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LPS Regulates Apolipoprotein E and Aβ Interactions with Effects on Acute Phase Proteins and Amyloidosis

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Abstract

Interactions between apolipoprotein E (apo E) and amyloid beta (Aβ) are associated with the peripheral clearance of Aβ and are important to the development of neurodegenerative diseases. Interests in acute phase proteins (APP) as biomarkers for the early progression of Alzheimer's disease indicate that the peripheral Aβ metabolism is perturbed and the role of nutritional diets are important to reduce APPs to maintain peripheral Aβ clearance with relevance to hepatic cholesterol homeostasis and brain amyloidosis. The role of nutriproteomic diets that reverse the effects of high fat diets are associated with the reduction in APPs, cholesterol homeostasis and improved clearance of Aβ. Nutritional diets that reduce the increase in plasma endotoxins (gut microbiotica) such as lipopolysaccarides (LPS) reduce the effects of LPS on cell membranes and increase the cellular uptake of Aβ by interactions with apo E. LPS alter hepatic lipid metabolism with an increase hepatic cytokines and APPs in plasma. Interactions between apo E and Aβ are altered by LPS with increased binding of LPS to apo E with effects on electrostatic alterations in Aβ oligomers. The role of LPS in neurodegenerative diseases includes the effects of LPS on alpha-synuclein metabolism with relevance to Parkinson's disease and Alzheimer's disease.

Keywords

Lipopolysaccharides, Apolipoprotein E, Amyloid Beta, Acute Phase Protein, Diet

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1. Introduction

In the aging populations in Western communities Alzheimer's disease (AD) has increased and the prevalence in the next 30 years may reach 20 - 30 million people. Diets such as nutriproteomic diets have become important to the reversal of neurodegeneration with the aging process related to unhealthy diets such as high fat diets that are closely linked to amyloidosis in rodents and man [1] [2]. The role of nutriproteomic diets has become critical to prevent accelerated brain aging with high fat diets involved in the induction of metabolic dysfunction. Monitoring the plasma reveals an array of acute phase proteins [3] with respective charges that may interact with electrostatic oligomers of Aβ and assist in the understanding of accelerated aging in Western communities. Healthy diets that prevent the induction of APP have become important to prevent non-alcoholic fatty liver disease (NAFLD) linked to obesity, diabetes and AD (**Figure 1**).

The understanding of apo E mediated hepatic Aβ [3] clearance has become important with lipid-protein interactions implicated in the metabolism of Aβ in the periphery and the central nervous system [3]. The kinetics and interactions that determine the binding of apo E to Aβ and the role of lipoproteins that possibly determine interactions between apo E and Aβ has become important to the prevention of neurodegeneration. Apo E is important in lipid metabolism with multiple roles in cell biology and is involved in the understanding of how apo E4 promotes risk of neurodegeneration. The cellular uptake of the apo E/Aβ complex has become important to early aging and AD with the interaction between these peptides determined by the nature of associated lipids, inflammatory markers (APP) that indicate relevance to NAFLD and neurodegeneration. Atherogenic diets promote abnormal hepatic cholesterol homeostasis and exist as the primary cellular mechanism involved in theperipheral aggregation and clearance of Aβ (**Figure 1**) [3]. Atherogenic diets that contain high fat contents have been discouraged in various communities with the role of these fat diets in the transport of gut microbiotica [4] that increase plasma endotoxins such as lipopolysaccarides (LPS) in the blood plasma [4]. LPS has been associated with metabolic diseases and diabetes [4] and the importance of the cellular Aβ has increased with relevance to the binding of LPS (amphipathic α-helix organization) to apo E [5]-[9] and the influence of LPS on Aβ release or generation in cells [10]-[12]. Peptides have been designed with α-helix organization to neutralizelipopolysaccharide endotoxins [13]-[15] with relevance to the binding of apo E to Aβ. Furthermore, LPS alter hepatic lipid metabolism with an increase hepatic cytokines and APPs in plasma that are involved in LPS inactivation [16]-[23] associated with Aβ dyshomeostasis [3]. Lipoproteins such as chylomicrons that are produced after a high fat diet contain the LPS binding protein (LBP) that bind LPS and essential interactions of LPS to apo B containing cholesterol-rich lipoproteins [4] clearly implicate dietary fat and LPS in peripheral Aβ metabolism in diabetes with relevance to neurodegenerative diseases.

