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High Fibre Diets and Alzheimer’s Disease

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ABSTRACT

The understanding of cholesterol and its pathogenesis to Alzheimer’s disease (AD) pathogenic process is important for the possible prevention of AD. High fibre diets that contain phytosterols have been shown to lower LDL and increase HDL cholesterol and are implicated in membrane cholesterol and amyloid beta (Aβ) homeostasis. The convergence of diet and AD may be related to the effects of phytosterols since plasma cholesterol is closely linked and regulated by phytosterols. Dietary fibre modifications that are low in fat and glucose reduce the risk for AD by not only effecting cell membranes and nutrient sensing G coupled receptors but also by regulating number of nuclear receptors such as histone deacetylases (HDAC) and peroxisome proliferator activated receptors (PPAR) that control glucose, fatty acids and cholesterol and have significant effects on the brain cholesterol homeostasis and amyloidosis. The peripheral sink Aβ hypothesis indicates that the peripheral clearance of Aβ and its regulation by dietary phytosterols is of substantial interest since it may delay hypercholesterolemia and the early onset of amyloid plaque development. Liver disease has been of central importance with aging and programmed cell death pathways. Nutritional therapy has emerged as a novel approach to control appetite and the role of nutrigenomics as an early nutritional therapy may assist genes to delay liver and brain diseases such as Parkinson’s disease (PD) and Huntington’s disease (HD) that are associated with aging. The understanding of phytosterols and the role of these lipids in drug therapy such as cholesterol lowering drugs may provide molecular mechanisms that are involved in the regulation of cell Aβ clearance and metabolism. High fibre diets also contain various fatty acids such as the short chain fatty acids (SCFA) and the understanding of synergistic effects of SCFA and phytosterols in glucose regulation and cholesterol homeostasis important to our understanding of diet, lifestyle and drugs in relation to peripheral amyloidosis and gene expression that play an early role in the development of AD.

KEYWORDS

Cholesterol; Phytosterols; Fatty Acids; Amyloidosis; Liver; Neurodegeneration

1. Introduction

Environmental factors such as exercise, circadian rhythms abnormalities, oxidative stress and aspects of various diets in Western countries are now of considerable importance when considering the risk for Alzheimer’s disease (AD). The consumption of high fat and high cholesterol diets (HFHC) has clearly been associated with increased plasma cholesterol and oxidative stress in various tissues. In various animal models of AD, a strong correlation has been found with HFHC diets and increased brain amyloid beta (Aβ) levels. The molecular mechanisms underlying the AD cholesterol connection are important in the prevention of the disease since considerable evidence indicates that cellular cholesterol levels, intracellular cholesterol transport and cholesterol esterification play an important role in Aβ generation and...
programmed cell death pathways. Specific diets and extending lifespan with avoidance of programmed cell death pathways have become an urgent therapeutic intervention for anti-aging related diseases [1]. In Western countries, age related diseases such as obesity and diabetes have become common as risk factors for appetite dysregulation, atherosclerosis and AD [2]. The Western diet is known to be high in fat and cholesterol with effects on the liver and brain lipid homeostasis and marked effects on peripheral amyloidosis [2].

The key element of this review is to improve the understanding of cholesterol metabolism and its role in the prevention of AD. The role of therapeutic lipids such as phytosterols and fatty acids will be discussed that reduce hypercholesterolemia and improve the liver clearance of Aβ (peripheral sink Aβ hypothesis). The significance of nutritional therapy has emerged as a novel approach to control appetite and improve nutrigenomics that may activate genes involved in Aβ clearance and delay liver and brain diseases that are associated with aging. Molecular mechanisms that are involved in the regulation of cell Aβ clearance and metabolism require appropriate changes to diets such as high fibre diets that promote caloric restriction and allow consumption of diets that are low in fat and high in antioxidants, trace minerals and fish that are associated with appetite control and decreased risk for AD. The aim of these dietary strategies will accelerate liver and brain cholesterol metabolism with improvements and reversal of non alcoholic fatty liver disease (NAFLD) and maintenance of peripheral Aβ metabolism (Figure 1 ref [2]).

