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# Links between Insulin Resistance, Lipoprotein Metabolism and Amyloidosis in Alzheimer's Disease

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## Abstract

The origins of premature brain aging and chronic disease progression are associated with atherogenic diets and sedentary lifestyles in Western communities. Interests in brain aging that involves non alcoholic fatty liver disease (NAFLD), the global stroke epidemic and neurodegeneration have become the focus of nutritional research. Atherogenic diets have been linked to plasma ceramide dysregulation and insulin resistance actively promoting chronic diseases and neurodegeneration in developed countries. Abnormal lipid signaling as observed in chronic diseases such as hypothyroidism, obesity and diabetes is connected to stroke and neurodegenerative diseases in man. Lipids that are involved in calcium and amyloid beta homeostasis are critical to cell membrane stability with the maintenance of nuclear receptors and transcriptional regulators that are involved in cell chromatin structure and DNA expression. Western diets high in fat induce hyperlipidemia, insulin resistance and other hormonal imbalances that are linked to alterations in brain calcium and lipid metabolism with susceptibility to various chronic diseases such as stroke. Nutrition and food science research identifies dietary components and lipids to prevent hyperlipidemia and calcium dyshomeostasis connected to neuroendocrine disease by maintaining astrocyte-neuron interactions and reversing hormonal imbalances that are closely associated with NAFLD, stroke and Alzheimer's disease (AD) in global populations.

## Keywords

Nutrition, Hyperlipidemia, Ceramide, Calcium, Neuron, Astrocyte

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## 1. Background

Alzheimer's disease (AD) is the commonest form of dementia initially identified by Alois Alzheimer in 1906. It is a chronic, progressive neurodegenerative disease manifesting clinically as a disturbance in multiple higher functions of the brain, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgment. It can also be accompanied by deterioration in emotional control, motivation or social behavior [1] [2]. In advanced stages, care by family members and caregivers is required to assist with daily living and ultimately an inability to recognize family members exacerbates the huge emotional burden. On average, the disease progresses from initial mild symptoms to severe dementia, with many sufferers requiring institutional care for many years.

Age stands as the greatest risk factor for AD and with an aging population a significant increase is predicted in the number of AD cases in both the developed and developing countries of the world [3] [4]. In Australia, approximately 300,000 people are suffering from dementia with this figure expected to reach to about 1 million by 2050 [3]. Current estimates put a direct cost of \$AUD3.2 billion to the healthcare system in Australia with a predicted increase of \$AUD6 billion within the next five years [5]. According to the Alzheimer's association in the United States unpaid care by family members and caregivers in 2009 represented \$144 billion. These alarming statistics emphasize the importance of gaining a greater understanding of the pathophysiology of AD with the aim of developing tests that will identify those at risk before the clinical hallmarks of AD manifest.

The type and amount of food eaten have a major influence on plasma lipid profiles [6]-[8] with dietary habits and nutritional status emerging as major contributors of any chronic degenerative disease. The well established risk factors for developing AD are elevated cholesterol and dyslipidemia, obesity, diabetes, hypertension, depression, cardiovascular and cerebrovascular disease, all of which are biochemically connected and are influenced by diet and possible nutrient deficiencies. Apart from dietary fatty acids being an energy generating nutrient, the amount and type of fat are important for determining disease risk due to the diverse functions of lipids in general; the structure and function of lipids are influenced by the diet. Intake of high saturated fat, trans-fatty acids, refined sugar, processed foods, and total calories [6] is strongly associated with the development of dyslipidemia, insulin resistance, obesity, diabetes, vascular disease and metabolic abnormalities; all risk factors for AD [9]-[11].

Neurodegeneration involves the accelerated aging of neurons leading to alterations in shape, size and stability of neurons. A link between premature aging, diet and nutrition is suggested with nutrigenomic research uncovering possible mechanisms such as epigenetic modifications that demonstrate the interaction between genes and environment. This includes various lipids species that influence calcium homeostasis and gene expression affecting cell survival [12]-[20]. Dietary modifications may help reduce the effects of metabolic dysfunction and associated endocrine abnormalities and lessen the global impact of chronic diseases such as diabetes, stroke, cardiovascular disease and neurodegenerative conditions, including Parkinson's disease (PD) and AD. Amyloid plaques are a characteristic feature of AD and contain aggregates of amyloid beta ( $A\beta$ ), a 4kDa peptide of 39 - 43 amino acids normally found in the brain, albeit at low concentrations [21] [22]. Cholesterol and other lipids play a major role in  $A\beta$  metabolism and abnormal lipid metabolism is emerging as a key feature of AD pathology [23]-[25], with AD related changes in brain lipid composition reported [26].

Additionally abnormalities in various lipoproteins such as low density lipoprotein (LDL), high density lipoprotein (HDL) and their sub-classes are reportedly linked to AD [27]-[29]. Lipids in the nervous system also show enormous structural diversity and studying abnormal lipid profiles and levels of individual species may lead to a greater understanding of AD pathology. It is evident that many neurological disorders involve a complex interaction of proteins and lipids, which lead to the increased formation of  $A\beta$  deposits [30]. A key development in the study of lipids and neurodegenerative disease has been in the advancement of technologies utilized in lipidomic research. These tools are leading to a greater understanding of AD and other conditions involving altered lipid metabolism, such as cardiovascular disease and diabetes and may facilitate the identification of disease biomarkers [31].

## 2. Metabolic Dysfunction Increases Ceramide Levels with Amyloidosis

In recent years numerous reports have highlighted the strong relationship between dementia and metabolic disorders such as dyslipidemia, obesity, diabetes, cardiovascular disease and hypertension (reviewed in [32]-[37]). While the mechanisms that underpin this association are beyond the scope of this review, it is important to em-

phasize that the above conditions rarely occur in isolation, and the complex network of metabolic dysfunction which occurs in these conditions has been shown to influence many aspects of AD pathogenesis and neurodegeneration. For example, insulin is required for blood glucose regulation in the periphery and the brain. When peripheral insulin resistance (IR) develops metabolic dysfunction occurs and brain insulin signaling is altered affecting glucose utilization, A $\beta$  and tau pathology, vasculature, mitochondrial function, inflammation, oxidation, neuronal maintenance and plasticity [32] [38]-[42].

Due to the integrated nature of the endocrine system virtually all hormones are likely to have some influence on lipid metabolism and therefore influence a myriad of cellular functions. The literature has many reports and studies into the effects of hormones on AD with virtually all known metabolic hormones being involved including insulin, thyroid, cortisol (and other non-sex steroids), growth hormone, leptin, ghrelin and adiponectin [43]-[45]. Insulin has a major influence on peripheral plasma lipid profiles such as very low density lipoproteins (VLDL), LDL and HDL and when insulin resistance is present such as in obesity the increased circulating free fatty acids (FFA) released from increased adipose tissue lipolysis eventually lead to increased hepatic VLDL secretion with disturbed cholesterol metabolism associated with increased amyloid burden [46].

