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REVIEW

The Involvement of Lipids in Alzheimer's Disease

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ABSTRACT

It has been estimated that Alzheimer's disease (AD), the most common form of dementia, will affect approximately 81 million individuals by 2040. To date, the actual cause and cascade of events in the progression of this disease have not been fully determined. Furthermore, there is currently no definitive blood test or simple diagnostic method for AD. Considerable efforts have been put into proteomic approaches to develop a diagnostic blood test, but to date these efforts have not been successful. More recently, there has been a stronger focus on lipidomic studies in the hope of increasing our understanding of the underlying mechanisms leading to AD and developing an AD blood test. It is well known that the strongest genetic risk factor for AD is the ε4 variant of apolipoprotein E (*APOE*). Evidence suggests that the ApoE protein, a major lipid transporter, plays a key role in the pathogenesis of AD, and its role in both normal and aberrant lipid metabolism warrants further extensive investigation. Here, we review ApoE-lipid interactions, as well as the roles that lipids may play in the pathogenesis of AD.

KEYWORDS: Alzheimer's disease; Lipids; ApoE; Oxysterols; Inflammation

INTRODUCTION

Alzheimer's disease (AD) is a multifactorial neurodegenerative disease, characterised by progressive decline in cognitive function and increasing memory loss (Strittmatter and Roses, 1996; Holtzman, 2002). A common early sign exhibited by individuals suspected of AD is an increasing difficulty in remembering recent events and retaining new information. AD individuals experience a multitude of difficulties which include loss of orientation, linguistic and memory problems, and difficulty in performing daily activities. These get progressively worse, reaching an end stage when AD individuals are totally dependent on others to care for them (Alzheimer's Association, 2010). In 2006, it was estimated that there were approximately 26 million AD sufferers worldwide (Brookmeyer et al., 2007), and it has been estimated in the Delphi Consensus that this number will reach 81 million worldwide by 2040 (Ferri et al., 2005). To date, post-mortem examination is still the only way to confirm an AD diagnosis, and the presence of narrowed gyri and widened sulci, the accumulation of extracellular amyloid plaques, intracellular neurofibrillary tangles, dystrophic neurites, as well as widespread neuronal cell death are the hallmarks of the disease.

AD can be categorised into early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD). EOAD

Abbreviations: AD, Alzheimer's disease; ApoE, apolipoprotein E; APP, amyloid precursor protein; Aβ, β-amyloid; BBB, blood brain barrier; Cer, ceramides; Chol, cholesterol; CSF, cerebrospinal fluid; DAG, diacylglycerols; GalCer, galactosylceramide; GM, gangliosides; HFHC, high fat high cholesterol; NAFLD, non-alcoholic fatty liver disease; OH, hydroxyl; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PEp, plasmalogen phosphatidylethanolamine; PS, phosphatidylserine; SM, sphingomyelin; SL, sulfatides; TAG, triacylglycerols.

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accounts for approximately 5%–10% of all AD cases, and includes people with AD symptoms that have been manifested before the age of 65, and sometimes as early as 35 years of age. EOAD cases have a strong autosomal inheritance, and genetic studies have revealed that they are linked to mutations in one of three genes: the amyloid precursor protein (*APP*) gene, the presenilin 1 (*PS1*) or presenilin 2 (*PS2*) genes (Selkoe, 2001). The majority of AD cases (90%–95%) belong to the late-onset category, which includes subjects who develop symptoms of AD after the age of 65 (Laws et al., 2003). AD incidence increases exponentially with every 5 years of age, such that about 5% of people aged 65 have AD, whereas 20% of people over 80 have AD (Brookmeyer et al., 2007). Risk factors for LOAD such as age, possession of *APOE* ε4 alleles, high cholesterol levels, mid-life obesity and diabetes have been implicated in the pathogenesis of AD and are also closely linked to aberrant lipid metabolism.

APOE — LIPID TRANSPORTER AND GENETIC RISK FACTOR FOR AD

ApoE is a protein involved in the transport of lipids including cholesterol, and is encoded on chromosome 19q 13.2 (Mahley, 1988; Strittmatter et al., 1993). ApoE mediates phospholipid and extracellular cholesterol transport by means of lipoprotein particles (DeKroon et al., 2006). The human ApoE protein is comprised of 299 amino acids, and exists as three major isoforms namely: ApoE ε2, ε3 and ε4 (Rall et al., 1982; Zannis et al., 1982). Their genetic differences result in changes in amino acid residues 112 and 158: ε2 (Cys112, Cys158), ε3 (Cys112, Arg158) and ε4 (Arg112, Arg158) respectively. The allele frequencies of *APOE* ε3, *APOE* ε4 and *APOE* ε2 in the Australian (Martins et al., 1995) and other Caucasian populations (Roses, 1996; Bales et al., 2002) in general are approximately 78%, 14%–15% and 7%–8% respectively. On average, *APOE* ε4 individuals who develop AD have a lower age of onset, whereas *APOE* ε2 carriers appear to be protected as evidenced by a higher mean age of onset. Possession of an *APOE* ε4 allele increases the risk of cognitive impairment as well as the likelihood of developing AD. There is also a gene dosage effect, such that possession of two *APOE* ε4 alleles increases the risk further, and therefore subjects with two copies of *APOE* ε4 alleles have the earliest age of onset (Corder et al., 1993; Poirier and Davignon, 1993).

PRODUCTION OF β-AMYLOID (Aβ), THE MAIN PEPTIDE IN AD AMYLOID

Aβ is a normal proteolytic product of the much larger transmembrane protein APP. APP is usually cleaved by three proteases, known as the α-, β- and γ-secretases (Esch et al., 1990; Bodovitz and Klein, 1996; Soriano et al., 1999; Vassar et al., 1999). The α-secretase cleaves APP within the Aβ region, thereby preventing Aβ peptide production. Aβ is produced from APP *via* a two-step process involving the β-site cleaving by the β-secretase (BACE1) followed by the intramembrane cleavage by the γ-secretase enzyme. Depending on the γ-cleavage site, the γ-secretase yields Aβ peptides of 39–43 amino acids, and the most common, Aβ40, is synthesized in the early secretory and endocytic cellular pathways, whereas the more toxic and more readily aggregating Aβ42 is generated mainly in the secretory pathway (Esch et al., 1990; Bodovitz and Klein, 1996; Soriano et al., 1999; Vassar et al., 1999).

CHOLESTEROL CONNECTION TO AD

Cholesterol is a lipid that is essential for cell membrane structure and function, particularly in ion pumps and lipid rafts, which are specialized membrane microdomains that compartmentalise certain cellular processes. In particular, due to their higher cholesterol and saturated fat content compared to surrounding more fluid lipid bilayer membrane regions, lipid rafts provide the structural framework for signalling molecules and other proteins on the cell surface. Lipid rafts are involved in protein trafficking, signal transduction, neurotransmission, immunoglobulin function and many ligand-receptor interactions.