Assessment of AD risk indicates that diet apart from genetic factors may provide a useful model for the prevention and management of the disease. Risk factors indicating that liver and metabolic health is central to AD have become important since memory loss and neurodegenerative damage become essentially irreversible. Therefore, nutritional research has concentrated on the identification of nutrient sensing diets that provide regulation of histone deacetylases (HDAC) that are involved in epigenetic control of gene expression that controls metabolic and tissue glucose and cholesterol homeostasis [3,4]. In calorie restriction epigenetic regulation of genes that control lifespan [5,6], fatty acid acid [7] and aging is associated with an increase in the Sirtuin 1 (Sirt 1) protein which is a member of the HDAC family [8]. HDAC and their dietary regulation are essential as therapy for peripheral Aβ metabolism (Figure 1 ref [2]).

Figure 1. Diets control appetite and cholesterol metabolism with the regulation of amyloid beta metabolism.

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Interests in cholesterol diets and sedentary lifestyles have become a major concern in Western countries and diets rich in fibre which may allow appropriate changes in calorie restriction and HDAC regulation with effects on liver cholesterol and glucose metabolism that main-

2. Cholesterol and AD Pathogenesis

The main constituent of senile plaques associated with AD, namely Aβ [32] is a proteolytic product of a larger protein, the amyloid precursor protein (APP). The Aβ (1-40) is synthesized in the early secretory and endocytic cellular pathways and the Aβ (1-42) is generated mainly in the secretory pathway [33]. APP is cleaved by three proteases, classified as α, β and γ secretases and formation of Aβ from APP is thought to occur via a two step process involving the β-site cleaving enzyme (BACE) and the putative γ-secretases [34-36]. The APP protein is...
cleaved into βAPPs (amino acids 18-671 of APP) and Aβ (amino acids 672-711/713 of APP). Cholesterol has been shown to be directly involved in membrane APP/αβ interactions and alterations in these interactions may be involved in the early stages of amyloidogenesis [37,38].

Detailed studies have previously shown that plasma high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol levels in AD patients when compared to age-matched individuals [39-41] were significantly correlated to cognitive decline [41]. The liver and membrane cholesterol homoeostasis has been shown to be involved with HDL levels and the ATP-binding cassette transporter (ABCA1) plays an important role in APP processing and peripheral cholesterol homoeostasis with maintenance of central nervous system and neuronal Aβ and cholesterol homoeostasis [42-45]. Interests in peripheral cholesterol metabolism have accelerated since clearance and metabolism of Aβ oligomers are important factors involved in the progression of amyloid plaque development. In the brain, cholesterol levels can also be regulated by sterol regulatory element-binding proteins (SREBP) that belong to the family of transcription factors that regulate intracellular cholesterol and lipid metabolism [46].

The role of cholesterol in modulating the expression of APP and the levels of Aβ has been reported [47-50]. Cholesterol modulates Aβ levels and Aβ acts on lipid metabolism by inhibiting cholesterol synthesis by inhibition of 3 hydroxy 3 methylglutaryl coenzyme A (HMG-CoA) and plays an important role in sphingomyelin metabolism to form ceramide [51]. The enzyme acyl-coenzyme A: cholesterol acyltransferase 1 (ACAT) esterifies cholesterol and long chain fatty acids and the enzyme controls Aβ and cholesteryl ester generation in the intestine and liver [52-54]. In the liver, the cholesteryl esters have a profound effect on APP processing and inhibition of the ACAT1 enzyme may reduce Aβ with effects on Aβ plaque development [54]. Both enzymes are closely involved in LDL receptor regulation and several reviews have shown that LDL receptors (LDLr) are involved in cholesterol homoeostasis, APP processing and AD pathogenesis [55-57]. In LDL receptor deficient mice, elevated LDL levels were associated with cerebral amyloidosis and in human, polymorphisms in the LDL receptor gene were associated with AD [55-56]. In the brain and liver, the LDL receptors play an important role in the metabolism of cholesterol and Aβ with the LDL receptor related protein 1 (LRP1) closely linked to AD. LRP1 also acts on blood brain barrier for the transport of Aβ to the periphery from the brain [58,59]. LRP1 is involved in the clearance of apolipoprotein E (apo E), alpha 2 macroglobulin, transforming growth factor-beta, and tissue plasminogen activator (tPA). Other members of the LDL receptor family such as apo ER2, LRP1B, and sorting protein related receptor containing LDL receptor class A repeats (SORLA) are involved in APP and Aβ metabolism [60, 61]. The receptor for advanced glycation end products (RAGE) may allow transport of Aβ from the plasma into the brain but LRP1 in man predominates for the major pathway for transport of Aβ from the brain into the plasma (Figure 2).