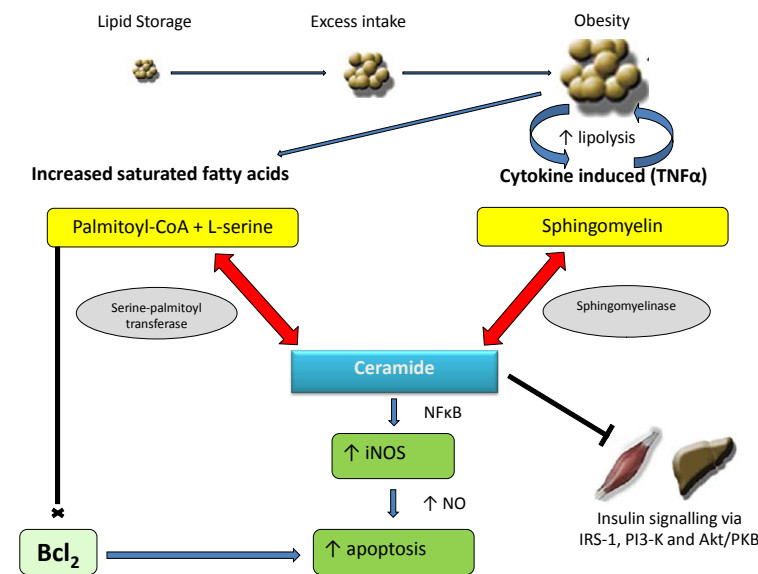
A neurodegenerative cycle consisting of AD pathogenesis, insulin resistance and inflammation has often been described. The components of this cycle have elevated ceramide levels as a common factor (Figure 1), suggesting these toxic lipids alter lipoprotein composition and may represent the link between pieces of the AD puzzle [47] [48]. Emerging evidence suggests an association between insulin resistance and ceramide where toxic ceramides may be the intermediate that links excess dietary saturated fatty acids and inflammatory cytokines with insulin resistance [48].

In obesity ceramide metabolism is abnormal with the release of various sphingolipids and their metabolites from adipose tissue [49]-[55]. In both rodent obese models and in man plasma levels of various ceramide species have been shown to be elevated. Sphingosine-1-phosphate (S1P), a break down product of ceramide has been shown to associate with various lipoproteins and albumin in human plasma and regulate receptor lipoprotein interactions when abnormal lipoprotein metabolism occurs [55]-[57]. Interaction of S1P with other blood components such as platelets indicates lipoprotein abnormalities [58]-[62]. Changes in AD plasma also include platelet abnormalities where abundant amounts of S1P are stored. The early activation of platelets in insulin resistance and obesity releases A $\beta$  into the periphery and the CNS with previous studies indicating the major involvement of platelets in A $\beta$  release as a major source of the peptide in the circulation. In obese individuals platelet dysfunction [62] [63] S1P and A $\beta$  may also be relevant to A $\beta$  homeostasis in AD [64] [65].

Abnormal ceramide metabolism in obesity and AD is important to the ceramide-cholesterol membrane interactions which can result in an imbalance in sphingolipid-cholesterol ratio in the cell membranes. Cellular ceramide accumulation alters a number of signal transduction events with marked shift in cellular bioenergetics with the progression of metabolic disease in the liver, heart and brain with particular relevance of insulin resistance and AD. Lipidomic profiling of plasma ceramide [66]-[69] has become important with ceramide levels associated with hepatocellular apoptosis (NAFLD), abnormal insulin synthesis and inflammation with ceramide now referred to as a cardiotoxin with lipotoxic cardiomyopathy [66]-[69]. Ceramide levels have been shown to be increased in the plasma, CSF and brain of AD individuals with abnormal sphingolipid metabolism linked to the metabolic syndrome and impairment of A $\beta$  generation and degradation in AD [70]-[76].

The link between AD and lipid metabolism was firmly established when the APOE $\epsilon$ 4 genotype was identified as a major risk factor for AD [77]. In humans the apoE gene is located on chromosome 19q13.2 [78] and encodes for a 299 amino acid protein of which has three isoforms;  $\epsilon$ 2,  $\epsilon$ 3 and  $\epsilon$ 4, resulting from the substitution of a cysteine with an arginine residue at codons 112 and 158 [79] [80]. Despite the amino acid difference at only one or two codons, the risk of developing various diseases is quite significant due to the conformational change and the influence this has on binding capacity [81] [82]. The following table (Table 1) shows allele frequencies in Caucasian and Australian populations and their influence on disease risk: It is estimated that being homozygous for APOE $\epsilon$ 4 increases the risk of developing AD by the age of 75 by ten to thirty times compared to non-carriers of APOE $\epsilon$ 4. APOE $\epsilon$ 2 appears to be protective in terms of risk even when present with APOE $\epsilon$ 4.

Apolipoprotein E (apoE) is an essential lipid transporter and component of triglyceride rich particles, such as chylomicrons and VLDL with cholesterol metabolism of chylomicron remnants and LDL regulated in an isoform-dependant manner via the LDL receptor family [24] [25]. In recent years the understanding of the interaction between apoE, lipids and A $\beta$  has been predicted lipids as key components of membranes, providing an environment conducive for fluidity, ion permeability and regulating trafficking and proteolytic activity of the



**Figure 1.** Ceramides—the toxic intermediate linking metabolic dysfunction, inflammatory cytokines and insulin resistance. When adipose tissue exceeds its storage capacity, adipokines increase inflammation which increases ceramides. This inhibits insulin signaling further increasing lipolysis and increasing the release of fattyacids for ceramide synthesis. Ceramide promotes apoptosis and the elevated saturated fatty acids inhibit the Bcl<sub>2</sub> of anti-apoptotic proteins.

**Table 1.** ApoE gene frequency and disease risk [84]–[89].

Genotype	Allele Frequency	Disease Association
APOEε2 (Cys <sup>112</sup> Cys <sup>158</sup> )	7%	↑ and ↓ risk for atherosclerosis [81] and ↑ risk for Parkinson's Disease [83]
APOEε3 (Cys <sup>112</sup> Arg <sup>158</sup> )	79%	Considered neutral
APOEε4 (Arg <sup>112</sup> Arg <sup>158</sup> )	14%	↑ risk for atherosclerosis, AD, cognitive impairment, ↓hippocampal volume, faster progression of multiple sclerosis, cerebrovascular disease and sleep apnea [84]–[91]

key membrane-bound proteins including (amyloid precursor protein) APP, ( $\beta$ -site APP cleaving enzyme) BACE and  $\gamma$ -secretase involved in AD [24] [25]. Lipid rafts are domains within the plasma membrane bilayer consisting of cholesterol, glycosphingolipids and protein receptors. APP clusters in cholesterol-rich lipid rafts of neurons, astrocytes and microglia [92] [93]. These specialized regions compartmentalize cellular processes and act as organizing centers for assembly of signaling molecules. Rafts also influence membrane fluidity and are involved with membrane protein and receptor trafficking and the regulation of neurotransmitters [94].

