vascular endothelial dysfunction[79–83]. Clinical evidence also supports the role of plasma cholesterol being positively associated with inflammation[84–87]. In addition, an accumulating body of evidence supports the concept that cholesterol increases neuroinflammation[43,88–92]. *In vivo* and *in vitro* studies have identified a possible association for BBB dysfunction with evidence of neuroinflammatory changes[43,46,93,94]. The latter demonstrated by increased expression of pro-inflammatory cytokines in cerebral extracts[46,83,93] and secretion by activated microglia[43,95,96].

Putative roles of pro-inflammatory cytokines on BBB dysfunction have been considered in experimental animal and cell culture models. Saija et al.[97] demonstrated a significant increase in BBB permeability in rats injected with IL-2, IL-6 and TNF-α. In addition, cultured human brain microvessel endothelial cells (HBMEC)[98] and rat cerebral endothelial cells[99] exposed to pro-inflammatory cytokines facilitated the permeability of the tight junctions[98,100]. More recently, an *in vitro* inflammatory BBB model (transfected HBMEC) induced significant endothelial activation and permeability in response to IL-1β[101]. Endothelial activation was evident when transfected HBMEC were treated with IL-1β resulted in increased expression of intercellular adhesion molecule-1 (ICAM-1), IL-6, IL-8 and TNF-α, and secretion of cytokines[101]. Furthermore, IL-1β-induced capillary permeability was associated with decreased expression of the tight junction protein ZO-1[101].

Oxidative stress in cerebral capillary dysfunction

Altered redox homeostasis and heightened oxidative stress have been reported to be associated with neurodegenerative disorders[102–104]. Furthermore, accumulating evidence suggests that oxidative stress plays a pivotal role in endothelial dysfunction in cerebrovascular disease[105–107] via increased production and release of reactive oxygen species (ROS) and superoxides[108–110]. Animal feeding studies have shown that SFA enriched diets increase protein oxidation and lipid peroxidation[111,112]. Similarly, oxidised cholesterols are more reactive than un-oxidised cholesterol[113] and are associated with numerous cytotoxic properties including vascular inflammatory response, endothelial cell injury and apoptosis[114–120]. Morgan[121] and Lu et al.[63] suggest that one of the mechanisms underlying the toxicity of SFA and cholesterol, respectively, is a consequence of disturbances in protein processing and ER stress generated by the heightened presence of ROS initiating oxidative stress. Zhou et al.[122] observed a significant decrease in cell proliferation and increased apoptosis in cultured HBMEC exposed to long-chain free fatty acids concomitant with a significant increase in intracellular ROS generation in a time- and dose-dependent manner. Furthermore, pro-apoptotic properties of stearate and palmitate were demonstrated in cultured human umbilical vein endothelial cells[123] and rat aortic endothelial cells associated with increased intracellular ROS levels[124]. In addition to ROS production and apoptosis, mouse aortic endothelial cells treated with palmitate inhibited cell proliferation[63]. Others have demonstrated that ROS-induced oxidative stress may modulate cerebrovascular integrity by changes in the localisation and structure of the tight junction proteins[125] and downregulation of tight junction protein expression[126].

SFA and oxidised-LDL-induced alterations in BBB include stimulation of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase derived ROS[110,127–130]. NADPH-oxidase activation is an important source of ROS, other than the mitochondria, and higher NADPH-oxidase activity in cerebral arteries have been demonstrated[131,132]. Human post-mortem studies have demonstrated that upregulation of NADPH-oxidase activity in frontal and temporal cortical brain tissues correlated with cognitive decline[133]. Furthermore, Bruce-Keller et al.[134] reported that NADPH-oxidase activity in aging brain can be exacerbated by high-fat diets.

Nitric oxide in cerebral capillary dysfunction

Studies have demonstrated the role of nitric oxide (NO) in regulation of cerebrovascular integrity[135–140]. NO is synthesised from NO synthase (NOS) and is constitutively produced by cerebrovascular endothelial cells and glial cells for regulation of cerebrovascular tone and vasodilation[135,140,141]. Altered production of NO has been implicated in regulation of BBB permeability[136,140,142]. NO overproduction in response to cytokines and other inflammatory mediators[135,140] has been reported in AD[141,143]. However, chronic inhibition of NO production enhanced endothelial cell permeability has been implicated in progression of several neurodegenerative and vascular-based disorders[141,144–149].