The γ-secretase cleavage of APP, the last step in Aβ peptide production, occurs in these cholesterol-rich lipid rafts. Aβ peptides are hydrophobic and their production and release from membranes are likely to be influenced by membrane lipid composition. For this reason as well as many others, membrane lipid composition plays an important role in the pathogenesis of the disease. Many studies have shown that changes in the levels of cholesterol in the lipid bilayer influence APP processing, resulting in changes in Aβ production (Sparks et al., 1994; Simons et al., 1998; Refolo et al., 2000; Kojro et al., 2001; Shie et al., 2002; Wahrle et al., 2002; Martins et al., 2009; Marquer et al., 2011). For example, Wahrle et al. (2002) demonstrated that γ-secretase activity could be abolished when membrane cholesterol is decreased, and restored by replenishing cholesterol. In other studies, a decreased level of membrane cholesterol was found to increase α-secretase cleavage of APP (Simons et al., 1998; Kojro et al., 2001). More recently, it has been shown that local increases in membrane cholesterol increase cleavage of APP by β-secretase (BACE1), and thus increase Aβ production, due to the resulting greater colocalisation of enzyme (γ-secretase) and substrate in lipid rafts (Marquer et al., 2011).

Placing rabbits and AD transgenic mice on high-cholesterol diets has been shown to increase Aβ deposition in the brain (Sparks et al., 1994; Refolo et al., 2000; Shie et al., 2002). Refolo et al. (2000) also have noted an increase in the deposit size of Aβ in hypercholesterolemic mice. A longer duration on a high-cholesterol diet also resulted in a more severe accumulation of Aβ in rabbit brains (Sparks et al., 1994). In our own study, a high-fat, high-cholesterol (HFHC) diet, known to influence Aβ levels, resulted in a significant increase in brain cholesterol esters (Lim et al., 2013). This increase in cholesterol esters was more profound in those older animals that carry the *APOE* ε4 alleles (Lim et al., 2013). These findings indicate that HFHC feeding is more deleterious in animals with the two major risk factors, age and *APOE* ε4 allele. The

effect of high-cholesterol feeding appears to target endolysosomes with the accumulation of free cholesterol, as reported by Chen and colleagues from their rabbit study (Chen et al., 2010).

It should be noted, however, that brain cholesterol levels are not thought to be altered in early stages of AD. Therefore, despite the increased levels of cholesterol in the diet, most studies have not found major changes in cholesterol levels in the brain, and in fact, evidence indicates that the brain controls its cholesterol levels independent of the periphery (Martins et al., 2009). On the other hand, the oxidative stress and inflammation that occur with ageing and AD, as well as diseases like cardiovascular disease and diabetes (often the consequence of HFHC diets), lead to oxidized cholesterol/phospholipids and oxidatively modified proteins (Yao et al., 2004; Gamba et al., 2012) which have been shown to disrupt normal membrane function, and accelerate Aβ aggregation and Aβ fibril formation.

OXYSTEROLS LINKED TO AD

Oxysterols are oxidized derivatives of cholesterol which mainly exist in combination with other oxysterols, in the presence of cholesterol (Brown and Jessup, 2009). Cholesterol does not enter the brain in significant amounts from the peripheral circulation, and therefore most of the brain cholesterol requirements are met by synthesis in the brain. However, the more polar oxysterols are able to pass freely through the lipophilic blood brain barrier (BBB) (Björkhem et al., 2006; Vaja and Schipper, 2007). Oxysterols are synthesised by various enzymes, and can also be produced non-enzymatically by reactive oxygen species. Oxysterols can control important lipid gene expression since oxysterols can bind liver X receptor, for example, and ultimately regulate the transcription of many lipid-related genes (Vaja and Schipper, 2007). Importantly, liver X receptors are known to regulate *APOE* expression.

Oxysterols such as 24-hydroxycholesterol (24-OH Chol) and 27-hydroxycholesterol (27-OH Chol) have been implicated in the pathogenesis of AD (Vaja and Schipper, 2007). 24-OH Chol is produced almost exclusively by brain-specific 24S-hydroxylase (CYP46A1; Fig. 1) and represents a homeostatic mechanism for the removal of excess cholesterol through the BBB *via* a concentration gradient. On the other hand, 27-OH Chol is produced mostly outside the brain, and it is formed by the enzyme sterol 27-hydroxylase (CYP27A1; Fig. 1) which is present in most organs and tissues (Heverin et al., 2005). Any 27-OH Chol in the brain is believed to be due to influx into the brain from the circulation *via* the BBB (Björkhem et al., 2006). In the brain, 27-OH Chol can be converted by the enzyme oxysterol 7α-hydroxylase (CYP7B1) into the steroid acid 7α-hydroxy-3-oxo-4-cholestenoic acid which is in turn eliminated from the brain (Meaney et al., 2007).

It has been suggested that alterations in oxysterol metabolism may contribute to the pathophysiology of AD and that oxysterols may be clinically relevant biomarkers (Björkhem et al., 2006). Levels of 24-OH Chol have in fact been reported to be altered in AD individuals (Table 1) (Lütjohann et al., 2000; Papassotiropoulos et al., 2002; Heverin et al.,