Increased cellular ceramide levels regulate cellular cholesterol levels with effects on APP-A $\beta$  processing [24] [25]. A $\beta$  is produced by cleavage of APP and APP can be processed by two different pathways a non-amyloidogenic pathway by  $\alpha$ -secretase or the amyloidogenic pathway by BACE [24] [25]. In both cases initial cleavage is followed by an additional cleavage by  $\gamma$ -secretase [95]–[97].  $\alpha$ -secretase cleaves within the A $\beta$  domain of APP liberating a soluble APP fragment (APPs $\alpha$ ) which precludes the formation of A $\beta$  which has neurotrophic and neuroprotective properties [95]. The immediate precursor to A $\beta$  is the C-terminal domain of APP called C99, which is the product of BACE cleavage of APP and has an affinity for cholesterol binding. Localisation of APP/C99 is therefore directed to the cholesterol rich rafts, where the BACE and  $\gamma$ -secretase are concentrated, thereby increasing amyloidogenic processing of APP [95] [98]. BACE has been shown to be stabilised by ceramides and therefore increased ceramides may promote amyloidogenic processing of APP [99] [100]. Furthermore SIP has been shown to adjust BACE activity in neurons with inhibitors of sphingosine kinase as targets for prevention of neurodegeneration in AD [101] [102].

In the brain apoE has been shown to be essential for ceramide metabolism and nerve sprouting and in these apoE knockout mice plasma lipoproteins were enriched in sphingomyelin [103] [104]. Individuals with neuro-

pathologic changes of AD and the apoE4 isoform are associated with abnormal sterol and sphingolipid biochemistry [105]. However the apoE4 isoform in normal brain tissue was not associated with perturbed sterol or sphingolipid metabolism and indicated that the abnormal liver ceramide metabolism may override apoE4 related brain events with promotion of insulin resistance in AD individuals [105].

### 3. Lipoprotein Metabolism, Phospholipid Transfer Protein, Insulin Resistance and AD

Lipoproteins are complexes of proteins and lipids that solubilize lipids so they can be transported in the circulation between tissues. Lipoproteins are synthesized in the intestine from dietary lipids or in the liver from endogenous lipids and can also be remodeled from precursor lipoproteins under the influence of various metabolic signals. Lipoproteins have generally spherical structures typically consisting of a neutral lipid core of cholesteryl esters and triglycerides and a surface layer of phospholipids, unesterified cholesterol and various apolipoproteins. These apolipoproteins not only solubilize the lipids but also act as ligands for cell surface receptors and cofactors for plasma enzymes. High LDL, VLDL and low HDL are known risk factors for vascular disease, diabetes and AD [106]–[108] and dyslipidemia has been shown to be more prevalent in AD patients with BBB impairment [109].

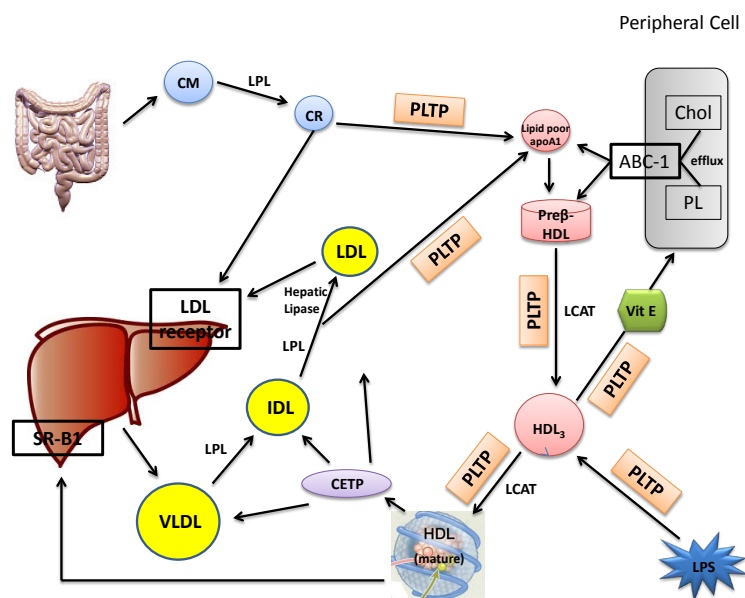
Lipoproteins are dynamic with constant modification by the action of enzymes, lipid transfer and apolipoprotein (apo) exchange. This ensures specific lipid delivery to different tissues. Phospholipid transfer protein (PLTP) plays a key role in HDL remodeling and redistribution of ceramide to denser HDL may facilitate rapid transport across the BBB to brain cells in AD (Figure 2). The physiological relevance of PLTP is significant in PLTP-deficient mice, which demonstrate a total absence of PL transfer from VLDL to HDL and markedly reduced PLTP and HDL levels [110] [111]. PLTP is a non specific lipid transport protein and is known to transport amphiphilic molecules including A $\beta$ , lipopolysaccharides/diacylglycerol to HDL [112]–[114]. PLTP deficient mice demonstrate A $\beta$  toxicity and memory deficits [115] [116]. PLTP also facilitates the transport of other lipophilic substances such as  $\alpha$ -tocopherol [117]. It is important in preventing LDL oxidation and subsequent uptake of oxidized LDL by vascular endothelium [118]. PLTP deficiency in the brain has been shown to result in reduced  $\alpha$ -tocopherol and an increase in oxidative injury, leading to neurological dysfunction [117] [118]. This suggests that PLTP is a local transporter of  $\alpha$ -tocopherol and may transport  $\alpha$ -tocopherol across the BBB. A major function of PLTP is to maintain the plasma sub species of HDL [119] [120] and the CNS HDL like lipoproteins [121] [122]. Most studies have been done in relation to atherosclerosis and metabolic disease and are contradictory with some finding higher PLTP activity levels and increased risk of disease [121]–[123] and others finding lower levels associated with disease [124] [125]. The protective or disease promoting effects of PLTP remain unclear as HDL cholesterol levels vary in response to PLTP gene overexpression or deficiency [126] [127]. It may be that the effect of PLTP on disease may depend on the background lipid profile, metabolic landscape, co-morbidities, medication use and dietary considerations.

In addition to PLTP in plasma, cholesterol ester transfer protein (CETP) is also involved in HDL speciation [128]. CETP is secreted mainly by the liver and circulates in plasma mainly bound to HDL. It redistributes cholesteryl esters from HDL to TG rich lipoproteins (CM and VLDL) and transfers TGs from VLDL and CM to LDL and HDL [128]. PLTP facilitates the transfer of phospholipids from TG rich lipoproteins to HDL and together with CETP is important in reverse cholesterol transport by modifying the size and function of HDL (Figure 2).