Several experimental models have explored the effect of SFA and cholesterol on NO-dependent endothelial function, but the findings are paradoxical. Javeshghani et al.[55] observed that high-fat diet aggravated vasodilation and vascular remodelling by altered NO in oestrogen deficient mice. Furthermore, endothelial NO production and endothelium-dependent relaxation was reduced in apolipoprotein E (Apo E)-knockout mice[150,151] and subjects with type II diabetes fed a Western type high-fat diet[151,152]. Roberts et al.[153] demonstrated inhibition of NOS protein expression in brain and other vascular tissues in rats fed high-fat/sucrose diet. Furthermore, endothelial NOS (eNOS) expression in aortic rings was abolished in rats randomised to a high-fat diet enriched in SFA and/or cholesterol[154], resulting in reduced NO bioavailability. Analogous observations were made in endothelial cells of hypercholesterolemic experimental models *in vivo* and *in vitro*[155–157]. In contrast to the downregulatory findings of NO synthesis reported, others have shown that a high-fat diet amplifies NO and associated vasodilatation and vascular remodelling. Several laboratories reported upregulation of inducible NOS (iNOS) in aortic specimens obtained from mice maintained on a

cholesterol-supplemented diet[158,159]. Other studies have also shown that an increase in iNOS expression was associated with increased cerebrovascular dysfunction and permeability under pathological conditions[160–165]. Another confounder in understanding the relationship between dietary fats, NO and vascular function is that the localised expression of iNOS can be modified depending on the focal abundance of pro-inflammatory cytokines[166,167]. The effect of dietary lipids on NO-induced BBB permeability is presently unclear. However, collectively these and other studies suggest that dietary SFA and cholesterol may influence cerebrovascular integrity in part by inhibiting eNOS and upregulating iNOS expression.

Aβ homeostasis in cerebral capillary dysfunction

The role of dietary fat in regulating cerebral Aβ production was demonstrated in several experimental models *in vivo* and *in vitro*. Increased cerebral Aβ abundance was reported in both wild-type mice and AD amyloid-transgenic models supplemented with high-fat diets enriched in SFA and/or cholesterol[88,168–171]. Puig et al.[168] reported a significant increase in neuronal amyloid precursor protein (APP) levels in high-fat fed wild-type mice. Aβ is produced from proteolytic processing of the APP by several proteases[172,173]. Others have observed that a key proteolytic enzyme β-secretase 1 was upregulated in response to cholesterol[88,174], resulting in augmented APP processing and increased Aβ production. Popp et al.[175] also showed an association between soluble APP production and cholesterol metabolism in the cerebrospinal fluid of AD subjects.

Accumulating evidence supports the notion that high-fat diets may exacerbate cerebral Aβ load through increased blood-to-brain delivery of Aβ complexed with lipoproteins. Mackic et al.[176] first suggested that brain parenchymal extravasation of plasma Aβ occurs if the BBB is significantly compromised. Evidence supporting this hypothesis was provided by Takechi et al.[29] in a dietary-fat induced model of BBB dysfunction. Lam et al.[177] reported retention of plasma derived lipoprotein-Aβ upon extracellular matrices and in other studies, retention was colocalised with increased microglial activation[178–180]. Several others have also suggested that exaggerated cerebrovascular exposure to peripheral Aβ might significantly contribute to cerebrovascular disturbances that feature in early AD[181–183].

We previously reported that chronic SFA and cholesterol consumption increased Aβ production in absorptive epithelial cells of the small intestine of wild-type mice[26,184,185] and secretion into circulation thereafter[29,186–188]. These effects were concomitant with heightened cerebrovascular permeability[29,189]. Similarly, Park et al.[190] highlighted the significance of peripheral Aβ in BBB dysfunction. Cerebrovascular dysfunction was markedly enhanced in Tg-2576 amyloid transgenic mice with elevated plasma Aβ1–40 compared to Tg-SwDI mice that expressed Aβ only in the brain[190]. Furthermore, intravascular administration of Aβ1-40 resulted in an increase in plasma Aβ and amplified BBB dysfunction in Tg-SwDI mice[190].

The cytotoxic properties of Aβ have been implicated in cerebrovascular degeneration. Xu et al.[191] reported in a murine cerebral endothelial cell line and in primary cultures of bovine cerebral endothelial cells, exposure to exogenous Aβ1–40 or Aβ25–35 resulted in cell death in a dose- and time-dependent manner. The authors characterised Aβ-induced cell death via nuclear condensation, mitochondrial dysfunction, and nuclear and mitochondrial DNA damage. Others have implicated Aβ-mediated activation of the endothelial NF-kB pathway[181] and NADPH-oxidase-derived free radicles[192,193] in cerebrovascular dysfunction.