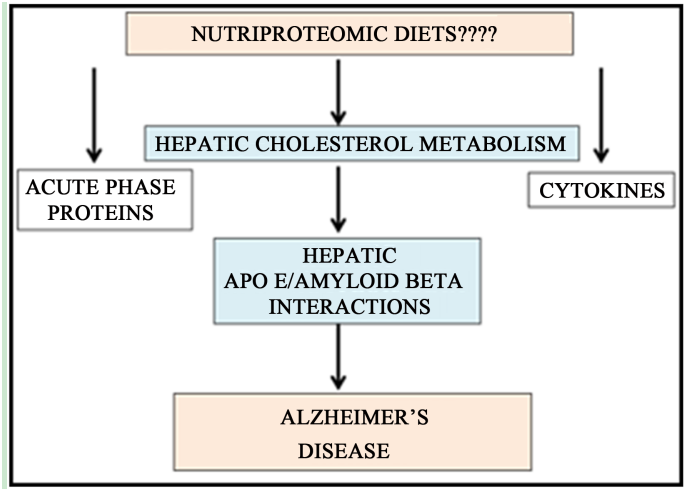

Figure 1. Nutriproteomic diets reduce the hepatic release of cytokines and APPs that are involved in peripheral inflammation associated with the increase in hepatic Aβ metabolism. In aging and AD nutriproteomic diets maintain hepatic cholesterol metabolism (3) with the decrease in brain inflammation/Aβ plaque density.

2. LPS Neutralize Apo E Binding to Membrane Lipids with Effects on Peripheral Aβ Metabolism

LPS are endotoxins and essential components of the outer membrane of all Gram-negative bacteria [24] [25]. LPS from bacteria share common features in their basic architecture and consists of three covalently linked segments [26], a surface carbohydrate polymer (O-specific chain), a core oligosaccharide featuring an outer and inner region and an acylated glycolipid (termed Lipid A). The O-specific chain shows the most diversity and Lipid A anchors the LPS molecule in the Gram-negative outer membrane and is most conserved in bacteria species [26]. Membrane-bound and soluble proteins have been shown to bind LPS such as LBP, toll-like receptor (TLR) and CD14 receptor. In the central nervous system systemic LPS injection initiates the acute phase response and upregulates membrane CD14 receptor that controls TLR4 endocytosis [27] and induces microglial activation that results in neurodegeneration and Parkinson's disease (PD) [26]-[29]. In AD the CD14 receptor is referred to as the LPS receptor and is involved in the phagocytosis of the Aβ peptide [30]. LPS induction of APPs are linked to the CD14 receptor with the levels linked to liver inflammation and NAFLD [31]. LPS has been shown to effect hepatic genomic stability [32] with effects on reverse cholesterol transport in macrophages [4] and with macrophage activation [33].

LPS can rapidly insert into cell membranes with a preference for insertion and partition into cholesterol/sphingomyelin domains in cell membranes [34]-[36]. Cholesterol is an essential membrane component and in association with phospholipids, glycosphingolipids such as ceramide or gangliosides, glycerophospholipids (plasmalogen) and sterols make up the membrane bilayers in cells. Lipid rafts containing sphingomyelin and cholesterol form microdomains in cell membranes for the recruitment of lipid modified proteins such as Aβ oligomers [4] with the binding of these hydrophobic proteins to membranes [3]. The essentiality of cholesterol determines Aβ binding to membranes with the addition of cholesterol important to the binding of Aβ oligomers to cells [3]. LPS may influence membrane cholesterol by binding to cell membranes and lipoproteins and its packing in the membrane allows the increased interaction or displacement of the Aβ peptide. In aging and AD membrane changes that lead to membrane alterations possibly involve the role of LPS in Aβ aggregation and fibril formation. Furthermore, amphipathic helices are critical to binding of peptides to LPS [13]-[15] with the role of apo E that contain these amphipathic helices linked to the binding to LPS that disrupt the role of apo E in the clearance and metabolism of Aβ in aging and AD. Apo E and its role in neutralization of LPS may be linked to its transport of LPS from macrophages to the liver [37] and support its critical role in LPS-lipoprotein (chylomicron, very low density lipoprotein) interactions to prevent inflammatory processes and closely linked to hepatic APP release (**Figure 2**). LPS has been shown to effect cholesterol efflux by the modulation of the anti-aging protein Sirtuin 1 (Sirt 1) with effects on LXR-ABCA1 interactions [4]. Monitoring dietary fat intake to reduce LPS has become important to metabolic diseases and neurodegenerative diseases such as Parkinson's disease [26] [38]-[41]. In obese mice altered inflammatory responses were found with LPS administration when compared with control mice with intestinal microbiota and NAFLD closely linked with connections to the systemic inflammation and the metabolic syndrome [42]-[45]. LPS effects on the release of alpha-synuclein [4] from cells in the periphery link the endotoxin to peripheral alpha-synuclein homeostasis (**Figure 2**) and to cholesterol metabolism with relevance to PD and AD [4]. LPS and cytokines have been shown to stimulate hepatic sphingolipid synthesis with the production of lipoproteins and with altered ceramide and sphingomyelin content [46]. Close connections between ceramide and LPS have been reported in cells [4] with disturbed cellular cholesterol efflux relevant to Aβ homeostasis in diabetes, AD and PD.