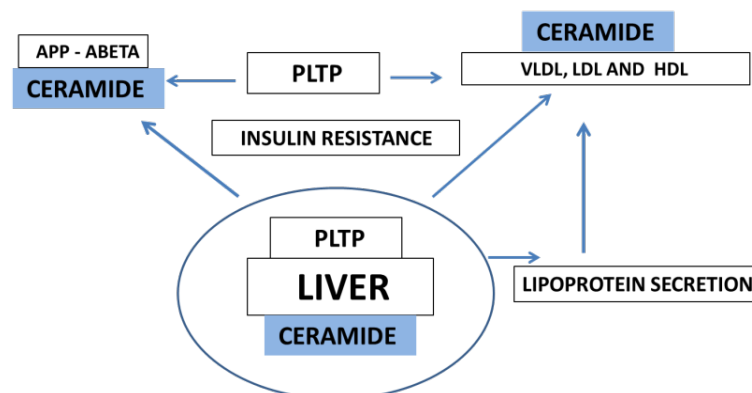
As previously mentioned insulin resistance is associated with elevated plasma ceramides which may also influence lipoprotein metabolism and amyloidogenic processing (Figure 3) with the central role of the liver in release of VLDL and LDL ceramide into the bloodstream. The elevation in plasma ceramides influence plasma lipoprotein toxicity which adversely affects intracellular processes and induces cell apoptosis [129] [130]. Within cells ceramide transport to the golgi apparatus is regulated by the ceramide transport protein [131] with elevated saturated ceramide levels or metabolites involved in membrane fluidity or organization and regulation of PLTP activity in sphingomyelin transport to cells and lipoproteins [132]–[136].

In the brain glial cells and astrocytes support function and promote survival of neurons with the central role of the astrocyte in the metabolism of neuronal A $\beta$  homeostasis with other astrocyte functions that include production of apoE, production of neurotrophic factors, angiogenesis, supply of glutathione (oxidative stress) and energy substrates, modulator of xenobiotic toxicity, maintenance of neuronal calcium homeostasis, lipid and cho-





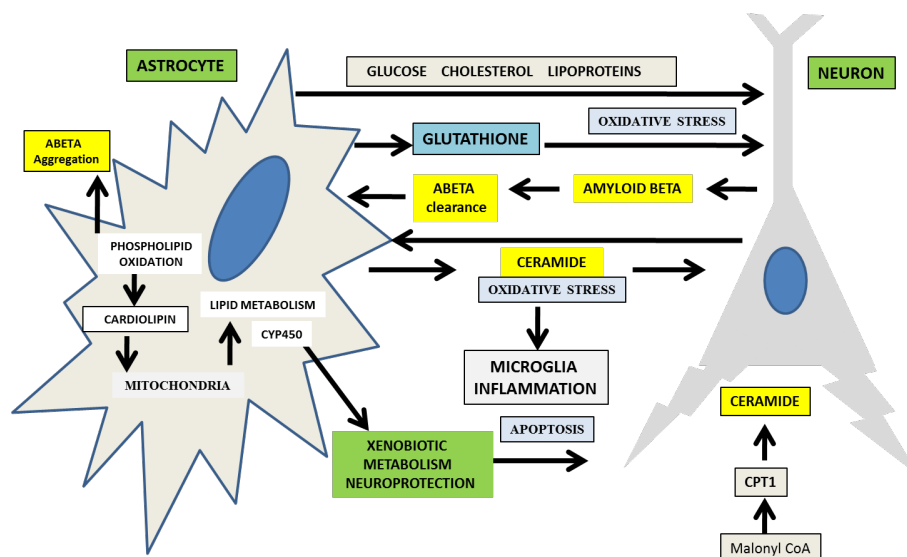
**Figure 2.** Lipoprotein metabolism and lipid transfer proteins (PLTP and CETP) with effects on dietary lipoproteins (chylomicrons), hepatic derived lipoproteins (VLDL, IDL, LDL) and HDL lipoproteins.



**Figure 3.** Effects of insulin resistance on PLTP, hepatic ceramide lipoprotein secretion and on ceramide APP-A $\beta$  processing.

lesterol synthesis (**Figure 4**) [137]-[146]. Astrocytes maintain cholesterol homeostasis in neurons by transport of cholesterol containing lipoproteins via apoE [147]-[150] with ATP binding cassette transporter 1 (ABCA1) involved in cholesterol efflux to lipoproteins such as HDL with S1P release [151]. Production of apoE by astrocytes is central to neuron cholesterol metabolism with apoE closely connected to activation of PLTP activity and in diabetes changes in apoE levels have been associated with PLTP activity [152] [153]. ApoE-PLTP interactions involve ABCA1 with the critical binding of PLTP to ABCA1 dependent cholesterol efflux [154]. Furthermore, astrocytic DAG has been shown to modulate PLTP activity and A $\beta$  homeostasis with DAG involved in astrocyte ATP release and adjustment of neuron excitability [155]-[158].

Peripheral lipid disturbances that involve ceramide are closely linked with to BBB disorders that jeopardize astrocyte-neuron interactions that may cause neuron cholesterol overload, A $\beta$  dyshomeostasis with damage to astrocytes by neuron A $\beta$  oligomers [159]-[162]. Ceramide has been shown to stimulate cholesterol efflux and involve increases in membrane ABCA1 activity without apoE-PLTP involvement [163] [164]. The peripheral sink A $\beta$  hypothesis indicates that the transport of A $\beta$  oligomers across the BBB is regulated by astrocytes (**Figure 4**) and transported from the central nervous system to the periphery for rapid metabolism by the liver [165] and this



**Figure 4.** Astrocytes are involved in neuron amyloid beta clearance, cholesterol homeostasis and xenobiotic metabolism.

process in metabolic dysfunction involves abnormal ceramide metabolism and AD. Interests in high fat diets with endocrine dysfunction and NAFLD override any apoE isoform effects with influences in brain lipid metabolism [43] [166] with the involvement of astrocyte disease possibly responsible for the brain cholesterol and A $\beta$  dysregulation as found in AD [137] [138] [143]. Lipid mediators exert numerous effects on cellular function. These effects involve astrocyte modulation of enzyme activity, neural cell differentiation, immune responses, inflammation, oxidation, cell migration, mitogenesis and apoptosis and therefore imbalances in any of these mediators would predictably contribute to AD pathology [167].

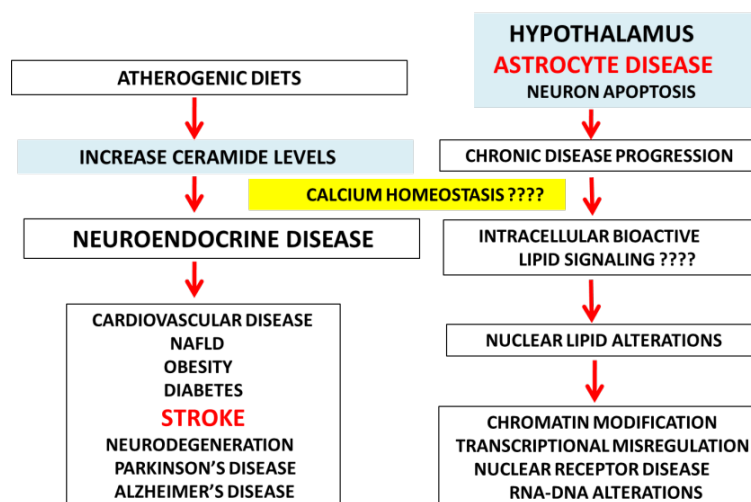
#### 4. Lipids Influence Lipoproteins, Cell Membrane and Nuclear Receptors with Chronic Disease Progression