Effect of anti-inflammatory lipid-modulating agents on saturated fat and cholesterol induced cerebral capillary dysfunction

The positive association between dietary fat intake, hypercholesterolemia and AD raises the possibility that lipid-modulating agents may delay onset or attenuate the progression of AD. Some population studies have reported beneficial effects of lipid-lowering agents in AD risk and dementia[16,17,194–196]. However, the mechanisms for this association are not clear and in some cases are independent of the lipid lowering effects.

Amongst several classes of lipid-lowering treatment, statins are the gold standard in the treatment of hypercholesterolemia and in primary and secondary prevention of coronary and vascular diseases[197]. Fenofibrate effectively reduces plasma triglycerides and its use in combination with statins has demonstrated beneficial additive effects on combined hyperlipidemia and endothelial function[197–199]. In contrast to statins and fibrates, probucol is known for its anti-inflammatory, anti-oxidative properties, is more beneficial in reducing atherosclerosis than lipid lowering and has continued its clinical use in Japan since 1985[200]. These drugs with pleiotropic properties demonstrated potential in ameliorating cerebrovascular dysfunction by modulating inflammatory pathways, redox homeostasis or direct effects on endothelium[17,195,201,202].

Table 1 summarises the pharmacokinetics of several classes of statins, probucol and fenofibrate. The following sections describe the effects of these major classes of drugs in the context of cerebral capillary integrity, lipid metabolism, inflammation, oxidative stress, NO production and Aβ homeostasis.

Putative mechanisms of statins in ameliorating cerebral capillary dysfunction

Statins are an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme of the cholesterol biosynthetic cascade[229], which limits hepatic cholesterol production and enhances clearance of circulating LDL-cholesterol[221]. In addition, statins have been effective in lowering triglycerides and increasing high-density lipoprotein (HDL)–cholesterol[230]. Their pleiotropic properties have also been shown to be beneficial in improving vascular dysfunction[231,232].

The therapeutic potential of statins for the treatment of AD/VaD via protection of cerebral capillary function has been considered *in vitro* and *in vivo*[136,233–235]. Beneficial effects of lipid lowering were observed in New Zealand rabbits, where cholesterol-induced BBB disruption was attenuated upon treatment with simvastatin[236]. The protective effect of

Table 1. Pharmacokinetic properties of statins, probucol and fenofibrate.

	Statins[210,221]							Probucol	Fenofibrate
	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin	Rosuvastatin	Pitavastatin		
Daily dosage (mg)	10–80	20–80	10–80	5–40	5–80	5–80	1–4	250–1000[203,204]	200–400[205,206]
Solubility	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	Hydrophilic	Lipophilic	Lipophilic[207,208]	Lipophilic[209]
Bioavailability (%)	12	24[210]	5	18	5	20	80[210]	<10[211,212]	60[213]
Effect of food on bioavailability (%)	↓13	↓15–25[214]	↑50	↓30	No	No	No	Increased[208,215]	↑35[216]
Protein binding (%)	>98	>98	96–98.5	43–54	>95	88	96	>99[208,217]	>99[213]
Half-life (h)	11–30	0.5–2.3	2.5–3.0	0.8–3.0	1.9–3.0	20	11	24–552[218]	19–27[213]
Metabolism	CYP 3A4	CYP 2C9	CYP 3A4	GI tract via non-enzymatic, acid-initiated reactions[219]	CYP 3A4	Limited metabolism via CYP 2C9 and 2C19[220,221]	Limited metabolism via CYP 2C9[222]	–	Hydrolysis catalyzed by tissue and plasma esterases[223]
Excretion									
Urinary (%)	2	6	10	20	13	10	<2	<2[224]	60–65[205,225]
Faecal (%)		90	83	70	60	90[226]	Major route[227]	80[224]	25[205,228]

The table compares the pharmacokinetics properties including the average dosage, solubility, bioavailability and effect of food on bioavailability in circulation in several classes of statins. Food consumption reduces the bioavailability of atorvastatin, fluvastatin and pravastatin, and increases for lovastatin. Most statins are metabolised by cytochrome P450 isoenzymes, however, this is limited for rosuvastatin and pitavastatin. Pravastatin is the only statin metabolised in the GI tract via non-enzymatic, acid initiated pathways. Faecal excretion is the major route of elimination for all statins. Bioavailability of lipophilic probucol is increased upon food consumption, however, its metabolism is presently unclear. Similar to statins, probucol is readily excreted through faecal matter. Fenofibrate bioavailability increases with food, undergoes metabolism by hydrolysis and excreted through urine. CYP, cytochrome P450; GI, gastrointestinal.