3. Hepatic Release of Acute Phase Proteins and Cytokines Is Regulated by LPS with Abeta Aggregation

The close connections between LPS and the liver involve the induction of lipoprotein synthesis with close connections between cytokines, apo E and RCT [3]. In addition to marked alterations in lipid metabolism (RCT) hepatic protein synthesis and serum protein levels (APP) are altered and associated with LPS levels (**Figure 2**). APPs have become important diagnostic markers for early progression of aging and AD [3] since APPs are now involved in important interactions with Aβ oligomers. LPS may prevent the clearance of Aβ by alteration in APP levels and by membrane receptor interactions. LPS may involve increase in hepatic cytokines that are connected to apo E sequestration with poor apo E redistribution from very low density lipoprotein and high density lipoprotein to peripheral membranes. Alterations in peripheral cholesterol homeostasis in neurodegeneration may involve

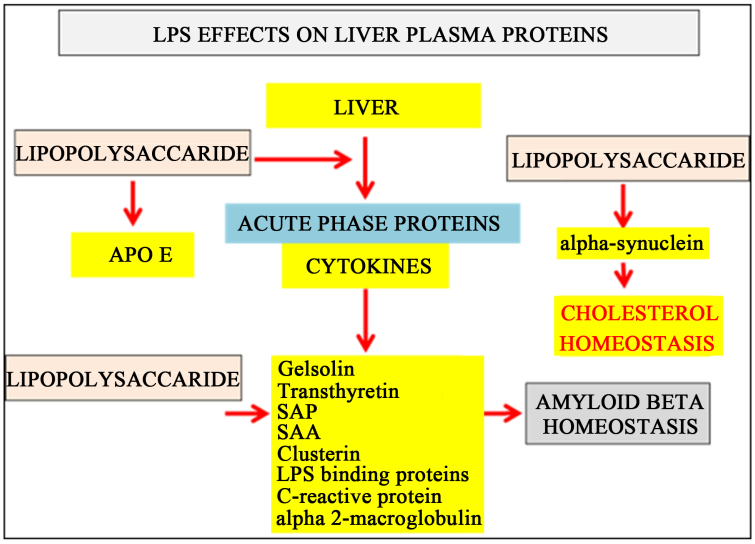

Figure 2. LPS increases the hepatic production of cytokines, APPs with marked effects on hepatic cholesterol homeostasis. LPS increases peripheral amyloidosis by interactions with APPs that interfere with the aggregation and deposition of Aβ. LPS stimulates the cellular expression of alpha-synuclein (4) that is linked to cell membrane cholesterol homeostasis and Aβ metabolism.

LPS related apo E interactions that determine the peripheral metabolism of Aβ (**Figure 2**).

The detection of misfolding in proteins associated with APP possibly involve LPS effects on APP with the reversal and the formation of amyloid fibrils determined by the levels of serum amyloid protein P (SAP) and serum amyloid A (SAA) involved in systemic amyloidosis and cholesterol metabolism [3] [21]. Gelsolin is an actin binding protein and is involved with actin filament assembly and Aβ binding [3]. Interactions with apo E are associated with gelsolin related stabliity of misfolded proteins [3]. Gelsolin and SAP have marked effects on LPS neutralization (amphipathic molecules) and compete more effectively than LPB [20] [22]. LPS has been shown to induce hepatic LBP and SAA with implications to peripheral amyloidosis [21]. Transthyretin and clusterin are protective on protein folding with a reduction in amyloid plaque formation [3] with increased plasma clusterin and transthyretin associated with LPS injections in animals [18]. Alpha 2 macroglobulinbinds to Aβ with Aβ metabolism connected to apo E/LRP receptor interactions [3]. Elevated levels of alpha 2 macroglobulin in diabetes may determine Aβ metabolism with LPS effects on alpha 2 macroglobulin homeostasis [47] connected to the peripheral amyloidosis in diabetes.