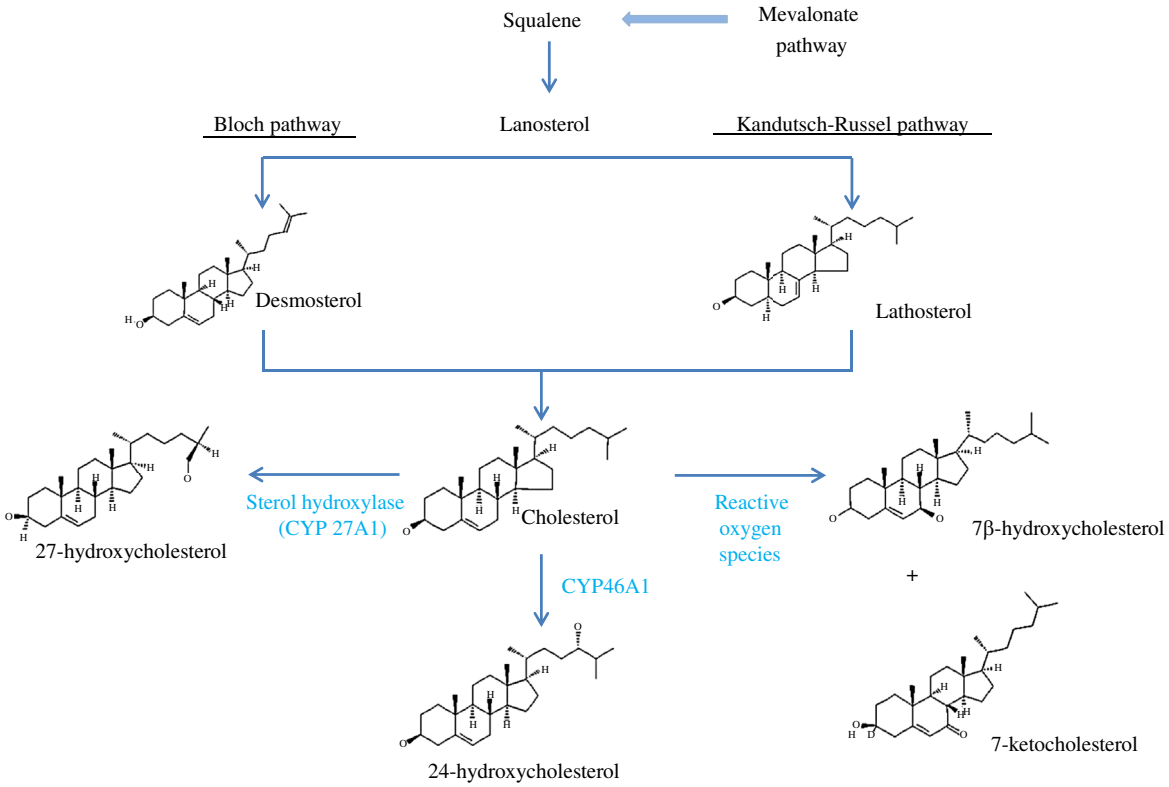

Fig. 1. Oxysterol synthesis pathway.

Table 1
24-hydroxylcholesterol (24-OH Chol) levels in Alzheimer's disease (AD) and mild cognitive impairment (MCI) individuals

Alteration of 24-OH Chol level	Reference
↑in AD (plasma)	Lütjohann et al., 2000; Shafaati et al., 2007; Zuliani et al., 2011
↑in AD (CSF)	Papassotiropoulos et al., 2002
↓in AD brain samples	Heverin et al., 2004
↓in AD (plasma)	Solomon et al., 2009
↑in MCI	Shafaati et al., 2007

2004; Shafaati et al., 2007; Solomon et al., 2009; Zuliani et al., 2011). However, the findings indicate that the levels of 24-OH Chol may vary depending on the stage of AD at the time of testing. When cholesterol-rich cell membranes are destroyed during neurodegeneration, excess cholesterol released may account for an increase in 24-OH Chol levels in the initial stages of AD (Lütjohann et al., 2000; Papassotiropoulos et al., 2002). However, as more neurons expressing 24S-hydroxylase die, the conversion to 24-OH Chol is reduced, and efflux from the brain could be less efficient (Papassotiropoulos et al., 2002). It has been suggested that higher 24-OH Chol level could reflect neurodegeneration that is occurring in the brain in early stages of AD, and thus may potentially be a biomarker of disease. For example, a recent study showed that people with higher plasma 24-OH Chol level and higher ratio of 24-OH Chol/27-OH Chol are more likely to develop cognitive impairment by an 8-year follow-up (Hughes et al., 2012). In this study, the higher 24-OH Chol was thought to reflect cholesterol-rich myelin degradation, believed to be a normal component of ageing, yet which is likely to be accelerated in cerebrovascular disease (a known AD risk factor) and early stages of AD (Bartzokis, 2011).

24-OH Chol has been shown to act as a signalling molecule, inducing ApoE-mediated cholesterol efflux from astrocytes, *via* direct effects on *APOE* transcription, protein synthesis and secretion. Interestingly, in the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL), it was observed that total plasma ApoE levels are significantly lower in patients with AD especially in the ε4 homozygous group. ApoE levels were also shown to decrease with increasing Aβ load, in the subset of people who underwent PiB-PET imaging (Gupta et al., 2011). In contrast, in a recent study of patients with cognitive impairment (patients with mild cognitive impairment or AD), the cerebrospinal fluid levels (CSF) of ApoE, tau (a highly soluble microtubule-associated protein that is abundant in neurons) and hyperphosphorylated-tau were significantly increased, together with 24-OH Chol, compared with controls. It was also found that the levels of tau and hyperphosphorylated-tau were significantly correlated with ApoE and 24-OH Chol levels in the same samples (Leoni et al., 2010). A significant correlation between CSF levels of ApoE and 24-OH Chol levels has also been observed in another study of both mild cognitive impaired and AD patients (Shafaati et al., 2007). CSF tau levels are considered to be indicative of levels of neurodegeneration, and the correlations between ApoE, 24-OH Chol and tau give evidence that changes in cholesterol metabolism may be involved in the generation of both tau and Aβ (Leoni et al., 2010).

Brain levels of 27-OH Chol have been shown to increase dramatically in AD. For example, in several areas of autopsied AD brains, levels of 27-OH Chol have been found to be significantly increased, and a greater influx of 27-OH Chol than efflux of 24-OH Chol has also been shown (Heverin et al., 2004). Similarly, an increase in 27-OH Chol levels has been observed in older mice carrying the "Swedish" mutation (Heverin et al., 2004), suggesting that age could possibly play a critical role in influencing 27-OH Chol flux into the brain. An examination of 27-OH Chol levels in the brains of familial AD patients with the Swedish *APP* 670/671 mutation has also revealed a 4-fold accumulation of this neurotoxic oxysterol (Shafaati et al., 2011). Interestingly, 27-OH Chol has been found to increase BACE1 activity in human neuroblastoma SH-SY5Y cells, apparently through its ability to influence the crosstalk between two transcription factors NF-κB and the growth arrest and DNA damage induced gene-153 (Marwarha et al., 2013). A review has also suggested that the transfer of 27-OH Chol from the circulation into the brain represents the missing link between AD and high cholesterol levels or hypercholesterolaemia (Björkhem et al., 2009).

Other less common oxysterols include 7β-hydroxycholesterol, 7-ketocholesterol, 5,6-α cholesterol epoxide, 5,6-β cholesterol epoxide and cholesterol triol which are formed as a result of oxidative damage to cholesterol. These oxysterols can be measured in trace amounts in human tissue (Iuliano et al., 2003; Lee et al., 2008). Since there is considerable evidence for oxidative damage during neurodegeneration, and cholesterol comprises a major lipid in the brain (about 2% w/w), oxysterols may be good indicators of neuropathology, and thus possibly serve as early biomarkers. However, oxysterol levels have been found to be elevated in other diseases that involve oxidative stress including atherosclerosis, liver cirrhosis and multiple sclerosis (MS) (Iuliano et al., 2003; Leoni, 2005; Jenner et al., 2007). Another study examined the effect of *APOE* genotype on the brain levels of oxysterols in *APOE* ε2, ε3, and ε4 knock-in (KI) mice at 2 months and 12 months, and observed significantly altered levels of 27-hydroxycholesterol, lathosterol, as well as oxidized cholesterol metabolites (Jenner et al., 2010) using GC-MS. Future lipidomics studies may reveal an AD-specific pattern of altered oxysterols that could form part of an AD diagnostic test.