simvastatin was concomitant with significant amelioration of plasma cholesterol; however, independent of modification of tight junction protein expression. In contrast, pitavastatin enhanced expression of the tight junction protein claudin-5 to strengthen the barrier integrity in primary cultures of rat brain endothelial cells[234]. In a study of normolipemic spontaneously hypertensive rats, atorvastatin prevented increased capillary permeability through enhanced expression of tight junction proteins ZO-1 and occludin[136]. Furthermore, in APP transgenic mouse models of AD, significant cerebrovascular disturbances were attenuated in response to atorvastatin, pitavastatin and simvastatin treatment[233,235]. Statin treatment was reported to improve vascular tone and increase cerebral blood flow[233].

Effects of statins on inflammation and oxidative stress

Statins may provide cerebrovascular protection via anti-inflammatory mechanisms including glial cell inactivation. Consistent with this, Kalayci et al.[136], Tong et al.[235] and Kurata et al.[233] reported that improved structural and functional cerebrovascular integrity by statin treatment was concomitant with attenuated inflammation and oxidative stress. Furthermore, statins inhibited the production of cytotoxic ROS, NO, cyclooxygenase-2 and cytokines such as IL-1β and TNF-α by activated glial cells[202,235,237,238]. Consistent with *in vitro* studies, in genetically unmanipulated mice with dietary SFA-induced cerebral capillary dysfunction, atorvastatin and pravastatin were shown to restore BBB integrity (Figure 2)[239]. Moreover, the latter occurred independent of significant changes in plasma lipid homeostasis. These findings are consistent with the concept that statins can attenuate neurovascular inflammation.

Current evidence suggests that statins provide neuroprotection and endothelial protection also by their anti-oxidative properties[108,240,241]. A recent preliminary study reported reduced cytotoxic and pro-inflammatory effects of oxidised-LDL on microvascular endothelium by statin treatment[130]. The exact mechanisms are unclear, however, may include modification of vascular NADPH-oxidase expression[242]. Otto et al.[243] showed that rosuvastatin treatment attenuated vascular superoxide formation via downregulation of the NADPH-oxidative stress pathway in eNOS-knockout mice. Similarly, rosuvastatin inhibited NADPH-oxidative stress-dependent superoxide production in cerebral arteries and improved cerebrovascular function in Zucker obese rats[240]. Atorvastatin pre-treatment attenuated cerebral infarcts and NADPH-oxidative stress-dependent ROS formation[241]. *In vivo* and *in vitro* observations by Wassmann et al.[108] and Hong et al.[241] suggest that statins effectively downregulate the messenger ribonucleic acid (mRNA) expression of essential NADPH-oxidase subunits and contribute to its vasoprotective properties.

Effect of statins on NO

In addition to the anti-inflammatory and anti-oxidant properties, statins enhance NO bioavailability that is essential for regulation of cerebral perfusion and improved endothelial function[202]. Altered NO levels have been implicated in vascular endothelial dysfunction. A cohort clinical study in