Interests in lowering peripheral cholesterol levels to reduce the risk of AD have been the focus of many research studies with particular impact in the regulation of brain Aβ metabolism. The interests in low HDL and high LDL in the plasma of AD patients have increased research in food and nutrition to assess the role of atherosclerosis in obesity and diabetes. Diets and brain cholesterol homeostasis has gained central interest to AD since cholesterol has not been reported to cross the BBB [62-64]. The brain must obtain cholesterol from de novo synthesis with astrocytes and oligodendrocytes mainly involved in cholesterol synthesis and neurons account for a small amount of the brain cholesterol [65,66]. Diets that promote neuron and maintain synapse are vital in the treatment of AD since there is a gradual loss of nerve synapses in brain regions in AD which is associated with disturbed cholesterol homeostasis [67,68]. Brain cholesterol homeostasis is maintained by cholesterol excretion in the form of 24S-hydroxysterol (24 S OHC) accomplished by the cytochrome P450 species [69] and in man the brain releases approx. 6 mg of 24S OHC into the periphery each day that is removed predominantly by the liver [70]. In AD patients, studies have shown that cholesterol metabolism is disturbed with elevated 24S OHC levels possibly related to neuronal death and neurodegeneration [71-73]. The release of 24 S OHC from the brain is critical to the maintenance of neurons and synapses and it cannot be excluded that with aging the elevated release of oxysterols from phytosterols in the brain may also be involved in abnormal neuron survival and synapse maintenance.

Drugs such as statins are inhibitors of HMG-CoA reductase and up-regulate LDL receptor levels with reduc-

**Figure 2. Phytosterols regulate intestine, liver and brain cholesterol and amyloid beta metabolism.**
tion in LDL levels [74,75]. Cholesterol lowering drugs have been shown to have marked effects on Aβ levels with statins involved in the reduction of Aβ levels [76-80]. The mechanisms of actions of statins on lowering the risk of AD may involve membrane interactions by adjusting cholesterol and other specific sterols sensitive to Aβ homeostasis. The role of diets and drug therapy may allow maintenance of membrane cholesterol levels that maintain proper synaptic function and abnormal events from drugs such as statins in relation to injury to mitochondria and muscles could be avoided with specific high fibre diet interventions that allow long term use of drug therapy.