Oxysterol formation can also be catalysed by Aβ (Nelson and Alkon, 2005) and several oxysterols including 24-OH Chol and 27-OH Chol have been reported to modulate protein aggregation and to accelerate Aβ misfolding (Brown et al., 2004; Bieschke et al., 2006; Famer et al., 2007), possibly leading to amyloid plaque deposition in AD. However, the molecular events that trigger or hasten Aβ misfolding and lead to amyloid plaque deposition in AD are still poorly understood, and many other lipids have been implicated.

LIPIDOMICS IN AD

As with the advent of genomics and proteomics, the rapidly growing field of lipidomics has allowed a new perspective into illnesses. Lipidomics can be defined as the global study of existing cellular lipid networks and pathways in biological systems (Wenk, 2005). Key technical advances in lipid analyses and their potential value in biomedical research have been recently reviewed (Lam and Shui, 2013).

Lipids, which include fatty acids, neutral fats, wax and steroids, are major constituents of cell membranes and also serve as intra- and intercellular signalling molecules (Mattson, 2004). They can be classified into fatty acyls, glycerolipids, glycerophospholipids, sterols, sphingolipids and prenol lipids (Wenk, 2005; Lam and Shui, 2013). Sphingolipids, which can be found in neuronal membranes, play an important role in signal transmission. There are three main types of sphingolipids: the ceramides (Cer), sphingomyelins (SM) and glycosphingolipids. Sphingolipid synthesis begins with the condensation of palmitoyl-coenzyme A and L-serine to form 3-dehydrosphinganine, which is metabolised by several enzymes to produce Cer (Futerman and Riezman, 2005; Grimm et al., 2007; Zinser et al., 2007). SM synthase metabolises Cer to produce SM (Futerman and Riezman, 2005).

Evidence that lipids apart from cholesterol are also involved in AD has been demonstrated by the major changes found in glycerophospholipids (Han et al., 2001; Goodenowe et al., 2007; Igarashi et al., 2011), Cer (Cheng et al., 2010) and sulfatides (Han, 2007; Cheng et al., 2010) in brain lipid composition. Furthermore, Kakio et al. (2003) have shown that lipid rafts act as surface catalysts, accelerating the aggregation of Aβ, a hallmark of AD and lipid raft lipid composition is critical for correct lipid raft function. Interestingly, an imbalance in phosphatidylinositol 4,5 biphosphate (PIP2) metabolism has been observed in individuals carrying *PS1* and *PS2* familial AD (FAD) mutations (Landman et al., 2006). These changes were shown in fibroblast cells from FAD individuals, indicating these changes may be detectable in peripheral cells, including cells from the circulation. The above studies give samples of the many changes in lipid metabolism that have been linked to AD. Some of these changes may prove to be valuable in the early diagnosis of AD, as discussed later.

Significant differences in plasmalogen phosphatidylethanolamine (PEp) have been observed in two AD studies investigating brain and serum lipids (Han et al., 2001; Goodenowe et al., 2007) respectively. Han et al. (2001) observed that the levels of PEp in the white matter decrease during very mild dementia and that when the symptoms of AD worsen, decreases in PEp levels are also seen in the gray matter. Goodenowe et al. (2007) noted a decline in serum levels of PEp that is in accordance with the severity of AD. Structural modifications in PEp have been observed in AD brain (Guan et al., 1999) and in a recent study of AD erythrocyte phospholipids, the respective ratios of PEp, phosphatidylethanolamine (PE) and phosphatidylserine (PS) to SM were low when compared to those of age-matched controls (Oma et al., 2012).

A depletion in sulfatide (SL) content (up to 90%) in gray matter and approximately 50% in white matter was demonstrated in some early lipidomics studies of AD, in all cerebral regions examined. Increases in Cer content were found in subjects with very mild AD, and was found to be related to the depletion of SL. The results suggest that the loss of SL content in very mild AD is lipid class-specific (Han, 2007). ApoE has been associated with SL transport through lipoprotein metabolism pathways where ApoE helps mediate SL homeostasis in the nervous system. It has also been found that alterations in ApoE-mediated SL trafficking can lead to SL depletion in the brain (Han, 2007). Recent transgenic mouse studies support this theory, as SL depletion did not occur in *APP* transgenic, $APOE^{-/-}$ animals relative to the $APOE^{-/-}$ littermates, whereas SL content was found to be deficient in *APP* transgenic, $APOE^{+/+}$ mice (Cheng et al., 2010). In our recent study investigating the effects of a HFHC diet on lipid profiles in young and aged *APOE* ε3 and ε4 KI mice, we found that SL levels were increased in the aged animals regardless of their *APOE* genotype and diet (Lim et al., 2013). Further studies are required to determine the potential role SL might play in the pathogenesis of AD.

Changes in levels of Cer content have been detected in AD. For example, levels of Cer 24:0 and galactosylceramide have been found to be significantly increased in the middle frontal gyrus in AD patients when compared to controls (Cutler et al., 2004). Han et al. (2002) have also observed an elevation in Cer content in the white matter of very early AD cases (Clinical Dementia Rating 0.5), yet the white matter Cer levels appear to decrease as dementia progresses beyond the mild cognitive impairment stage. Interestingly, higher Cer levels have been observed in the CSF of moderate AD cases, when compared to either mild or severe AD individuals (Satoi et al., 2005).

In other lipidomics studies of brain tissues of *APP* transgenic mice, an increase in arachidonic acid and its metabolites has been found, suggesting increased activity of the group IV isoform of phospholipase A2 (GIVA-PLA2). It was also found that activated GIVA-PLA2 levels in the hippocampus are higher in AD patients and in *APP* transgenic mice and that Aβ could cause a dose-dependent increase in GIVA-PLA2 phosphorylation. When the levels of GIVA-PLA2 were reduced in these AD-model mice, it was found that this could protect the mice against Aβ-induced deficits in learning and memory, suggesting that inhibition of this enzyme could be of therapeutic benefit in AD patients (Sanchez-Mejia et al., 2008). This study also found that hippocampal, but not cortical, levels of prostaglandin (PG) E2 and PGB2 are higher in the *APP* transgenic mice than in the non-transgenic mice (Sanchez-Mejia et al., 2008), consistent with increased hippocampal cyclooxygenase levels (COX-2).