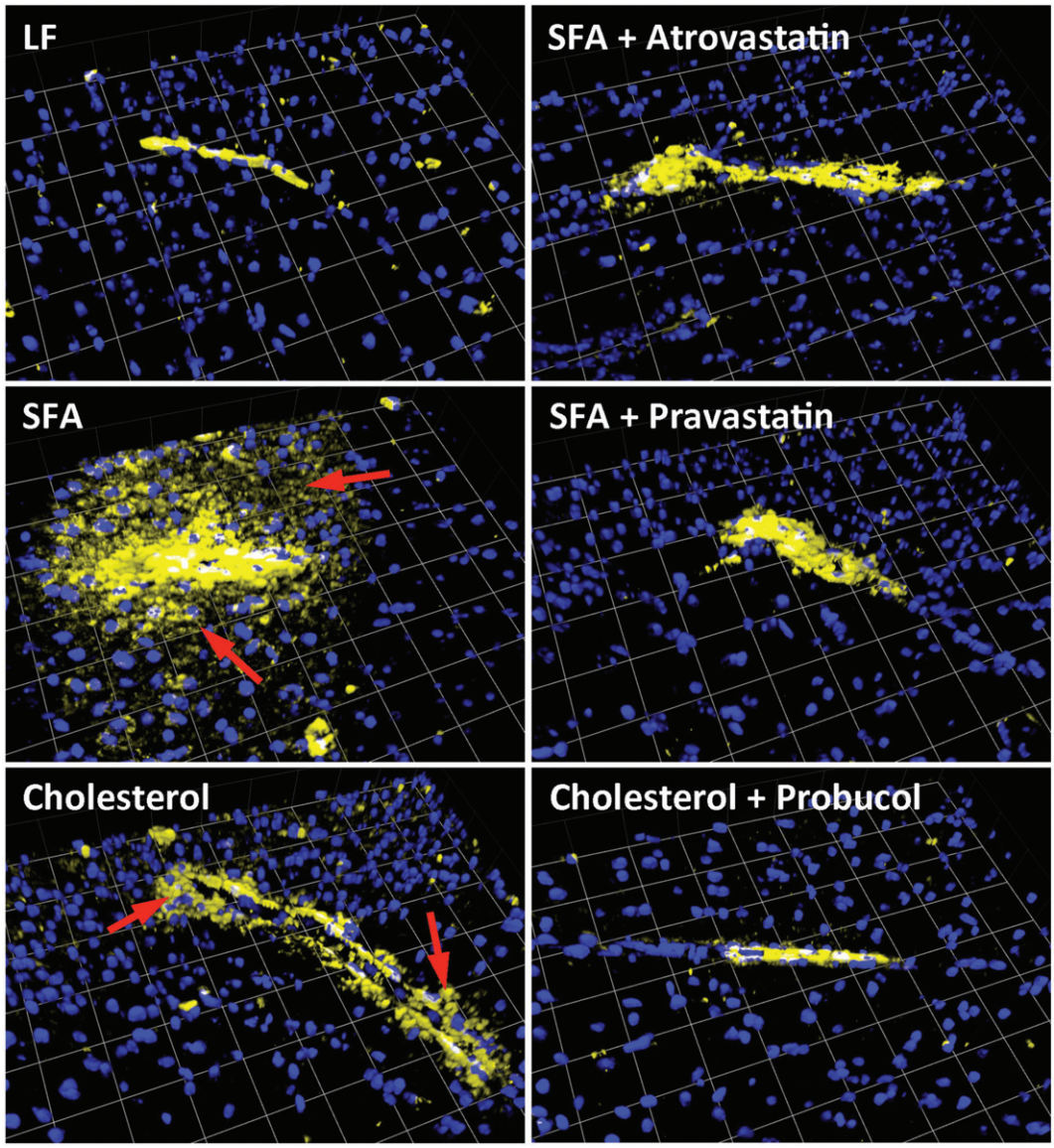

Figure 2. Three-D immunofluorescent illustrations demonstrate amelioration of SFAs/cholesterol induced BBB permeability by lipid-lowering agents. Apo B is shown in yellow (or bright color in grey scale) and nuclei are shown in blue (or dull color). The compromised BBB integrity was demonstrated by the diffuse extravasation of app B surrounding the cerebral microvessels in wild-type mice fed SFA and cholesterol that is indicated by arrows. BBB disruption was non-existent in mice fed a low-fat (LF) control diet, where Apo B was found confined within the lumen of the brain capillaries. In the same mouse model, atorvastatin and pravastatin treatment (3 months) reversed SFA induced BBB dysfunction[239]. Similarly, probucol prevented cholesterol induced BBB permeability and abolished leakage of Apo B[189].

patients with dementia demonstrated a correlation between lower serum NO level and cognitive decline in individuals with VaD[244]. NO-mediated improvement in cerebrovascular function by statin treatment has been implicated in VaD[17,245]. In addition, *in vivo* and *in vitro* experiments demonstrated that atorvastatin[136] and fluvastatin[246] treatment enhanced NO bioavailability associated with improved BBB integrity.

Several lines of evidence have shown that statins increase NO production by upregulating eNOS[17,109,247]. The significance of eNOS activity in the cerebrovascular structural integrity has been demonstrated in knockout mice lacking the eNOS gene[248]. These mice had significantly larger cerebral infarcts following middle cerebral artery occlusion compared to their wild-type controls. Further cerebrovascular aberrations including reduced endothelial dysfunction, smooth muscle proliferation and impaired cerebral perfusion have also been demonstrated in the same mouse model[249]. Jick et al.[17] demonstrated that statin treatment had favourable effects on eNOS and modulation of cerebrovascular function. Others have indicated that statins may provide neuroprotection during cerebral ischemia via modulation of cerebral eNOS[247]. Beneficial effects of simvastatin, rosuvastatin and lovastatin on improving endothelial dysfunction via upregulation of eNOS expression have been demonstrated *in vitro* and in animal models[109,250,251]. Collectively, statin-mediated increase in NO levels by upregulation of eNOS expression may improve cerebrovascular endothelial function.