3. Phytosterols and Cholesterol Homeostasis

In large scale studies in man Western diets that contain high fat and high cholesterol contents have been associated with increased risk for AD and in experimental studies in rodents HFHC diets lead to increased brain Aβ levels and abeta plaque like deposits in the brain [81,82]. In studies with mediterranean diets high in fibre low in fat content, high in antioxidant, trace mineral and fish content with active lifestyles was associated with decreased risk for AD [81,82]. Interests in high fibre diets and their effects on other neurodegenerative disease such as Parkinson’s disease (PD) and Huntingdon’s disease (HD) have been reported with the higher caloric intake associated with the increased risk for PD and HD [83-90]. Nutritional therapy in neurodegeneration has become important with effects on nutrient sensing receptors such as Sirt1 and GPCR in the liver and brain with particular interests in pharmacotherapy with GPCR targets in PD and HD [91,92]. GPCRs or fragments may bind second messengers that directly initiate or regulate transcriptional events in the nuclear domain [93-95] and GPCR regulation of nuclear events are possibly associated with control of cell and membrane cholesterol homeostasis [119-123]. The interest in phytosterols in AD has accelerated since the incidence of liver disease, obesity and diabetes has increased with the incidence of AD. Interests in the peripheral sink Aβ hypothesis in relation to phytosterol metabolism and their regulation of peripheral cholesterol homeostasis (vice versa) have been the focus of dietary fibre and relevance to AD. In Western countries, nutritional therapy has targeted the therapies for liver diseases and NAFLD is common in these countries [118]. Phytosterols have clear effects on the liver X receptors (LXR) and ATP-binding cassette transporters (ABCA1) pathways unravelling the mechanisms for the control of cell and membrane cholesterol homeostasis [119-123]. The LXR receptors that are found in the brain and influence a variety of genes involved in cellular cholesterol efflux and cells of the CNS [81,82]. The target gene for LXR is ABCA1 and activation of LXR has been shown to stimulate ABCA1 levels and decrease Aβ levels [81,82].

Sirt1 belongs to the HDAC family and the role of this anti-aging protein is linked to cholesterol and Aβ metabolism with links to obesity, diabetes and AD [2,124]. Sirt1 positively regulates the nuclear receptor LXR and in vivo reduces the expression of LXR targets such as ABCA1. In obesity and diabetes, Sirt 1 is switched off and the effects of phytosterols may be ineffective on cholesterol.
homeostasis via LXR and ABCA1 pathways that provide important dietary modulation of the nuclear receptor control of cholesterol and Aβ homeostasis in the liver and brain. Sirt 1 is involved in fatty acid metabolism, appetite and circadian control with involvement of peroxisome proliferator-activated receptors (PPAR) that are affected by fatty acids with significance to the PPAR alpha-Sirt 1 complex and peripheral amyloidogenesis [2]. Phytosterols regulate gene expression and cell cholesterol homeostasis and determine the LDL receptor membrane expression with effects on LDL concentrations in man. Phytosterols are closely involved in nutrigenomics with control and regulation of the nuclear receptor Sirt 1 actions that control cholesterol and Aβ levels (Figure 3 (ref [2,119-123, 124]).

Diet and cholesterol therapy using drugs has been the central focus for the treatment of AD. Caloric restriction and exercise do not only affect cholesterol metabolism but also phytosterol metabolism with prevention of the accumulation of oxysterols and phytosterols in the liver and brain membranes [115,116]. A major focus on the use of diet, cholesterol lowering drugs and lifestyles is to increase neuron number and decrease the size of plaques in the brain with aging. The membrane interactions of Aβ require cholesterol for clearance and metabolization with the increase in the membrane cholesterol involved in the regulation of Aβ assemblies [125-127]. The role of caloric restriction in activation of HDAC genes which control membrane cholesterol and the role of phytosterols and phytostanols (Figure 4 [99-102] have become of central interest since membrane interactions with cholesterol and Aβ may be required for the clearance and metabolism of Aβ. Increasing membrane phytosterol contents may control unstable protein/lipid complexes with the composition of phytosterols essential for neuron number and survival. Membrane phospholipids have been shown to be important for insertion of Aβ and the role of phytosterols (beta-sitosterol) in the determination of cholesterol/phospholipid stability has been reported [128-130]. Furthermore, the displacement of cholesterol by phytosterols or phytostanols may have implications for Aβ insertion and aggregation [131-133].