Gangliosides are sialic acid-containing glycosphingolipids (GSL) that are expressed in the outer leaflet of the plasma membrane of all vertebrate cells. Aβ oligomerisation has been accelerated following the addition of lipid vesicles containing GM1 gangliosides. GM1 gangliosides are concentrated in microdomains or lipid rafts, and in AD brain, a complex of

GM1 and Aβ, termed "GAβ", has been found to accumulate. Kakio et al. (2003) showed that lipid rafts are able to accelerate the aggregation of Aβ and as mentioned above, these GAβ complexes have been suggested to act as seeds for further β sheet-like aggregation of Aβ (Ariga et al., 2008). More recent studies have shown that condensed membrane nanodomains or microdomains formed by sphingolipids and chol are privileged sites for the binding and oligomerisation of amyloidogenic proteins. It has been suggested that by controlling the balance between unstructured Aβ monomers and α or β conformers (the chaperone effect), sphingolipids can either inhibit or stimulate the oligomerisation of amyloidogenic proteins (Fantini and Yahi, 2010).

The above studies have shown that in the brain, membrane lipid composition can affect Aβ production and oligomerisation. However, many studies have shown that peripheral lipid levels that are highly affected by diet, also have effects on Aβ in the brain, and thus are likely to affect risk of AD. For example, studies have shown that high chol (or high chol and high fat) diets, which are known to affect plasma high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very low-density lipoprotein levels (VLDL), ratios and lipid composition, also influence Aβ deposition in the brain (Sparks et al., 1994; Refolo et al., 2000; Shie et al., 2002). In addition to this, *APOE* allele status and age are likely to influence the effect of diet, as many studies including previous studies by our laboratory have demonstrated subtle differences in the levels of lipids such as phosphatidylinositol (PI), phosphatidylcholine (PC), Cer, and SM between *APOE* ε4 and *APOE* ε3 KI mice, based solely on age (2 months *vs.* 12 months of age) and when fed a standard rodent diet (Sharman et al., 2010b).

Many reasons have been suggested for such effects of peripheral lipids on brain Aβ metabolism: 1) the modulation of Aβ metabolism; 2) diet significantly influence cerebrovascular integrity and may alter Aβ kinetics across BBB; 3) high saturated fatty acids and cholesterol diets appear to alter BBB integrity resulting in plasma protein leakage into the brain (Takechi et al., 2010). Dysfunction of the BBB is also believed to lead to decreased clearance of Aβ from the brain. Furthermore, lipids are generated and metabolised by enzymes, which are in turn influenced by environmental factors, especially diet (Wenk, 2010). Finally, high fat/high chol diets that are recognised to enhance the risk of heart disease, midlife obesity, insulin resistance and diabetes type II, are known to be involved with unfavourable plasma lipid profiles, as well as reduced blood flow to the brain, all of which are associated with AD.

LIPIDS ROLE IN ENDOSOMAL FUNCTION AND Aβ METABOLISM

Endosomes represent major sorting compartments within cells. They are membrane-bound vesicles that can transport proteins for example from the plasma membrane to the lysosome, or internally from the Golgi to the lysosome, and are usually differentiated into early, late or recycling endosomes. Many lipid and protein studies have led to findings of endosomal dysfunction in metabolic diseases as well as in AD (Cataldo et al., 2003; Zehmer et al., 2009; Yu et al., 2010; Treusch et al., 2011). Firstly, the endosomal-lysosomal pathway is involved in the proteolytic processing of APP to Aβ, and secondly, endosomal abnormalities have been found in AD, and importantly these can be found prior to amyloid and tau pathology in the neocortex (Burns and Rebeck, 2010). As a result, drug strategies that target endosomes and the transport of Aβ are gaining much interest (Zhang, 2008). Lipids such as cholesterol (Fig. 2) have been shown to be critical in endosomal transport. Other lipids and their distribution in membranes are also proving to be important in Aβ metabolism and transport, for example SM and glycosphingolipids on the inner membrane and anionic phospholipids on the outer membrane (PS and PE). The "health" of such lipids is also important in Aβ metabolism, since changes such as lipid peroxidation can disrupt normal lipid and membrane function (Gruenberg, 2003; Pichler and Riezman, 2004; Fadeel and Xue, 2009; Nichols, 2009). Maintaining healthy PI levels (Fig. 2) is essential for membrane cholesterol and Aβ homeostasis in AD (Stokes and Hawthorne, 1987; Bothmer et al., 1994; McLaurin et al., 1998; Zubenko et al., 1999; Stamler et al., 2000; Burgess et al., 2003, 2005; Alarcon et al., 2006) as this lipid influences APP processing, endosomal protein sorting, Cer generation and cell survival (Burow et al., 2000; Cordy et al., 2003; Nichols, 2009; Vetrivel et al., 2011).

The "Aβ peripheral sink" hypothesis involves the flow of Aβ from the brain to the periphery followed by rapid degradation or removal by tissues such as the liver and kidneys. This removal appears to require healthy sphingolipids and cholesterol metabolism and is critically dependent on endosomal Aβ transport (Pichler and Riezman, 2004; Fantini and Yahi, 2010; Tamboli et al., 2011; van Echten-Deckert and Walter, 2012; Petelska and Figaszewski, 2013) and the endosomal/lysosomal pathways (Ditaranto-Desimone et al., 2003; Soreghan et al., 2003). In *APOE* ε4 individuals, membrane lipid composition is altered to an extent, and these alterations lead to significant changes in membrane biology causing the promotion of pathways that increase the likelihood of Aβ accumulation (Hatters et al., 2005; Morishima-Kawashima et al., 2007; Altenburg et al., 2008). ApoE is important in the rapid trafficking of Aβ to the liver from the brain. Both ApoE and LDL receptor are essential for the metabolism of Aβ in the brain and liver. In many studies, *APOE* ε4 has been shown to be less efficient compared to *APOE* ε3 and *APOE* ε2 in helping Aβ exit the brain and less efficient in helping Aβ is delivered to intracellular degradation pathways *via* the LDL receptor, indicating why *APOE* ε4 individuals may be more susceptible to developing AD (Sharman et al., 2010a; Li et al., 2012). However, some studies have shown that ApoE and Aβ interactions occur minimally in plasma and in the CSF of human subjects, while this ApoE isoforms can influence astrocyte Aβ clearance rates. It had been suggested instead that ApoE and Aβ compete for the low-density lipoprotein receptor-related protein 1 (LRP1)-dependent cellular uptake pathway for