Intake of saturated and trans fatty acid is positively correlated with increased cholesterol levels and unfavorable shifts in LDL:HDL ratios [168]–[170]. Excess palmitic acid can also upregulate ceramide production, which is considered a major contributor to hypercholesterolemia, insulin resistance and obesity [45] [171]. The most commonly consumed fatty acids are myristic (14:0), palmitic (16:0), stearic (18:0), oleic (18:1) and linoleic (18:2). Each of these fatty acids “affects” plasma cholesterol levels differently due to their impact on the LDL receptor, whose activity is regulated by the sterol content of the cell viasterol regulatory element-binding protein(SREBP) [9] [11]. Dietary fatty acids and cholesterol can increase the sterol regulatory pool by their effects on the hepatic enzyme acylCoA-cholesterol acyl transferase (ACAT) [172] [173]. Saturated fatty acids such as palmitic acid partially inhibit cholesteryl ester (CE) formation by ACAT, therefore increasing the amount of free cholesterol. In liver cells enriched with monounsaturated fats (MUFA) and polyunsaturated fats (PUFA) ACAT activity is increased as it is a preferred substrate and CE formation is promoted [173]. Furthermore, ceramide decreases SREBP post transcriptional regulation and these effects are independent of intracellular cholesterol levels [174].

Dietary trans fatty acids are known to contribute to dyslipidemia and associated increased disease risk [175] have been associated with brain aging and impaired cognition [176] [177]. Atherogenic diets (Figure 5) increase membrane cholesterol and ceramides that influences membrane fluidity with altered APP-A $\beta$  processing and their tendency to promote abeta aggregation with relevance to chronic disease and neurodegeneration.

Most naturally occurring fatty acids have double bonds in a cis configuration which allows the chain to bend. The *trans* bond imparts a rigid structure which is similar to that of saturated fatty acids and increased consumption from processed and fast foods can lead to dyslipidemia [175]. *Trans* fatty acids alter membrane fluidity and responses of various membrane receptors by their incorporation into membrane phospholipids. The effects on lipid metabolism are due to several mechanisms. *Trans* fatty acids alter the secretion, composition and size of apo-





**Figure 5.** Atherogenic diets are closely associated with oxidative stress, lipid peroxidation with the generation of second messengers that promote chronic disease progression and neurodegeneration.

lipo-protein B-100 produced in the liver and increase the cellular accumulation and secretion of free cholesterol and cholesterol esters by the liver [178]. The effects on reducing HDL are associated with an increase in CETP with abnormal transfer of cholesterol esters from HDL to LDL and VLDL [179]. Additionally the fluidity, determined by the fatty acid at the sn-2 of PC is a major regulator of lecithin:cholesterol acyltransferase (LCAT), which is required for the formation of mature HDL. *Trans* fatty acids affect membrane fluidity and reduce LCAT activity [180] with effects on abeta aggregation and on important signaling lipids in the membrane bilayer, lipid rafts and lipoproteins that are involved in the generation of second messengers (Figure 5).

As fatty acids act as ligands for nuclear receptors (Figure 5), such as sirtuin 1 (Sirt1), peroxisome proliferator activated receptors (PPARs), liver X receptor (LXR) and SREBP, regulation of gene transcription can be altered [181]–[184], directly modulating metabolic and inflammatory responses in the periphery and brain. Sirt1 are nicotinamide (NAD<sup>+</sup>) dependent histone deacetylases which are activated by cellular stresses to enhance cellular defense and repair pathways and to mediate adaptive responses to changing energy requirements. This is achieved by deacetylation and transcriptional control of numerous genes involved in lipid, glucose and A $\beta$  metabolism [184]–[186]. Saturated fatty acids such as palmitic acids have been shown to inhibit Sirt1 with the development of hepatic steatosis as observed in Sirt1 knockouts [187] [188]. Additionally Sirt1 has been closely linked to obesity and AD [189] and shown to regulate liver cholesterol metabolism and attenuate amyloidogenic processing of APP both in cell culture models and in transgenic mice [185] [186], suggesting a possible mechanistic link between saturated fatty acids, peripheral cholesterol/ceramide metabolism and AD pathology.

Brain aging associated with dyslipidemia and oxidative stress coupled with altered gene expression profiles delays DNA repair mechanisms that underlie aging, stroke [190] and neurodegeneration. The anionic glycerophospholipid phosphatidylserine and phosphoinositides are located in the chromatin and the regulation of chromatin structure, gene expression and transcription is determined by the nuclear lipids [191]–[194]. Inflammation and oxidative stress associated with hypercholesterolemia generate reactive chemical species with oxidation of membrane and nuclear lipids with chronic damage to DNA and RNA in astrocytes and neurons. Diets that accelerate inflammatory processes disturb the astrocyte-neuron interactions affecting neuron survival and synapse formation. Diets that stabilize neuronal membrane and nuclear lipids are important for the maintenance of astrocyte and neuron function and may slow disease processes associated with amyloidogenesis and also involved in neurodegeneration.

Epigenetic changes induced by alteration in nuclear lipids (Figure 5) change the expression of genes through transcription and other lipids such as diglycerides, phospholipids, cholesterol and cholesterol esters also determine chromatin structure [195]–[197]. High fat high cholesterol (HFHC) diets induce oxidative stress that accelerates lipid peroxidation of phospholipids and cardiolipin involved in nuclear stability and neuron proliferation [197]–[199] and also involved in A $\beta$  fibrillization. Additionally, sphingomyelin is involved in chromatin assem-

bly and dynamics and different sphingolipid species have varying effects on nuclear domains, envelope and chromatin structure. Sphingomyelin and phosphatidylcholine are associated with cholesterol in the nuclear membranes but play different roles in nuclear lipid micro-domains. Different sphingolipid species are localized in various subnuclear domains, including chromatin, the nuclear matrix, and the nuclear envelope, where sphingolipids exert specific regulatory and structural functions [200]-[204]. Nuclear lipid peroxidation and altered gene profiles affect the delicate balance of lipid sensing in liver and brain [205] [206]. These altered brain gene expression profiles may involve the intake of high fat diets and affect the whole body lipid, calcium and glucose metabolism with disturbances in nuclear receptors (PPAR-sirtuin 1 complex, liver X receptors, sterol regulatory element-binding proteins, nuclear factor  $\kappa$ B, farnesoid X receptor) [207]-[209] and membrane receptors such as G protein-coupled receptors (GPCR) involved in lipid and calcium homeostasis [210]-[213]. Furthermore in studies assessing the effects of HFHC diets in mice, dyslipidemia associated with altered brain lipids and NAFLD are possibly related to significant changes in enzymes involved with brain nuclear lipid signaling that generate second messengers derived from phospholipids such as the phosphoinositides, ceramide, glucosylceramide (GlcCer), sphingolipid metabolites and cannabinoids involved in gene regulation that control a variety of cellular survival processes in the liver and brain [214]-[233]. In mice HFHC diets (**Figure 5**) increase oxidative stress and free radicals which alter various lipids [234] and show marked changes in brain cardiolipin content and acyl chain composition affecting neuron mitochondria and resulting in nuclear disturbances in these mice. Cardiolipin is bound to DNA with the component unsaturated fatty acyl residues involved in regulation of gene expression. Brain cardiolipin content decreases with aging and lipid peroxidation is responsible for the reduction or biosynthesis of cardiolipin content. Decreased cardiolipin content has also been found in NAFLD, cardiovascular disease, diabetes and neurodegenerative diseases and is also associated with mitochondrial dysfunction [235]-[239]. Furthermore alterations in ceramide levels in chronic diseases (**Figure 5**) that involve the induction of mitochondrial apoptosis also involve  $\alpha$ beta oligomers that are involved in membrane pore forming or ion channel formation with entry of calcium into cells [240]-[242].

