Diabetes and cholesterol dyshomeostasis involve abnormal \( \alpha \)-synuclein and amyloid beta transport in neurodegenerative diseases

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Diabetes and Cholesterol Dyshomeostasis Involve Abnormal α-Synuclein and Amyloid Beta Transport in Neurodegenerative Diseases

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Abstract
The understanding of molecular mechanisms underlying diet and Alzheimer’s disease and the cholesterol connection are important for the prevention and treatment of Alzheimer’s disease linked to Type 3 diabetes and aberrant lipid metabolism. Cholesterol modulates amyloid beta generation with the ATP-binding cassette transporter 1 as a major regulator of cholesterol and phospholipids from cell membranes that are involved in amyloid beta transport from the brain to the liver for metabolism. In Parkinson’s disease, the α-synuclein protein binds to cholesterol (tilted peptide 67-78/isooctyl chain) in cell membranes. Fatty acids and phospholipids such as phosphatidylinositol in membranes sensitive to amyloid beta and α-synuclein binding/aggregation indicate the involvement of lipids in the progression of Alzheimer’s disease. Atherogenic diets with abnormal cell cholesterol homeostasis exist as a cellular mechanism, which is common to the aggregation of amyloid beta and α-synuclein proteins that induce both Alzheimer’s disease and Parkinson’s disease. Sirtuin 1, a nuclear receptor known to regulate cell functions by deacetylating both histone and non-histone targets when down regulated is associated with circadian abnormalities and with poor glucose and cholesterol metabolism linked to normal amyloid beta metabolism in Alzheimer’s disease and increased α-synuclein aggregation in Parkinson’s disease. The global obesity and Type 2 diabetes epidemic indicate that the down regulation of Sirtuin 1 with increased inflammatory processes and abnormal immune responses associated with increased plasma α-synuclein levels, has become important for the modulation of membrane ion channels and impairments in protein degradation with abnormal endoplasmic reticulum-mitochondrial interactions associated with disturbed peripheral amyloid beta metabolism common to both Parkinson’s disease and Alzheimer’s disease.

Keywords: α-synuclein; Amyloid beta; Cholesterol; Ceramide; Sirtuin 1; Lipopolysaccharide

Introduction
The main constituent of senile plaques, namely amyloid beta (Aβ) [1], is a proteolytic product of a larger protein, the amyloid precursor protein (APP). The main protein component of Alzheimer’s disease (AD) senile plaques, Aβ, was firstly purified and sequenced from cerebrovascular amyloid deposits which manifest as congophilic amyloid angiopathy [2]. Aβ are found to be peptides of 39 to 43 amino acids in length, with an approximate molecular mass of 4.2 kDa [2]. Another study published from the same research group has linked Aβ to adult Down’s syndrome and AD [3]. The understanding of molecular mechanisms underlying the AD-cholesterol connection has become important for the possible prevention and treatment of AD and it is now linked to diabetes and poor cholesterol metabolism. Plasma cholesterol profiles such as elevated low density lipoprotein and decreased high density lipoprotein (HDL) levels have been associated with AD and are important risk factors for cardiovascular diseases. Furthermore, diets that are rich in fat and cholesterol have been associated with brain amyloidosis in rabbits and AD transgenic mice. Diabetes and dyslipidemia are linked to amyloidosis with relevance to calcium dyshomeostasis and neurodegenerative diseases [4]. Cholesterol modulates APP processing and Aβ generation with the action of 3 proteases [5-7]. Depletion of cholesterol and inhibition of intracellular transport of cholesterol or cholesterol esterification by drugs inhibited the production of Aβ formation in hippocampal neurons [8-13]. Studies indicate that cholesterol ester (CE) levels are correlated with Aβ levels, and that cholesterol lowering drugs such as ACAT inhibitors directly modulate Aβ generation through the control of CE generation [14]. The ATP-binding cassette transporter 1 (ABCA1) is a major regulator of HDL with the transport of cholesterol and phospholipids from cell membranes to HDL possibly plays a central role in cholesterol flux and Aβ transport from the CNS.
to the periphery where it is transported to the liver for metabolism and subsequent excretion [15]. High fat and cholesterol diets may induce both AD and PD with the indications that abnormal cholesterol homeostasis exists as the cellular mechanisms that are common to the aggregation of Aβ and α-synuclein proteins [15-17]. In PD, the movement disorder is characterized by the aggregation of α-synuclein protein (14 kda) in Lewy body inclusions with dopaminergic neuron apoptosis in the substantia nigra [18,19]. Epidemiological studies indicate that Type 2 diabetes and PD are closely linked with shared dysregulated pathways that involve molecular genetics, cell biology and insulin resistance in the pathogenesis of these diseases [20,21]. In Parkinson’s disease, the α-synuclein protein is an amyloidogenic protein and has been shown to bind to cholesterol (tilted peptide 67-78) and α-synuclein has also been shown with binding to the isoctyl chain of cholesterol in membranes [22,23]. In recent publications, the binding of Aβ has been associated with cholesterol in membranes with the regulation of liver Aβ metabolism regulated by lipoprotein cholesterol levels [15]. The peripheral sink abeta hypothesis [16] is closely associated with cholesterol regulation and possibly connected to the metabolism of Aβ and α-synuclein proteins in diabetes, AD, PD and Huntington’s disease. In diabetes, circadian clock abnormalities [24] are central to disease progression and circadian disturbances are also found in neurodegenerative disease that involves AD and PD [25-28]. Regulation of the peripheral Aβ clearance is central to the disease of diabetes with circadian clock abnormalities now believed to be the origin of poor liver glucose, cholesterol and Aβ metabolism in diabetes [16]. Neurons in the hypothalamus are responsible for various connections to other brain regions and one of the important functions of the hypothalamus is control of the daily light dark cycle. The suprachiasmatic nucleus (SCN) may regulate the sleep-wake cycle and peripheral oscillators with effects on anxiety, stress, depression and food intake. In response to the daily sleep/wake cycle Aβ metabolism, α-synuclein metabolism is controlled by the circadian rhythm, SCN [29-32] with relevance to food intake and release of pineal gland melatonin. Disturbances in the SCN will alter energy and liver glucose and Aβ metabolism with hyperglycemia closely involved with abnormal resetting of circadian rhythms and melatonin release.