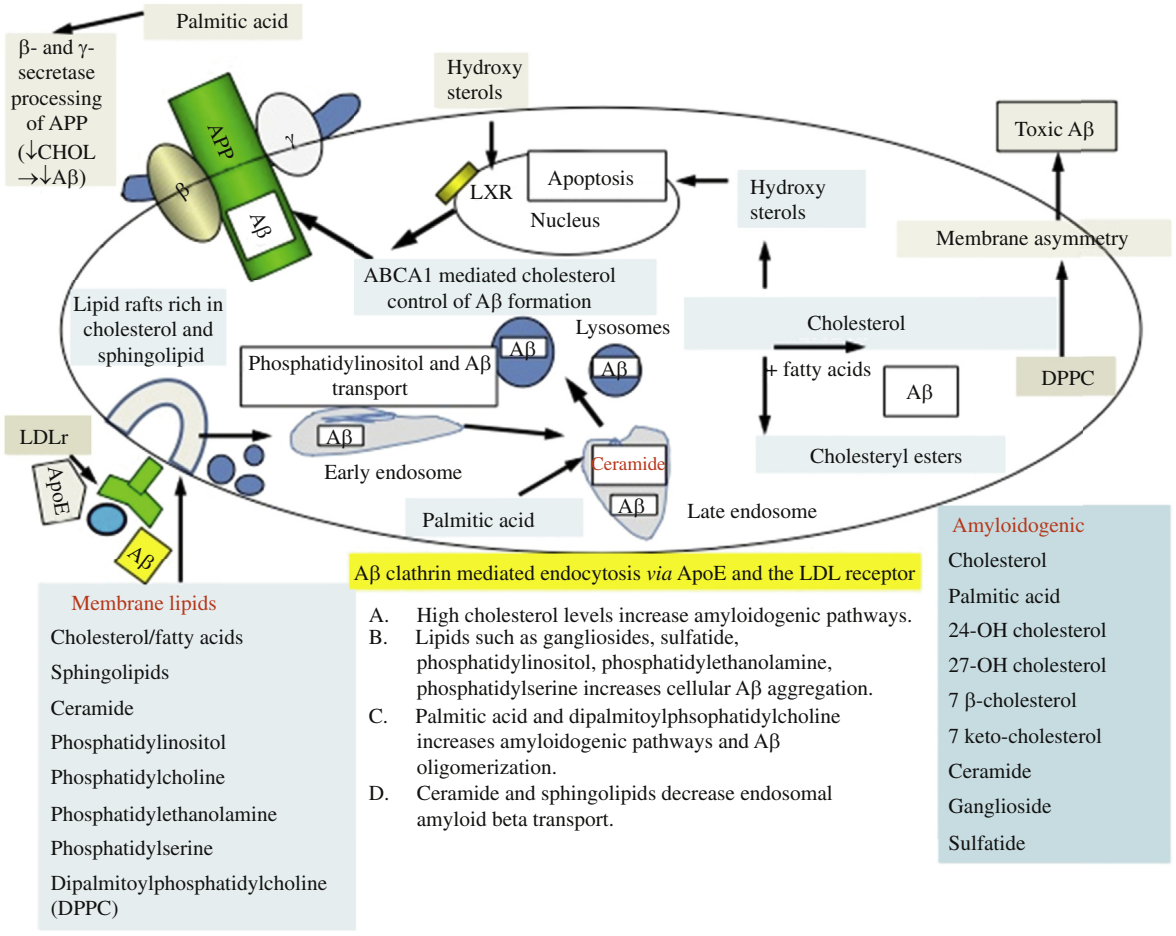

Fig. 2. Diets that are high in fat and cholesterol increase lipids that promote Aβ aggregation with abnormal endosomal transport of Aβ to lysosomes.
A−D show roles of lipids during AD pathogenesis. Aβ, β-amyloid; APP, amyloid precursor protein; Chol, cholesterol; LXR, liver X receptor; β, β secretase; γ, γ secretase; DPPC, dipalmitoylphosphatidylcholine.

example, suggesting that ApoE isoform effects may be due to different ApoE isoform affinities for certain receptors or transporters (Verghese et al., 2013).

MEMBRANE LIPIDS AND Aβ AGGREGATION AND TOXICITY

Many studies have concluded that the interactions between Aβ and cellular membranes contribute to the toxicity and cell death observed in AD. Aggregated Aβ species have been shown to disrupt membranes, leading to physical instability and ion leakage. It has been found that oligomeric Aβ binds more avidly to membranes and causes greater permeation than fibrillar Aβ, which may explain the findings that Aβ oligomers are the most toxic Aβ species (Williams and Serpell, 2011). Some studies have investigated Aβ aggregation and toxicity by adding Aβ in aqueous solution to artificial membranes or cells, whereas other researchers have investigated Aβ production from the transmembrane APP, membrane Aβ aggregation or release from membranes. Thus, studies have produced apparently conflicting results, yet these will eventually produce a clearer picture of Aβ-membrane interactions.

The influence of the lipid composition of plasma membranes in Aβ insertion, aggregation and/or toxicity has been investigated. Membrane fluidity in certain domains, and the charge of membranes have also proven to be relevant when investigating Aβ aggregation (Vargas et al., 2000; Choucair et al., 2007; Sabate et al., 2012; Lemkul and Bevan, 2013). For example, the presence of ganglioside GM1 promotes release of the peptide into the extracellular medium. Lemkul and Bevan (2011) found that Aβ interacted with GM1 largely through hydrogen bonding, producing configurations containing β-strands with C-termini that, in some cases, exited the membrane. However, in another recent study, it was found that once Aβ aggregates had formed within a membrane, they were unlikely to exit the membrane (Lemkul and Bevan, 2011). Interestingly, a recent study has found that an enzyme necessary for GM1 production, SM synthase, influences Aβ generation — inhibition of enzyme activity significantly reduces the level of Aβ in a dose- and time-dependent manner (Hsiao et al., 2013). In another study, it was found that Aβ β-pleated sheets formed preferentially in non-polar environments, and the study concluded that ganglioside (Fig. 2) clusters mediate the formation of toxic

amyloid fibrils of Aβ with an antiparallel β-sheet structure by providing less polar environments (Fukunaga et al., 2012).

An investigation into the effect of membrane charge on Aβ found that lipids did not need to be anionic for interaction with Aβ, as Aβ inserts into both cationic dipalmitoyltrimethylammonium propane (DPTAP) and anionic dipalmitoylphosphatidylglycerol (DPPG) monolayers under physiologically relevant conditions (Ege and Lee, 2004). More recently, it was again found that charge influences Aβ soluble species, such that the insertion and surface association of Aβ peptide with membrane increase in a membrane charge-dependent manner (Sabate et al., 2012). The study found that there may be a balance between peptide insertion and surface association that modulates Aβ aggregation, influencing amyloid fibrils concentration as well as morphology. In other studies, electrostatic interactions between Aβ and phospholipid headgroups were found to influence the association and insertion of Aβ monomers into lipid monolayers, and Aβ exhibit enhanced interactions with charged lipids compared with zwitterionic lipids. It has also been suggested that the adsorption of Aβ to anionic lipids, which could become exposed to the outer membrane leaflet as a result of cell injury or oxidative damage, may promote Aβ aggregation (Chi et al., 2008).