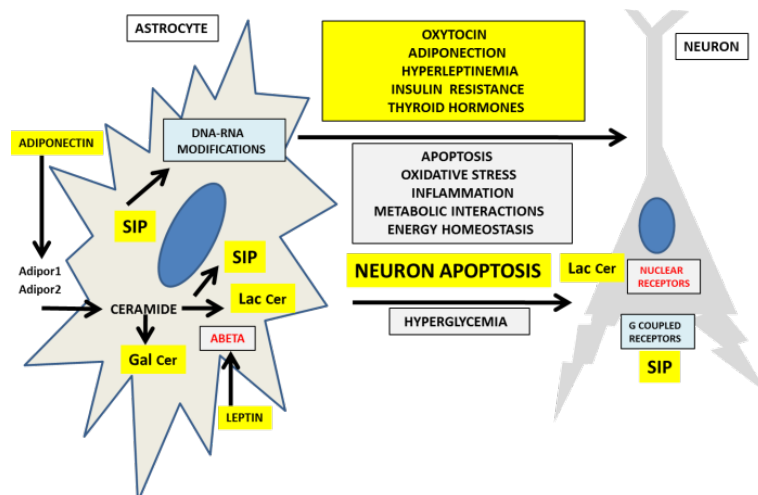
HFHC diets that induce an increase in sphingolipid metabolites including S1P in the periphery and CNS may affect various astrocyte-neuron-endothelial interactions (**Figure 6**) and adversely affect BBB function. S1P binds to GPCR or S1P receptors and modulates or increases the activity of cytochrome P450 enzymes responsible for cholesterol and xenobiotic metabolism [243]-[245]. S1P and other second messengers may enter the nucleus and initiate cell-modifying processes without the GPCR leaving the plasma membrane [210] [211] [246]-[248]. Otherwise entry into the nuclear membranes of intact GPCRs or fragments that bind S1P directly initiate or regulate transcriptional events in the nuclear domain.

## 5. Calcium, Lipids and Hormone Dysregulation Effect Astrocyte and Neuron Membrane Biology and Promote Amyloidogenic Pathways

In developed countries chronic metabolic diseases that involve altered lipid metabolism and insulin resistance affect the neuroendocrine system which leads to premature aging in neurons that promotes  $A\beta$  protein aggregation. This contributes to astrocyte dysfunction and generates signals initiating neuronal death. In addition to abnormal insulin signalling, other hormone imbalances present in neuroendocrine disease affect lipid and calcium metabolism. Hormones (**Figure 6**) play an important role in the interactions between neurons, astrocytes, oligodendrocytes, microglia, endothelial cells and other cells in various regions of the brain and BBB.

Nutritional research identifies diets that reduce oxidative stress, hormone imbalances and dyslipidemia that adversely affect calcium-membrane lipid interactions have become important to the maintenance of premature brain aging and AD. Astrocyte stability appears to be influenced by diet which affects hormone and calcium balance and the levels of bioactive lipids. High fat diets and obesity in both rodents and man have been shown to promote astrocyte dysfunction which compromises neuronal survival and due to the effects on energy homeostasis increases the risk for obesity and other metabolic diseases [249]-[262]. Insulin resistance compromises astrocyte survival as insulin plays a role in the maintenance of astrocyte function. Diabetes and hyperglycemia lead to abnormal communication between neurons with the death of astrocytes [263]-[265]. Research into how blood lipids and hormone imbalances affect astrocyte lifespan and function is an active area of research and may contribute to the understanding of neurodegenerative processes that occur in disorders such as AD, PD and Huntington's disease [266]-[271].

Lipid signaling between astrocytes, and microglia is essential for neuron survival and determine the senescence



**Figure 6.** Peripheral metabolic hormones and bioactive lipids regulate astrocyte survival and oxidative stress with neuronal apoptosis.

of neurons. Lipids such as cardiolipin, anionic phospholipids and sphingolipids including ceramides not only affect astrocyte and microglia function but also influence neuron calcium homeostasis. Abnormal calcium homeostasis is linked to excitotoxicity and neuronal cell death and recent studies have shown that elevated calcium levels are linked to insulin resistance and diabetes [272]–[277]. Furthermore, metabolic disorders such as obesity and diabetes in which endocrine disturbances are present appear to promote bioactive lipid interactions affecting astrocyte function and neuron calcium homeostasis, which influences membrane function, nuclear lipids and cell receptors such as the GPCRs. Hormones binding to receptors such as the GPCRs in astrocytes result in signal transduction and are linked to a heterotrimeric G protein which alters the amount of astrocytic calcium released from endoplasmic reticulum (ER) and may result in altered neuron activity (Figure 6). Abnormalities in intracellular neuron calcium and lipid regulation are strongly linked to ER stress that accelerates protein aggregation disorders such as occurs in non-alcoholic fatty liver disease (NAFLD), diabetes and AD [278]–[282].

Lipids such as ceramide-1-phosphate, phosphoinositides, arachidonic acid (AA), docosahexaenoic acid (DHA), DAG and prostaglandin E2 have significant effects on intracellular calcium affecting calcium dysregulation in the ER and mitochondria leading to cell death [283]–[286]. Polyunsaturated fatty acids such as DHA and AA may have neuroprotective effects by regulation of phospholipase A2 activity with marked effects on astrocyte and neuronal calcium levels involved in ER stabilization in brain and peripheral cells [286]–[288]. Other bioactive lipids present in astrocyte and neuronal cell membranes such as endocannabinoids (Figure 6) and platelet activating factor (PAF) which participates in signaling cascades associated with calcium channels and calcium homeostasis may also play a role in neuroendocrine disease [289]. In diabetes, neurodegeneration and stroke [290] [291] PAF is being shown to contribute to the pathological processes by its influence on eicosanoid synthesis which participate in inflammatory and chronic neurological processes.