Sirt1 and insulin resistance involve circadian dysregulation with connections to membrane lipids and protein aggregation

Sirtuin 1 (Sirt1) is one of the nuclear receptors that is known to regulate several cell functions by deacetylating both histone and non-histone targets [33]. Sirt1 is an NAD(+)-dependent class III histone deacetylase protein that targets transcription factors to adapt gene expression to metabolic activity, insulin resistance and inflammation in chronic diseases [34-38]. Nutritional regulation (calorie restriction and high fat feeding) of Sirt1 that is involved in the hypothalamic and SCN control of food intake with regulation of the central melanocortin system via the fork head transcription factor has been reported [39-42]. Sirt1 dysregulation has been closely linked with alterations in appetite regulation and with circadian clock disorders that are associated with obesity and diabetes. In support of Sirt1’s role in circadian rhythms [43-47] subjects carrying minor alleles at Sirt1 and CLOCK loci, displayed a higher resistance to weight loss as compared with homozygotes for both major alleles, suggesting links between the circadian clock and Sirt1 function. Sirt1 is involved in neuron proliferation with effects on cellular cholesterol and lipid homeostasis by the regulation of liver X receptor (LXR) proteins. Sirt1 has been closely linked to Aβ metabolism in AD (Figure 1) and α-synuclein metabolism in PD with circadian dysregulation that is associated with protein aggregation [29-32] and with implications to Sirt1 research and therapeutics in Huntington’s disease [48].

Sirt1 is involved in the deacetylation and ubiquitination of LXR with regulation of the expression of LXR targets that are involved in cellular cholesterol metabolism such as ABCA1 (Figure 1) and SREBP-1c [49-51]. AMP-activated protein kinase (AMPK) activation by Sirt1 may be involved in the LXR-SREBP-1c expression involved in glial-neuron interactions that are associated with the circadian clock disorder in neuron proliferation with effects on cellular cholesterol and lipid homeostasis by the regulation of liver X receptor (LXR) proteins. Sirt1 has been closely linked to Aβ metabolism in AD (Figure 1) and α-synuclein metabolism in PD with circadian dysregulation that is associated with protein aggregation [29-32] and with implications to Sirt1 research and therapeutics in Huntington’s disease [48].