Lipid peroxidation can itself be induced by Aβ, particularly by Aβ42, producing 4-hydroxynonenal (HNE) and 2-propenal (acrolein), two reactive products. Synaptic loss occurs early in AD, and an early signal of synaptosomal apoptosis is the loss of correct phospholipid asymmetry and the appearance of PS in the outer leaflet of the membrane. It has been shown that the enzyme flippase, which is critical for the right positioning of PS, may be damaged by HNE or acrolein (Mohmmad Abdul and Butterfield, 2005). Put together, these few studies demonstrate how Aβ aggregation appears to be highly dependent on membrane lipid composition and membrane damage level, yet in turn Aβ can itself also cause oxidative damage to lipid membranes, forming part of the vicious circle of oxidative stress and increasing Aβ production and toxicity that lead to AD pathogenesis.

Interactions between lipids in cell membranes (non-clathrin-mediated) and Aβ possibly contribute to the toxicity and cell death found in AD. Amyloidogenic lipids such as chol and zwitterionic dipalmitoylphosphatidylcholine (DPPC) form aggregated Aβ oligomers that disrupt membranes leading to physical instability and alterations in receptors and ion channels. The presence of DPPC on the membrane surface increases the Aβ aggregation with interpeptide interactions. The preferential accumulation of Aβ on these DPPC domains suggests that rigid domains may act as platforms to enhance its aggregation. ApoE bound to DPPC membranes (Peters-Libeu et al., 2007) indicate that ApoE-DPPC particles are ellipsoidal and compatible with a twisted-bilayer cell model with binding of ApoE to the LDL receptor (clathrin-mediated endocytosis). The transport of Aβ in endosomes is controlled by the cell membrane. An increase in lipids such as chol, DPPC and sphingolipids influences membrane interactions resulting in increased membrane Aβ aggregation (Fig. 2) compared with the cellular endosomal Aβ transport (Ege and Lee, 2004; Mohmmad Abdul and Butterfield, 2005; Hane et al., 2011; Williams and Serpell, 2011).

DIET, OBESITY, DIABETES, NAFLD, CARDIOVASCULAR DISEASE AND LINKS TO AD

Obesity, type 2 diabetes, cardiovascular disease and many associated conditions are all on the rise around the world, and are also known risk factors for AD (Martins et al., 2006, 2012, 2013a). Non-alcoholic fatty liver disease (NAFLD), the most common liver disease, is also rising rapidly as a result of the increased incidence of obesity and type 2 diabetes (Puppala et al., 2013). These conditions can all be linked to high-fat diets and sedentary lifestyles (Puppala et al., 2013). Diets low in SM and Cer prevent NAFLD (Bikman and Summers, 2011; van Echten-Deckert and Walter, 2012), and these sorts of diets also favour the non-amyloidogenic pathways for rapid Aβ liver endocytic breakdown (Fig. 2).

Diets that are high in fat and cholesterol that increase the amyloidogenic pathways resulting in an increase in brain Aβ levels have become important to research into neurodegeneration and AD (Fig. 3). These atherogenic diets without calorie restriction elevate brain Aβ levels and activate the SMase-Cer pathway, causing increases in lipid mediators such as Cer, sphingosine, sphingosine-1-phosphate that act as second messengers, which in turn have been shown to accelerate

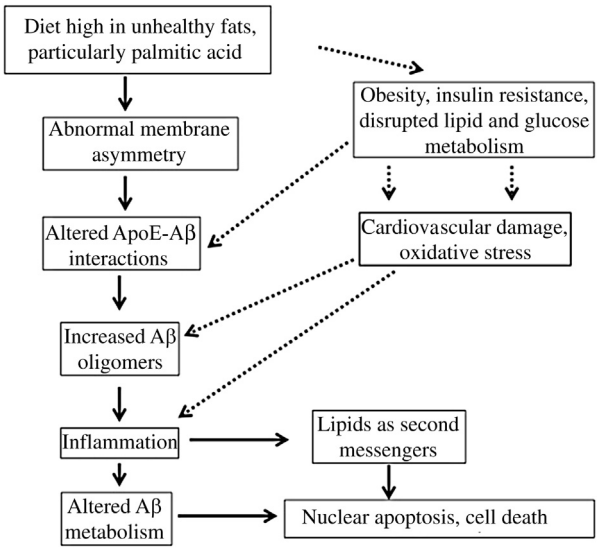

Fig. 3. Diets that induce the metabolic syndrome and cardiovascular disease are associated with abnormal lipid membranes and increased Aβ oligomer formation.

Diets high in unhealthy fats, particularly palmitic acid, have been shown to disrupt normal lipid membrane structure, thus affecting Aβ metabolism directly. Such lipids are also likely to influence APP and Aβ metabolism indirectly *via* the health consequences of obesity, insulin resistance, type 2 diabetes, cardiovascular disease, causing oxidative and metabolic stress, eventually leading to cell death. The dashed arrows illustrate that increased insulin resistance and oxidative stress are associated with altered ApoE-Aβ interactions with reduced Aβ metabolism.

neuronal apoptosis, partly *via* endosomal/lysosomal dysfunction (Burow et al., 2000; Ditaranto-Desimone et al., 2003; Soreghan et al., 2003; Zinser et al., 2007).

Diets high in palmitic acid result in an increase in DPPC in membranes (Fig. 2). This has been shown to cause acceleration of Aβ formation and aggregation, which disturbs the maintenance of correct charge, membrane fluidity and membrane phase, eventually leading to cell apoptosis (Ege and Lee, 2004; Ji et al., 2005; Patil et al., 2006; Hane et al., 2011). There is much evidence that small Aβ oligomers are the most toxic forms of Aβ for cells and membranes. Lowering the palmitic acid (and/or other saturated and unhealthy fats) levels in the diet would reduce oxidative stress and inflammation and allow correct membrane bilayer and domain interactions, facilitating ApoE interactions amongst others. This would promote the normally rapid endosomal/lysosomal Aβ transport important in the prevention of toxic oligomers and fibril formation. Lowering saturated fat intake would also reduce Aβ production and accumulation *via* a more indirect route − by reducing the metabolic disturbances caused by obesity, insulin resistance and other health conditions, as shown in Fig. 2. The global obesity pandemic which is causing huge increases in the incidence of health conditions such as insulin resistance, type 2 diabetes, cardiovascular disease and hypertension, amongst others, is likely to cause an increase in neurodegeneration (Martins et al., 2012, 2013a) as all of these conditions are risk factors for AD.