The APP C-reactive peptide (CRP) that has been shown to be increased in obesity and has been closely related to BBB permeability and disruption [3]. Increases in CRP in obesity is associated with the release of SAA [3]. These APPs induce systemic inflammation and hypercholesterolemia with induction of blood brain barrier (BBB) disturbances and release into the brain of APP may involve LPS binding to CRP [48] [49] with the regulation of brain amyloidosis. LPS induced the expression of alpha-synuclein [4] [50] has been associated with the permeability in the BBB [49] and involve cholesterol homeostasis (**Figure 2**). Nutriproteomic diets are essential to prevent the rise in APPs such as CRP and SAA as associated with aging [51]. Diets that reduce APPs are connected to the rapid clearance of plasma LPS with the prevention of LPS transport across the BBB to the CNS connected to brain cholesterol homeostasis and neurodegeneration.

The peripheral clearance of Aβ and its relationship to high fibre diets [52] has now become of particular interest to neurodegenerative diseases such as PD and AD. Nutriproteomic diets (**Figure 1**) that are low in fat and glucose activates the liver and brain anti-aging protein Sirt 1 [53]-[55] and accelerates Aβ and cholesterol metabolism. Nutriproteomic diets such as high fibre diets/low protein diets [3] increase adiponectin levels [54] [56] [57] that facilitate rapid transport of LPS from the brain across the BBB to the liver with LPS removal connected to the reduced inflammatory effects of APP, increased adiponectin levels and prevention of NAFLD [54] [58]. Functional foods (yoghurt) that contain prebiotic and probiotics may reduce gram negative bacteria in the intestine [59] [60]. However, diets high in fat (yoghurt, cream, cheese) and alcohol stimulate the rapid transport of

LPS (gram negative bacteria) across the intestinal tract that corrupt hepatic membrane receptor interactions and peripheral Aβ homeostasis. High fibre diets(fatty acids and phytosterols) have become important to the peripheral Aβ homeostasis with effects of nutritional therapy by phytosterols (ABCA1 pathways) relevant to rapid LPS transport mediated by ABCA1 in macrophages and the liver [4] [52] [61]. Furthermore polysaccarides found in food colloids [62] [63] and yoghurt may increase polysaccharides in plasma and involve pathological-polysaccaride-protein interactions with membrane fouling [64] relevant to mimickry similar to bacterial LPS cell membraneinteractions.

4. Conclusion

Interactions between apo E and Aβ have become important and associated with the peripheral clearance of Aβ and the development of neurodegenerative diseases. Accelerated aging is connected to high fat diets with the release of increased LPS from the intestine into the blood plasma closely linked to abnormal hepatic cholesterol metabolism, increased cytokine release with amyloidosis. LPS directly interact with apo E and apo B in lipid particles with marked effects on LPS mediation in the inflammatory process and hepatic cholesterol homeostasis. LPS rapidly transfer to cholesterol and sphingomyelin domains in membranes with abnormal membrane interactions with Aβ oligomers. Dietary fat increases LPS levels that neutralizes apo E, increases alpha-synuclein levels and prevents the rapid peripheral clearance of Aβ with the promotion of accelerated aging. APPs directly interact with Aβ oligomers and the role of LPS on these interactions has become important to the increased inflammation in aging populations in Western communities. The nature and amount of dietary fatty acid, cholesterol and carbohydrate have become important to assess LPS effects on hepatic APP and cytokine production associated with inflammation and the reduced peripheral clearance of Aβ. Healthy nutriproteomics diets that prevent the LPS induction of APP prevent NAFLD linked to obesity, diabetes and AD.

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Abbreviations

LPS, Lipopolysaccharides,
Apo E, Apolipoprotein E,
Aβ, Amyloid beta,
APP, Acute phase protein,
Sirt 1, Sirtuin 1,
AD, Alzheimer's disease,
PD, Parkinson's disease,
NAFLD, Non alcoholic fatty liver disease,
LBP, LPS binding protein,
SAP, Serum amyloid protein P,
SAA, Serum amyloid A,
CRP, C-reactive peptide,
BBB, Blood brain barrier.