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become important to diabetes, PD and AD since its comparison and inclusion with other biomarker panels will allow sensitive detection and early diagnosis of metabolic dysfunction and its relevance to AD [74]. Interests in proteins and their interactions with membrane lipids in neurodegenerative diseases have accelerated with the existence of Aβ and α-synuclein pathologies in individuals with neurodegeneration [75]. In particular, α-synuclein has been linked to mitochondria and endoplasmic reticulum interactions with endoplasmic reticulum stress associated with calcium levels and α-synuclein aggregation [76-79]. The role of diet on α-synuclein aggregation in the modulation of the Aβ cascade, has become important with Aβ oligomer or toxic fibril formation that is associated with membrane cholesterol, sphingomyelin, phospholipids and fatty acids (Figure 2). The role of cholesterol in membranes is essential for protein interactions and metabolism of lipoproteins [80] with the isooctyl chain in cholesterol essential as a regulator of lipid metabolism [80]. The binding of α-synuclein to the isooctyl chain of cholesterol in membranes allows regulation of peripheral cholesterol metabolism with relevance to α-synuclein biology and the peripheral sink abeta hypothesis [15,16].

Neurodegenerative diseases and abnormal protein and cholesterol interactions (isooctyl chain of cholesterol) and other membrane lipids may involve the consensus cholesterol-binding motifs CRAC, CARC or a tilted peptide [22,23]. α-synuclein has been shown to bind to specific sites on the cholesterol such as the tilted peptide [67-78] and with binding to the isooctyl chain of cholesterol. The formation of cholesterol-rich domains [81,82] in membranes may involve both α-synuclein and Aβ and the insertion of both proteins in membranes are influenced by the various fatty acids, glycosphinglipids, phospholipids (anionic lipids) and gangliosides that may determine Aβ oligomer formation and α-synuclein aggregation (Figure 2) in cells [83-92]. The oligomers that contain both Aβ and α-synuclein have recently been reported with indications that nutrition and dietary lipids such as phosphatidylinositol [15] may be important in the mechanistic links between Aβ accumulation and α-synuclein pathogenesis (Figure 2) [16]. Fatty acids such as butyric acid [93] have become important for nutrition and neurodegenerative diseases and the used phenyl butyric acid has been assessed for the reduction of Aβ plaques and increased α-synuclein content in the brains of transgenic mice [94,95]. Furthermore, the interactions between α-synuclein and Aβ (Figure 2) may corrupt apo E-Aβ interactions [15,96] or apo E-ABCA1 interactions [97] with relevance to α-synuclein’s role in brain amyloidosis and neurodegeneration [98-100]. Down regulation of Sirt1 affects LXR-ABCA1 that regulates apo E-ABCA1 [97] interactions with effects on cholesterol efflux, α-synuclein aggregation and Aβ metabolism.

**Cholesterol-ceramide connections provide links between diabetes, PD and AD**

The global increase in chronic diseases such as obesity and diabetes supports a role for lipids such as ceramide and their metabolites in the pathogenesis of these diseases [74]. The link between the cholesterol-ceramide connections to diabetes and AD [102-104] has indicated the role of ceramide in the pathogenesis of PD and AD that is also referred to as Type 3 diabetes [105]. The cholesterol-ceramide connection linked with aging, diabetes and AD, is associated with increased α-synuclein-Aβ interactions in membranes that are associated with conformational Aβ transitions to benign or toxic amyloid assembly states [106]. Aβ intermediates modulated by α-synuclein (Figure 2) possibly determine the role of calcium channels [4,77-79,107] with relevance to membrane biology and neurodegeneration. α-synuclein is found in peripheral tissues and plasma with release of the protein from the gastrointestinal tract, macrophages, glands and skin that has been measured [108-113]. Macrophages may overexpress α-synuclein [109,111,112] and implications for the rise in plasma α-synuclein in human plasma, are sensitive to beta-cell function and insulin secretion [114]. α-synuclein and its role in inflammatory responses is closely linked to obesity and diabetes [114] with the γ-synuclein [115] regulation of lipid and Aβ metabolism in adipose tissue controlled by Sirt1 [116]. Effects of lipopolysaccharide (LPS) on the induction of α-synuclein and ceramide synthesis in macrophages [117,118] and α-synuclein release from the intestine [119] increased the α-synuclein levels in human plasma. LPS has been shown to effect cholesterol eflux by the modulation of the LXR-ABCA1 [120,121] pathways via Sirt1/LXR-ABCA1 interactions and lowering LPS has become important to reduce metabolic diseases with LPS models now reported for PD [122,123]. LPS effects macrophage SREBP expression and inhibits liver PGC 1α expression linked to abnormal Sirt1 cell regulation [124-126]. LPS mediated corruption of cholesterol eflux in macrophages that has been reported with the importance of cholesterol-rich lipoprotein interactions for the neutralization of LPS in metabolic diseases and diabetes [127-133]. Close connections between ceramide and LPS, have been reported in cells [134,135] with disturbed cellular cholesterol eflux in diabetes, AD and PD.