The mechanisms linking obesity with diabetes are not fully understood, but the statistics do indicate that most patients with type 2 diabetes are obese. The health problem is substantial: for example, in the US, over a third (34%) of adults are obese and about 11% of these individuals have diabetes (Martins et al., 2013a). The incidence of diabetes is predicted to increase to 21% by 2050, and the understanding of mechanisms which connect these two conditions, is becoming central to AD research due to the growing evidence of links between insulin resistance and neurodegeneration. Lipid homeostasis is disturbed in both conditions, and lipidomics studies are being carried out to help characterise lipid biomarker profiles for each of these conditions as well as AD (Meikle and Christopher, 2011). Comprehensive lipid studies may provide lipid biomarkers (most likely in conjunction with protein biomarkers) useful in terms of specificity, sensitivity and standardization with respect to AD. Biomarkers that can indicate disease severity or progression stage would be ideal. For the foreseeable future, reversal of AD damage is unlikely, and thus at best clinicians can suggest preventative treatments and lifestyle (diet and exercise) changes that will reduce the progression of neurodegeneration, with the added benefit of reducing the progression of cardiovascular and liver disease.

The links between obesity and diabetes indicate that systemic inflammation, amyloidogenic pathways and neuroinflammation are important factors that connect the two conditions. In recent publications, inflammation, disturbances in lipid metabolism and lipid peroxidation have been shown to occur in early stages of AD, along with evidence that these factors lead to neuroinflammation (Tuppo and Arias, 2005; Wyss-Coray and Rogers, 2012). Inflammatory cellular components that have been linked to AD include complement proteins, inhibitors, Aβ, cytokines and chemokines (Grimble, 1998; Calder, 2002; Nagao and Yanagita, 2008). The metabolic syndrome, inflammation and cardiovascular risk factors have been shown to be associated with dementia and cognitive decline (Yaffe et al., 2004). Oxidized lipids and apoptosis induced by the inflammatory changes in the metabolic syndrome are possibly linked to AD (Holvoet, 2008).

Lipids that have shown changes due to the metabolic syndrome and/or AD that have been linked to inflammation include n-3 polyunsaturated fatty acids (arachidonic metabolites), conjugated fatty acids, sterols, medium-chain fatty acids, diacylglycerols and phospholipids (Nagao and Yanagita, 2008). Changes in these lipids have been shown to be involved in liver nuclear disturbances in conditions such as NAFLD, and similar changes are now being shown to be associated with the early stages of neurodegeneration and the development of AD (Nagao and Yanagita, 2008; Malaguarnera et al., 2009). For example, in AD, lipid mediators and second messengers (eicosanoids, docosanoids, diacylglycerols, platelet activating factor, lysophosphatidic acid, Cer and Cer 1-phosphate, sphingosine and sphingosine 1-phosphate and hydroxycholesterols) derived from glycerophospholipids, sphingolipids and chol are involved with inflammation and neuronal apoptosis (Puglielli et al., 2003; Lee et al., 2004; Holland and Summers, 2008; Gill and Sattar, 2009; Farooqui et al., 2010; Schmitz-Peiffer, 2010; Lipina and Hundal, 2011).

Individuals with the conditions of obesity and diabetes, known risk factors for AD (Martins et al., 2006, 2012, 2013a), have elevated levels of sphingolipids and Cer, and these lipids are known to be closely involved in defective insulin actions in these conditions (Holland and Summers, 2008; Gill and Sattar, 2009; Arana et al., 2010; Schmitz-Peiffer, 2010; Lipina and Hundal, 2011). AD individuals have also been shown to have elevated levels of sphingolipids and Cer in the blood plasma (Puglielli et al., 2003; Lee et al., 2004; De La Monte, 2012). Elevations of lipids such as sphingolipids and Cer in the plasma of insulin resistant and AD individuals provide further evidence of the disruption of hepatic Aβ endosomal/lysosomal pathways that involve inflammation and lipid metabolism (Holland and Summers, 2008; Gill and Sattar, 2009; Arana et al., 2010; Schmitz-Peiffer, 2010; Lipina and Hundal, 2011). Abnormally high levels of Cer result in damaged endoplasmic reticulum function and disrupted endosomal/lysosomal pathways, leading to inflammation. It has been suggested that Cer may transfer across a damaged BBB to cause inflammation and insulin resistance in the central nervous system (CNS), leading to neurodegeneration and AD (De La Monte, 2012).

LIPIDOMICS AND AD BIOMARKER DISCOVERY

Abnormal lipid profiles have been known to be associated with the metabolic syndrome and AD for over a decade (Kuo et al., 1998; Roher et al., 1999; Merched et al., 2000). Plasma

lipidomics allows the detection of sphingolipids and glycerophospholipids such as Cer, PI and PE that are present in very small amounts in the plasma. Changes in lipids disturb plasma membrane asymmetry (Axelsen et al., 2011), and this is likely to disturb peripheral liver Aβ endosomal metabolism that is essential for mediating the clearance of Aβ *via* ApoE- or another apolipoprotein-mediated pathway.

It is also known that peroxisome function is disturbed in AD, and this has been shown to lead to deficits in both ethanolamine and choline plasmalogens and the accumulation of very long chain fatty acids (Wood, 2012). The major changes detected in brain lipid composition can be summarised as follows − in white matter, over 50% depletion in SL content large increases in Cer and decreases in PEp early in the disease process (Iqbal et al., 2005), whereas in grey matter SL are reduced by about 90%, and PEp levels decrease with increasing disease severity (Han et al., 2001, 2002). With such major alterations in CNS glycerophospholipids and sphingolipids, it is highly likely that plasma lipid profiles might also be altered.

Lipidomics studies have shown that there may be up to 500 different plasma and cell lipid molecular species (Quehenberger et al., 2010). Thus, it is likely that changes or disturbances in the normal profile of this array of lipids will one day assist in the understanding of the roles of lipids in the circulation as well as in cell membranes in AD pathogenesis, and will help provide much-needed disease biomarkers. Lipidomics has also recently been shown to be capable of differentiating the subcortical ischemic vascular dementia (SIVD) and mixed dementia (SIVD and AD) (Lam et al., 2014).

In summary, lipids are closely associated with AD through their involvement with membrane fluidity, Aβ transport and metabolism, Aβ aggregation and toxicity and endosomal function. Lipidomics is a powerful approach not only as a diagnostic tool but providing powerful insight into the mechanism involved in AD as well as other diseases. This approach has the propensity to differentiate between SIVD and mixed dementia and will be useful in the differentiation of various neurodegenerative diseases such as Parkinson, AD, Schizophrenia, etc. Lipids have been shown to play a fundamental role in influencing the various risk factors of AD and to be closely involved in the pathogenesis of AD. The race is now on to develop a diagnostic kit which will then allow for early detection and potential intervention of this debilitating disease.

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