In various species, phytosterols are absorbed with different rates with low phytosterol absorption rates in rabbits and high phytosterol absorption rates in man. The role of diet and membrane phytosterols in cell membranes has attracted interest since the important role of cholesterol in ion channel regulation has been reported. Membrane lipids are an important part of the structure of neurons and conduct electrical impulses in association with membrane proteins [134-136]. Lipids are an integral component of bilayer membranes and maintain ion channels that are involved in intercellular communication [134,135]. Lipids within membranes are involved in maintaining membrane potentials by regulating the movement of ions across neuronal membranes, maintain synaptic function and produce lipid messengers for signal transduction [137]. The association of phospholipids, glycosphingolipids such as ceramide or gangliosides, glycerophospholipids (plasmalogen) and sterols makes up the membrane bilayers in neurons and packing of cholesterol within membranes may have marked effects on membrane protein structure and function and regulation of ion pumps [138]. Lipid rafts containing sphingomyelin and cholesterol form micro-domains for the recruitment of lipid modified proteins and ion channels [134]. Cholesterol has been shown to be involved in the regulation of ion channels and Aβ has been shown to closely regulate various ion channels [139-142]. In particular, Aβ oligomer formation is cytotoxic and leads to neuronal death with alterations in membrane ion channel activity and synaptic plasticity [143,144]. The role of specific phytosterols in the brain and their effects on the regulation of cholesterol and ion channels are poorly understood and diets that contain specific phytosterols and their relationship to Aβ and ion channels may have important implications for aging and AD.

4. Synergistic Effects of Phytosterol and Fatty Acids

Phytosterols and SCFA are natural food components with potential health benefits. Both compounds are mainly derived from high fibre diet and have properties such as anti-cancer [145] anti-atherosclerotic, anti-inflammatory [146-149] and anti-oxidant [150,151]. Phytosterol reduce cholesterol levels and an increase in the level of butyric acid, propionic and acetate in the blood is associated with a significant reduction in plasma cholesterol levels [152, 153]. Low molecular size, short carbon chain length and a high water solubility of SCFA have facilitated its rapid absorption in the portal vein and metabolism [154]. Higher metabolism rate of butyric acid has reduced its
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Figure 4. Phytosterols and phytostanols found in high fibre diets.

clinical potential. Thus it is reasonable to suggest that combination of phytosterol and SCFA may further reduce cholesterol and increase its efficacy as an anti cancer, anti inflammatory and anti-oxidant agent. Esterification of phytosterol with short chain fatty acids may improve its integration into a variety of foods without disturbing the efficiency of phytosterol as with omega 3 fatty acids and phytosterol.

Phytosterol esters with fish oil have been found to lower the plasma cholesterol levels than conventional phytosterol esters [155]. Furthermore, this synergistic supplement has a more hypotriglyceridemic effect than the conventional fish oil [155]. Esterification of phytosterol with oleic acid and esterification of beta sitosterol with conjugated linoleic acid have been previously reported [156]. Esterification of phytosterol with SCFA or especially with butyric acids has been poorly reported. Recent studies have shown formation of phytosterol esters via direct esterification with butyric acid and via trans esterification with tributyrin and ethyl butyrate [157]. Animal studies will be helpful to understand this combination while human studies are required to identify its long term effects. On the other hand, aliphatic and steroid esters of gamma-amino [U-14C] butyric acid (GABA) which is a synthesized compound have proved to have a high penetration capacity across the blood brain barrier [158].

The combination of SCFA and phytosterols on cholesterol homeostasis indicate that high fibre diets are regulators of amyloidosis and may prove effective as AD therapy. Studies have shown that SCFA are formed as a result of fibre fermentation could be affected by the consumption of phytosterol. Consumption of margarine enriched with phytosterol esters did not show any effect on the micro flora profile or to their metabolic activities or SCFA content [159]. SCFA have effects on appetite control and are considered to be important to HDAC inhibition (Figure 3) which is currently an important therapy for AD. SCFA exhibit marked effects on free fatty acid metabolism on binding to G coupled receptors that are involved in appetite control and play an important role in obesity and AD [160-162]. SCFA have been shown to have marked effects on insulin sensitivity and lipid metabolism and are associated to the field of insulin resistance syndrome and AD. Apart from synergistic effects of phytosterol and SCFA as AD therapy in particular butyric acid may have independent effects on AD. Interest
in the effects of butyric acid on liver has increased since NAFLD has become common in Western countries with close association with obesity and diabetes that are high risk factors for AD. Sodium butyrate contains anti-inflammatory and cancer chemo-preventive properties in colon [163-165]. Acetate, propionate and butyrate have the ability to transport through the blood brain barrier and could be utilized as the energy source by short-chain L-3-hydroxyacyl-CoA dehydrogenase [166]. This enzyme is highly important to Aβ and known as endoplasmic reticulum amyloid beta-peptide-binding protein and as a multifunctional protein has the capacity to oxidize 17β-estradiol [166]. The anti-cancer and anti-proliferative features of butyrate are not important to energy metabolism but may be vital to the modulation of gene expression [167] via the inhibition of histone deacetylases [165] and NF-κB signaling [168]. Studies have shown that butyrate could effect gene expression in microglial cells, as in colonocytes [167].