Effect of statins on amyloid-β homeostasis

Growing evidence suggests that compromised BBB may facilitate blood-to-brain delivery of circulating Aβ,

contributing to cerebral amyloid load. Statins may be beneficial in treatment and regression of cerebrovascular dysfunction, attenuate plasma Aβ extravasation and reduce AD/VaD progression. In addition to the anti-inflammatory and anti-oxidative effects on the BBB, statins may lower circulating Aβ and contribute to reduction in cerebral Aβ load. Others have demonstrated cytotoxic properties of Aβ[252–255], thus attenuating circulating Aβ may be beneficial for sustaining the cerebrovascular endothelium.

Although statin effects on circulating Aβ are controversial, one clinical study by Buxbaum et al.[256] demonstrated that lovastatin treatment significantly lowered serum Aβ in subjects with AD. The decrease in Aβ levels may be a consequence of statin-mediated inhibition of Aβ synthesis and secretion. Ostrowski et al.[257] observed *in vitro* that simvastatin and lovastatin treatment in murine neuroblastoma cell culture inhibited Aβ1-40 production and secretion. It was suggested that the statin effects were attributed to the inhibition of protein isoprenylation of APP[257,258]. In addition, others suggested the potential of statins in Aβ degradation. In wild-type mice fluvastatin treatment resulted in decreased cerebral Aβ1-40 and Aβ1-42 as a result of increased intracellular lysomal degradation of the APP-C terminal fragment[259]. Recent investigations by Tamboli et al.[260] observed that lovastatin treatment enhanced extracellular Aβ1-40 and Aβ1-42 degradation by insulin degradation enzyme (IDE) release by microglia *in vitro*, via an exosome-related unconventional secretory pathway. Moreover *in vivo*, serum IDE was enhanced in wild-type mice injected with lovastatin[260]. Liu et al.[261] observed that individuals with probable AD and amnestic mild cognitive impairment had lower Aβ degrading enzymes, IDE and angiotensin converting enzyme in blood, compared to elderly individuals with normal cognition. In addition, contrasting effects were seen between individuals with VaD and those with probable AD in the absence of or with minimal cerebrovascular pathology[261]. However, the role of these Aβ degradation proteases on cerebrovascular dysfunction is unclear. In intervention studies, high-fat diets suppressed IDE expression in neurones[262] and cortical-membranes[263]. Furthermore, long-chain free fatty acids (C16–C20) inhibited IDE activity by 50–90% *in vitro*[264]. Collectively, statin treatment may counteract dietary lipid effects by enhancing Aβ degradation protease activity to facilitate Aβ degradation in circulation.

Putative mechanisms of probucol in attenuating cerebral capillary dysfunction

Probucol is a potent lipid-lowering agent that has been beneficial in treatment and prevention of cardiovascular diseases[200,265,266]. There has been much recognition for its anti-atherosclerotic properties including plaque stabilisation[267–269], plaque reduction[270], preservation of endothelial and smooth muscle function[271,272] and attenuation of monocyte adherence and infiltration[267,268,273]. Limited observations report the putative role of probucol on AD risk. Poirier et al.[274] examined the effect of probucol on subjects with mild–moderate AD. Beneficial effects of probucol treatment were suggested with stabilisation of cognitive function[274–276], although the underlying mechanisms were not explored. In other models of neurodegenerative conditions featuring significant neurovascular disturbances, probucol conferred neuroprotection in murine models of Parkinson's disease[277] and Huntington's disease[278].

Effects of probucol on inflammation and oxidative stress

Studies have identified potent anti-inflammatory and anti-oxidative effects of probucol that may be relevant to preservation of vascular function[268,279]. Although the effects of probucol on cerebrovascular disorders are unclear, a recent study by Takase et al.[280] observed that combination therapy of probucol (500 mg/day) with cilostazol (200 mg/day) resulted in improved endothelial function in hypercholesterolemic patients with silent lacunar cerebral infarcts. Takechi et al.[189] reported positive effects of probucol on SFA and cholesterol-induced BBB dysfunction. Wild-type mice supplemented with probucol (1% w/w) for 3 months showed attenuation in cerebral extravasation of plasma proteins IgG and apolipoprotein B (Apo B) (Figure 2)[189] and the effects were sustained for up to 12 months of feeding[281]. The positive effects of probucol in maintaining cerebral capillary function were associated with suppression of neurovascular inflammation demonstrated by decreased parenchymal expression of glial fibrillary acidic protein and plasma S100B[189], a surrogate marker for BBB permeability and astroglial activation.