As previously stated obesity and diabetes lead to abnormal peripheral lipid metabolism and also involve disturbances in several hormones including triiodothyronine (T3), thyroxine (T4), leptin, adiponectin, and insulin [292]–[294]. In the brain hormones such as insulin, leptin, adiponectin, oxytocin, corticotropin releasing hormone (CRH) and thyroid hormones bind to extracellular receptors in astrocytes (Figure 6). Astrocytes play a central role in thyroid hormone metabolism in the brain and are responsible for uptake of thyroxine from the blood and its conversion to 3,5,3'-triiodothyronine. The supply of the biologically active form of thyroxine to neurons is important to neuron survival, neuriteogenesis and synapse formation [295] [296]. Thyroid hormones, adiponectin and leptin have been shown to target the oxytocin neurons with control of body weight regulation and lipid metabolism [297]–[301]. Thyroid hormones have profound effects on adipokines, lipid metabolism and carbohydrate homeostasis with alteration in plasma lipids and zinc deficiency linked to hypothyroidism [302]. Other peripheral hormones such as cortisol are also associated with insulin resistance and dyslipidemia with hypothalamic CRH involved in its regulation and peripheral calcium homeostasis. This suggests that the existence of a complex network of hormones that regulate neuronal function involves calcium/energy homeostasis and is in-

fluenced by nutrient status.

ApoE is an essential protein synthesized by astrocytes and is involved in peripheral lipid metabolism with various effects on neurons such as induction of endocytosis and neurotransmission mediated by calcium alterations [148] [149] [303]-[305]. Calcium alterations determine the conformation and therefore activity of the low density lipoprotein receptor (LDL r). The activity of the LDLr is linked to neuronal plasticity and cell proliferation [306]. In neurons physiological regulation of calcium influx and its associated second messengers affect contractile proteins that determine shape, size and positioning of cells [307] [308] and a number of neuron processes and circuits [309]. In cell membranes the distribution of lipid species in the lipid bilayer determines lipid asymmetry which influences numerous cellular functions [310] [311]. Calcium dysregulation alters this lipid asymmetry (Figure 7) which can lead to an imbalance of sphingolipids promoting apoptotic processes and cell death. The role of calcium homeostasis in membrane biology is particularly relevant to neurodegeneration as calcium modulates negatively charged lipids in membranes (Figure 7) such as phosphatidylinositol, phosphatidylserine and phosphatidyl 4, 5-bisphosphate and the subsequent release of lipid mediators [16]-[20].

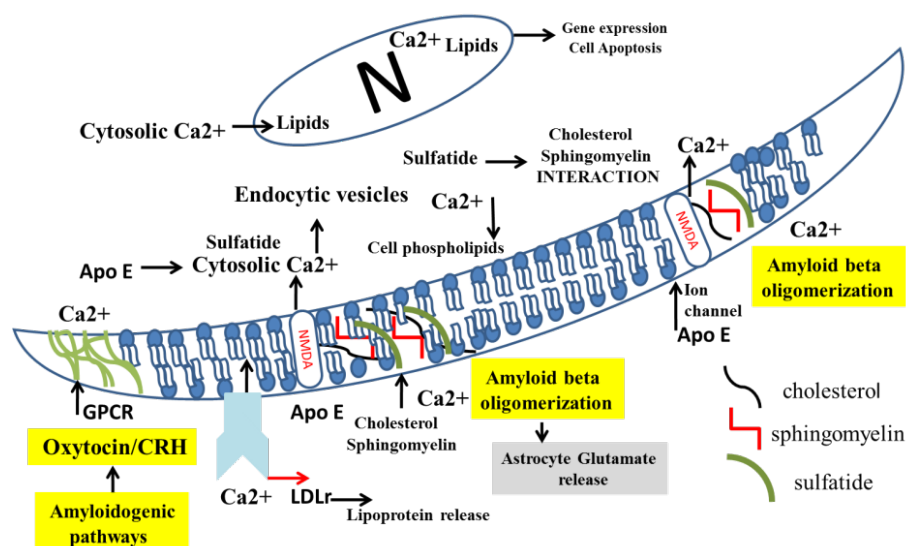
The sphingomyelin-cholesterol interaction is the physicochemical basis for the formation of cholesterol/sphingolipid domains in plasma and cell organelle membranes [311]. Sulphatides, myelin specialized sphingolipids, have been shown to participate in ordered domain formation in cholesterol/phospholipid/sphingomyelin membranes (Figure 7) and these sulphatides are influenced by the presence of  $\text{Ca}^{2+}$  in these membranes [312] [313]. Sulphatides are synthesized mainly in astrocytes and in AD the sulphatides are markedly decreased in the brain [314] [315]. In the brain apoE containing lipid particles, similar to HDL also contain astrocyte derived sulphatides [316] [317] and are essential for promoting neuron survival by maintenance of the neuron membranes. Alterations in apoE mediated sulphatide trafficking have been shown to deplete sulphatide in the brain, and CNS levels of sulphatide have been shown to be apoE isoform dependent, with the lowest levels observed with APOE $\epsilon$ 4 [25] [318]. Low sulphatide levels have also been associated with diabetes and insulin resistance [319] and sulphatides have been shown to control insulin secretion by modulation of ATP-sensitive K channel activity in rat pancreatic beta cells [320]. Sulfatides stimulate the calcium-sensitive, K $_{\text{p}}$  channel (BKCa channel) [320] and direct calcium binding alter cellular membrane potentials which may be relevant to neurological dysfunction and AD.

The transport of the neurotransmitter glutamate from astrocytes to neurons appears to regulate astrocyte calcium [321]. Glutamate is involved in a number of physiologic processes including learning and memory and the N-methyl-D-aspartate (NMDA) receptor has been shown to play an important role in emotional memory and fear [322]. Astrocytes can release glutamate in a calcium-dependent manner possibly under A $\beta$  induction or hormonal regulation [323] [324]. However, glutamate is also involved in pathologic processes as in neurons and astrocytes glutamate toxicity can lead to cell death which can be induced by alterations in calcium levels [324] [325]. The calcium levels are regulated by GPCRs [212] [213], or via activated ion channels such as the NMDA receptors that are also under regulation by oligomeric abeta, GPCRs/protein kinase C or effects mediated by apolipoprotein E (apoE), oxytocin and leptin [326]-[333].

## 6. Nutrition Based Strategies to Prevent Insulin Resistance, Cardiovascular Disease, Stroke and Alzheimer's Disease

Many studies have confirmed the link between high fat/high sugar (HFS) diets and declining cognitive function and suggest a role for insulin resistance and diet-induced endocrine abnormalities in this process [6] [8] [38] [334]-[338]. Diets that contain high saturated fat, cholesterol, added sugar, including high fructose corn syrup (HFCS), and high glycemic containing foods contribute to dyslipidemia [338], ceramide and cholesterol dysregulation associated with APP-abeta processing abnormalities. In contrast to the standard Western diet, containing high fat, high refined sugar, low fibre and high salt, the Mediterranean diet low with all these contents [7] [8] has been shown to reduce the risk for AD. These diets are associated with high intakes of vegetables, legumes, fruits, cereals and unsaturated fatty acids (mainly as oleic acid 18:1n-9, the monounsaturated fatty acid found in olive oil). The focus is on high fibre, non-refined carbohydrates, making this a low glycemic eating plan which helps prevent insulin resistance and NAFLD.