Butyrate could induce the adaptive responses in NF-κB signaling and has a capacity to regulate the responsiveness of microglial cells to lipopolysaccharides (LPS). Research studies on colonocytes [164], intestinal epithelial cells [169] and murine macrophages [168] has demonstrated that butyrate could down-regulate NF-κB signalling induced by cytokines or LPS. Yin et al. (2001) have shown that butyrate could inhibit proteasome activity and has the ability to up-regulate the level of inhibitory IκB proteins and thus prevents the cytosolic NF-κB activation. In other studies, butyrate has been shown to [170] down-regulate the expression of Toll-like receptor 4 (TLR4) that transmits LPS signals to activate NF-κB system and suggests that butyrate could suppress NF-κB activation. It may be interesting to understand the effect of sodium butyrate on the inhibition of NF-κB signaling in microglial cells. Discharge of proinflammatory and/or cytotoxic factors, including tumor necrosis factor-alpha (TNF-α), interleukin 1-beta (IL-1β), interleukin-6 (IL-6), interleukin-12 (IL-12), andnic oxide (NO) could cause gradual damage in neurodegenerative diseases such as stroke, trauma, AD, multiple sclerosis, and human immunodeficiency virus (HIV)-associated dementia.

Dietary fibre also contains other fatty acids such as medium chain fatty acids and long chain fatty acids and also affects nuclear receptors with particular relevance to the PPARγ involved in an increase in insulin sensitivity and diabetes. LCFA activates nuclear receptor PPAR α and gene transcription with control of lipid and glucose homeostasis. Diets rich in fibre lead to synergistic effects of phytosterols and SCFA, MCFA and LCFA on nuclear receptor activity (PPAR-Sirt1) expression and activation that allow control of glucose and cholesterol homeostasis involved in prevention of obesity and diabetes being the risk factors for AD.

5. Conclusion

Phytosterols and phytostanols and their esters are found in oils, fats, nuts, seeds, cereal, vegetables and fruits and their effects on reducing cholesterol absorption and cholesterol lowering therapies have been reported. High levels of SCFA have been found in barley, oats, brown rice, bran, green beans, legumes, leafy greens, apples, kiwi and oranges. Medium chain such as lauric acid and long chain fatty acids has been found in coconut oil. Interest in high fibre diets as anti-Alzheimer’s or anti-diabetic and their effects on drug therapy such as statins have attracted considerable interest although plasma cholesterol is clearly reduced in the drug therapy and effects on phytosterol interactions on membranes need to be further addressed in relation to promotion of Aβ binding, clearance and metabolism. The peripheral clearance of Aβ and its relationship to high fibre diets is of particular interest to therapy in AD because high fibre diets are particularly effective in NAFLD treatment and assist in the rapid brain transport of Aβ to the liver. The role of SCFA and phytosterols on nutrient sensing genes such as Sirt1 and G coupled protein receptors indicates the therapeutic role of high fibre diets on appetite regulation and the metabolic syndrome in chronic diseases such as obesity and diabetes and their increased risk for AD, PD and HD. Dietary fibre intake may improve the actions of statins by activation of nutrient sensing genes with synergistic effects of cholesterol lowering drugs and diet on improving peripheral Aβ metabolism in AD individuals.

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