Effects of probucol on NO

There is a paucity of information with respect to the potential effects of probucol on NO metabolism. In one study, synergistic administration of probucol significantly reduced cerebral infarct volume in high-fat fed Apo E-knockout mice with focal cerebral ischemia[271]. The latter effects correlated with a marginal increase in eNOS expression in cerebral cortex[271]. Similar effects were reported in Sprague Dawley rats with endothelial injury with improved endothelial function associated with increased NO levels in a dose-dependent manner[282].

Effect of probucol on amyloid-β metabolism

Probucol was found to attenuate dietary SFA and cholesterol-induced exaggerated enterocytic Aβ abundance, and it was suggested that less Aβ would be secreted associated with postprandial lipoproteins[184]. Takechi et al.[281] confirmed and extended those observations by demonstrating in the same model that concomitant cerebral capillary permeability was associated with enterocytic abundance of Aβ. These observations are consistent with the notion that cerebral capillary integrity is compromised as a result of exaggerated exposure to lipoprotein-Aβ, and probucol prevents cerebral capillary dysfunction by suppressing secretion. However, direct effects of probucol on cerebrovascular function independent of dietary fats or lipoprotein-Aβ metabolism cannot be excluded.

Putative mechanisms of fenofibrate attenuating cerebrovascular dysfunction

Fibrates have been used in the clinical practice for the treatment and management of dyslipidemia due to their ability to lower triglycerides, total cholesterol, LDL–cholesterol and chylomicron remnants, and increase

HDL-cholesterol[206,283–287]. Fibrates activate peroxisome proliferator-activated receptor-α (PPARα), which stimulates transcription of genes central to lipid metabolism[283,284,286,288]. Peroxisome proliferator-activated receptor-α receptors are found expressed in liver, heart, kidney and skeletal muscle, which are primary sites of fatty acid metabolism[284,286,289], as well as in vascular endothelial cells, smooth muscles and macrophages[284,288].

Potential effects of fibrates on AD risk and cognitive decline are controversial[16,195,196]. However, studies in animal models suggest neuroprotective effects and improved cognitive performance associated with fibrate therapy. Greene-Schloesser et al.[290] showed that unabated consumption of dietary fenofibrate (0.2% w/w) prevented fractionated whole-brain irradiation-induced perirhinal cortex-dependent cognitive impairment; however, no effect was observed on hippocampal neurodegeneration and microglial activation. Similarly, Uppalapati et al.[291] reported that fenofibrate treatment improved cognitive function and reduced neurodegeneration in a dose-dependent manner in a rat model of Parkinson's disease. Fibrate prescription generally follows failure in statin treatment, therefore resulting in limited clinical experimental evidence specifically on fibrates[195]. Although the putative effects of fibrates on dietary lipid-mediated cerebral capillary functionality have not been specifically investigated, beneficial effects of fenofibrate were demonstrated in rodent and cell culture models of cerebrovascular dysfunction where treatment significantly improved BBB integrity in these models[292,293].

Effect of fenofibrate on inflammation and oxidative stress

Few clinical studies have reported beneficial effects of the lipid lowering fibrates on AD risk and dementia[16,195,196] in the context of potential modulation of inflammation. However, PPARα receptor agonists can modulate an array of key proteins recognised for anti-inflammatory, anti-oxidative and anti-atherosclerotic effects[284,294–298] that have proven beneficial in reducing risk, prevention and/or treatment of coronary artery disease[299–301], atherosclerosis[302–304], myocardial infarction[305,306], stroke[307] and diabetes[298,302,308,309]. The indicated effects of fibrates have been implicated in attenuation of vascular endothelial dysfunction. Clinical intervention trials using fenofibrate, one of the most commonly used fibrates[284], have proven effective in attenuation of markers of vascular inflammation. In a small randomised, double-blinded clinical study reported by Undas et al.[299], short-term treatment with fenofibrate in hypercholesterolemic patients at high risk of coronary artery disease significantly lowered plasma CRP, IL-6, MCP-1 and cluster of differentiation (CD)-40 ligand, independent of changes in plasma lipid profile. In addition to lipid lowering, Tkacheva et al.[308] observed that fenofibrate treatment lowered plasma CRP levels in patients with type-2 diabetes concomitant with normalised vascular function. The latter was demonstrated by increased endothelium dependent vasodilatation and improved parameters of brachial artery thickness[308].