Diet with low calorie contents (high fibre), nutritional interventions, appropriate protein contents (low to moderate), xenobiotic free and activators of Sirt1 nuclear receptor and transcription factors [4,15,16,73] have been shown to improve the cell and lipoprotein metabolism of cholesterol and ceramide

**Figure 2:** Membrane lipids determine and influence A oligomer formation and α-synuclein interactions with cell membranes. 1. Membranes with increased ceramide-cholesterol interactions and low PI promote Aβ oligomerization. 2. Membrane lipids such as sulfatide (101) determine the aggregation of α-synuclein with effects on Aβ oligomerization. 3. Apo E-ABCA1 interactions determine membrane cholesterol contents and regulate interactions between α-synuclein and Aβ that are influenced by various fatty acids, gangliosides, sphingolipids, ceramide and phospholipids (anionic lipids). Mechanistic links to Aβ accumulation indicate the importance of oligomers that contain both Aβ and α-synuclein that develop with unhealthy diets that are low in phosphatidylinositol (PI) and butyric acid.
[74] with implications for α-synuclein and abeta metabolism in obesity, diabetes and neurodegenerative diseases. Effects of exercise on ceramide metabolism have been measured with the increased ceramide or normal ceramide levels in the muscle and heart [136-138]. Adiponectin has been shown to suppress α-synucleopathies in animal models with systemic effects of adiponectin on ceramide metabolism [139-141]. Nutritional interventions to increase plasma adiponectin levels require lifestyle and dietary changes to prevent stroke, PD and AD [142]. Increases in ceramide levels in cells displace cholesterol with effects on α-synuclein and Aβ interactions [143,144].

Polycations and polyanions have an electrostatic role in α-synuclein aggregation with drugs such as suramin (polyanionic) that are used to inhibit LPS inflammatory effects and shown to increase ceramide levels [145-148] in cells with effects of suramin on Sirt1 inhibition [149]. Suramin has been shown to bind to low density lipoproteins and to the low density lipoprotein receptor and to block LDL uptake [150,151]. Coumarins [152-154] and adiponectin [155-156] have been used to inhibit LPS effects and modulate the activation of Sirt1 with therapeutic effects in the treatment of PD. LPS [157,158] and Sirt1 [159,160] are linked to food intake and appetite regulation. Nutritional diets that contain phytosterols and butyric acid may control glucose homeostasis and stabilize membrane cholesterol-ceramide interactions [107]. However, butyric acid effects on T cell apoptosis have been reported and induced by an increase in cellular ceramide [161,162]. High fibre diets that control membrane cholesterol and cellular ceramide contents [74,102-104] are particularly relevant to activate the liver and brain nuclear receptors and stabilize membrane α-synuclein and Aβ transport in neurodegenerative diseases.

Conclusion

In the current global obesity and diabetes epidemic chronic diseases such as NAFLD, cardiovascular disease, kidney disease and neurodegenerative diseases such as PD and AD have increased in the developing and developed world. Links between metabolic diseases and AD indicate that Type 3 diabetes is on the increase in various countries. The Type 2 diabetes epidemic is linked to PD and associated with the Type 3 diabetes in AD. Unhealthy nutrigenic diets down-regulate brain and hepatic Sirt1 associated with insulin resistance, α-synuclein aggregation and Aβ dyshomeostasis in AD and PD. Nutritional diets that are low in calories activate the brain and liver Sirt1 activity and increase α-synuclein and Aβ metabolism. Specific dietary lipids requirements such as increased PI contents may act to stabilize membranes and favour lipid-protein interactions that promote the metabolism of α-synuclein and Aβ in various cells. The current global epidemic with the risk of accelerated brain disease such as stroke may involve peripheral organ diseases where abnormal cholesterol and ceramide interactions may determine toxic α-synuclein and Aβ assemblies that lead to early apoptosis and cell death in chronic diseases.

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