High fish consumption is inversely correlated with the development of dementia and moderate alcohol consumption appears to offer a protective effect [6] [339] [340]. Fish contains high levels of omega-3 fatty acids, docosahexaenoic acid (DHA 22:6n-3) and eicosapentaenoic acid (EPA 20:5n-3). The brain relies on a supply of



**Figure 7.** The role of calcium and lipids on neuron proliferation with affects on cell and nuclear membranes that control cell function and metabolism.

arachidonic acid (AA) and DHA from the periphery, which are delivered via plasma lipoproteins and lysophospholipids. The PUFAs are converted via the action of cyclooxygenase and lipoxygenase enzymes to prostaglandins, leukotrienes, thromboxanes and other metabolites which are important mediators of cellular function and therefore the signaling molecules generated are partly influenced by dietary intakes [341]. High intakes of omega-6 fatty acids and AA from processed food can elevate pro-inflammatory eicosanoids and up-regulate pro-inflammatory cytokines. Levels of the non-enzymatically derived isoprostanes, which are vasoconstrictive, are also elevated in AA enriched diets [342].

Conversely, diets enriched with DHA from fish and fish oil are more anti-inflammatory, anti-thrombotic and vasodilatory and have neuroprotective effects in terms of synaptic function and plasticity via generation of docosanoids [342] [343]. The ratio of dietary AA to DHA may also contribute to the increased risk of developing several diseases, including cardiovascular disease and AD and relative amounts may be an important consideration in the design of nutrition-based strategies for disease prevention [344]. DHA and EPA are important in reducing triglyceride levels as they regulate the activity of various nuclear receptors resulting in a repartitioning of fatty acids away from storage as triglycerides and towards oxidation and reducing the amount of free fatty acids available for VLDL synthesis. EPA and DHA are highly unsaturated and are prone to peroxidation which stimulates the degradation of apolipoprotein B (apoB), required for VLDL synthesis and their presence in lipoproteins may also enhance postprandial chylomicron clearance by stimulating lipoprotein lipase activity [345]. The carbohydrate responsive element binding protein (ChREBP) is a transcription factor that responds to glucose levels and is involved in hepatic lipid synthesis by the transcription of genes involved in lipogenesis, such as fatty acid synthase and acetylCoA carboxylase [346]. ChREBP activity can be inhibited or normalized by omega-3 fatty acids [346].

Dietary calcium intakes in individuals with neuroendocrine disease and chronic disease may also be an important factor to consider when designing nutrition based strategies for the prevention of stroke, neurodegeneration and chronic disease [190] [347] [348]. The mechanistic intervention of diet to maintain cellular calcium and A $\beta$  homeostasis possibly involves cell membranes, receptors and calcium regulating hormones. Interests in dietary calcium such as low calcium intake have been associated with stroke and chronic disease in Asian populations [349]. However in United States and European populations low calcium intake as a mechanism was inadequate to explain the risk for stroke [350]. The use of calcium supplements and calcium fortified foods with low fat content from dairy food may assist in the poor dietary choices that lead to low calcium intake in various populations. Excessive intake of calcium with calcium supplements should be monitored to prevent stroke and myocardial infarction [350] [351].

Flavonoids and their effects on astrocyte-neuron interactions [352]-[355] are being studied in relation to the



consumption of diets that include fruits, vegetables and beverages rich in phytosterols and short chain fatty acids [356]. Flavonoids are also found in high fibre diets and are polyphenolic compounds such as flavonols, flavones, flavanones, isoflavones, catechins, anthocyanidins and chalcones. Flavonoids are considered to be anti-amyloidogenic and are being investigated as potential therapeutic agents to prevent the formation of A $\beta$  fibrils [357]-[360] and also for reversal of NAFLD [361] [362]. Furthermore flavonoid intake may also prevent and reduce the risk of stroke, AD and PD [363]-[365]. Flavonoids have also been shown to affect calcium homeostasis via modulation of Ca pump function [366]. However high flavonoid intake has been suggested to interfere with many aspects of thyroid hormone synthesis and availability [367]-[370], however these effects may be influenced by the type of flavonoid and natural food sources. Commercial sources of flavonoid (e.g. quercetin) present in commercial wines [371] may be more readily oxidized than the flavonoids found in natural foods (myricetin, kaempferol, luteolin, and apigenin, hesperidin, rutin, glycosides and tangeritin) which may explain the association between flavonoids and thyroid disease with effects on stroke and AD [372]-[376]. Diets rich in fibre are suggested to be important in the treatment of NAFLD. Additionally diets rich in selenium, iodine, zinc, iron, copper, omega 3 fats, coconut oil and antioxidant vitamins A, B, C, E can help neutralize oxidative stress and inflammation in the periphery and also support thyroid gland function. In the CNS these diets may promote astrocyte-neuron interactions by maintaining of thyroid hormone synthesis and brain oxytocin release which also influences brain calcium homeostasis. High fibre diets minimize rapid changes in blood glucose and therefore stabilise insulin, leptin, and triacylglycerol levels in addition to effects on satiety [356]. Furthermore, reduced total calorie intakes [356] with adequate protein intake activate specific astrocyte and neuron nuclear receptors that act as metabolic sensors for the calorie sensitive Sirt 1 gene involved in DNA repair [165] [189] [377]-[379]. Sirt1 acts with other transcription factors such as PGC-1 $\alpha$  and adenosine monophosphate-kinase (AMPK) to regulate energy intakes which may help prevent development of metabolic syndrome, NAFLD [45] [165] [189] and other associated diseases such as stroke [380] [381], cardiovascular disease and neurodegenerative disease. Apart from dietary considerations data from observational studies indicate that several lifestyle factors can reduce the risk of developing insulin resistance and AD, including physical activity, mental stimulation, being a non-smoker, and social interaction. Being physically active has known beneficial effects on insulin sensitivity, lipid profiles and NAFLD with intensity of physical activity positively associated with improved insulin resistance and cognition [382] and A $\beta$  metabolism.

## 7. Conclusion

The global epidemic of obesity and metabolic dysfunction and its related diseases such as diabetes, cardiovascular disease, hypertension, stroke and neurodegeneration is a major concern in Western countries. Consideration of nutrigenomic factors may increase the effectiveness of dietary programs designed to reduce the incidence of these conditions. The combination of increased oxidative stress and dyslipidemia adversely affects calcium-membrane lipid interactions which are accompanied by marked changes in transcription factors and gene expression in the liver and brain. The nature of dietary lipids and calcium intake in man may determine the severity and progression rate of chronic diseases. In developed countries high glycemic load and high fat diets induce ceramide dysregulation with insulin resistance which has been shown to affect astrocyte and neuron function with particular effects on calcium and lipid homeostasis, which in those individuals with neuroendocrine abnormalities can increase susceptibility to cerebrovascular disease and AD. Abnormal lipid and calcium metabolism as observed in hypothyroidism, obesity and diabetes lead to connected to premature brain aging with the poor maintenance of astrocyte survival and additionally abnormal A $\beta$  metabolism. Specific diets, by their cellular nutrigenomic effects may improve astrocyte-neuron dysfunction in these chronic diseases. Calorie restricted diets that contain adequate protein and important unsaturated fatty acids activate nuclear receptors that may help prevent astrocyte dysfunction, thereby reducing the severity of neurodegeneration and lessening the impact of the AD and stroke epidemics in developed and developing countries.

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