In a rat model of Parkinson's disease, fenofibrate showed significant reduction in makers of cerebral inflammation such as TNF-α, IL-6 and malondialdehyde (marker for lipid peroxidation), increase in the anti-oxidant level of glutathione, improved cognitive function and less evidence of neurodegeneration[291]. Furthermore, fenofibrate administration resulted in cerebrovascular protection in rat and mouse models of cerebral ischemia concomitant with improved neuronal function and regulation of neuroinflammation[310] via activation of PPARα[311]. The anti-inflammatory and anti-oxidative effects of fenofibrate were consistent with reduced cerebral IL-6, TNF-α, IL-1β, cyclooxygenase-2, ICAM-1 and VCAM-1 levels in a mouse model with neuroinflammation[312]. The latter occurred concomitant with significant attenuation in microglia/macrophage activation, neutrophil recruitment and neuronal injury.

An accumulating body of evidence recognises the potential of PPARα agonists in modulating cerebrovascular permeability. Fenofibrate attenuated BBB dysfunction induced by Tat protein in an *in vivo* experimental mouse model[293]. Compromised BBB integrity was associated with a significant reduction in cerebrovascular tight junction protein expression via activation of redox regulating ERK1/2 and Akt pathways, inducing matrix metalloproteinases (MMP)-9 expression[293,313]. Fenofibrate treatment reversed the latter observations reducing BBB permeability concomitant with less pronounced microgliosis and neurodegeneration[293]. In an *in vitro* mouse cerebral capillary endothelial cell culture model, fenofibric acid (the active metabolite of fenofibrate) treatment reduced BBB permeability[292]. Fenofibric acid effects were specifically indicated in endothelial cells and dependent on the activation of PPARα[292]. Previous findings have demonstrated the protective role of PPARα activation against cerebral injury. Deplanque et al.[314] observed improved middle-cerebral artery endothelial function independent of NOS activity, by preventing VCAM-1 and ICAM-1 expression and increasing cerebral anti-oxidants, including copper/zinc superoxide dismutase, glutathione reductase, glutathione peroxidase, and glutathione S-transferase activity in ischemic mice treated with fenofibrate. Furthermore, the neurovascular protective effects of fenofibrate were absent in PPARα-deficient mice compared to their wild-type controls[314].

Effect of fenofibrate on NO

In addition to regulation of inflammatory and oxidative stress pathways, others have observed improved vascular endothelium-dependent relaxation in response to fenofibrate treatment via improved NO availability[315]. Fenofibrate restored the decreased expression of mRNA for eNOS induced by nicotine in rats and improved aortic endothelial integrity[316]. A clinical study by Walker et al.[317] showed that fenofibrate improves vascular endothelial function by increasing eNOS in healthy normolipidemic adults.

Effect of fenofibrate on Aβ homeostasis

Effect of fibrates on Aβ homeostasis is controversial. Although some studies have demonstrated reduced plasma Aβ with fenofibrate treatment[318], others demonstrated significant increase in secretase activity on APP resulting in enhanced Aβ production[319,320]. Limited experimental evidence supports the concept that a decrease in Aβ levels is attributable to enhanced clearance. Abdul-Hay et al.[321]

observed fenofibric acid increased extracellular proteolysis of Aβ1-42 in the Aβ producing neuroblastoma cell line transfected with human APP. Given that fibrates are potent at clearance of triglyceride rich lipoproteins, clearance of lipoprotein associated Aβ may be increased with fibrate treatment. In addition, Aβ-induced cytotoxicity may be alleviated by PPARα activation via decreased ROS production, β-catenin degradation and preventing cytoplasmic calcium influx[322].

Conclusion

Cerebrovascular dysfunction is common in several neurodegenerative disorders including AD/VaD. Increased cerebral capillary permeability is associated with neurovascular inflammation and phenotypic changes thereafter in neurons that may be central to loss of cognitive function. Chronic consumption of Western-style diets enriched in SFA and cholesterol compromise cerebrovascular integrity via several pathways including exaggerated vascular exposure to lipoproteins enriched in Aβ, altered redox homeostasis and possibly changes in blood flow dynamics. By extension, pharmacological agents may attenuate capillary dysfunction as a consequence of an improvement in lipoprotein-Aβ homeostasis, redox state or other pleiotropic properties. This review presented potential synergistic anti-oxidant, anti-inflammatory and Aβ metabolic effects of statins, probucol and fenofibrate. The concepts presented in this review suggest that the putative role of anti-inflammatory pharmacotherapy on cerebrovascular integrity will be informative for translation of appropriate clinical intervention studies.

Declaration of interest

The authors report no declarations of interest.

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