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Short Communication Open Access

Bacterial Lipopolysaccharides Change Membrane Fluidity with Relevance to Phospholipid and Amyloid Beta Dynamics in Alzheimer's Disease

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Abstract

Bacterial lipopolysaccharides (LPS) and their increase in plasma in individuals in the developing world has become of major concern. LPS can transform cells by their rapid insertion into cell membranes that partition into cholesterol/sphingomyelin domains. LPS alter cell phospholipid dynamics associated with the recruitment of the Alzheimer's disease amyloid beta (Aβ) peptide with the promotion of toxic Aβ oligomer formation. The common pattern of naturally occurring phospholipids such as1-palmitoyl-2-oleolyl-phosphatidylcholine in cells confers cells with the rapid transfer of Aβ and phospholipids. Phospholipids such as dipalmitoylphosphatidylcholine (DPPC), dimyristoylphosphatidylcholine (DMPC) and dioleoylphosphatidylcholine (DOPC) are poorly transported with delayed metabolism of Aβ oligomers. LPS can alter cells with POPC cell membrane characteristics by insertion of itself and promotion of ganglioside GM1-cholesterol as the seed for Aβ oligomerization. LPS modification of cell membrane fluidity in neurons involves the phospholipid transfer protein that affects vitamin E, phospholipid and Aβ metabolism. Healthy diets that contain olive oil, canola oil and vegetable oil promote membrane fluidity and Aβ metabolism but in the developing world increased LPS levels interfere with healthy diets and their regulation of phospholipid and Aβ dynamics. Unhealthy diets that contain palmitic acid should be avoided that promote DPPC cell membrane contents with poor phospholipid and Aβ metabolism. Nutritional therapy may improve metabolic disease and Alzheimer's disease by the delay of LPS toxic induced Aβ interactions that involve various proteins such as albumin (Aβ self-association) with reduced toxic effects of LPS to astrocyte-neuron crosstalk in the brain.

Keywords: Lipopolysaccharide; Amyloid beta; Phospholipid; Ganglioside; Cholesterol; Membrane; Fluidity; Diet; Olive oil; Palmitic acid

Short Commentary

The interests in bacterial lipopolysaccharides (LPS) and their influence on cell membrane fluidity in the brain has accelerated with the increase in plasma LPS in individuals of the developing world with elevated LPS levels in 30% of individuals in United States of America, Australia, Germany and India [1]. LPS are endotoxins and essential components of the outer membrane of all Gram-negative bacteria. LPS from bacteria share common features in their basic architecture and consists of three covalently linked segments, a surface carbohydrate polymer (O-specific chain), a core oligosaccharide featuring an outer and inner region and an acylated glycolipid (termed Lipid A). LPS is an amphiphile that can rapidly insert into cell membranes and transform mammalian cells with a preference for insertion and partition into cholesterol/sphingomyelin (SM) domains in cell membranes [2-4] leaving the hydrophilic polysaccharide chain exposed to the exterior of the cell. LPS in cholesterol/SM-rich domains partition into ordered lipid phases of ratios phosphatidycholine such as DOPC (55), sphingomyelin (15) and cholesterol (30) membranes [2,5].

Lipid rafts preferentially sequester saturated-chain lipids and proteins such as the hydrophobic Alzheimer's disease amyloid beta (Aβ) peptide into the disordered phase and alter cells phospholipid dynamics [6] in cell membranes with the promotion of non-brownian Aβ dynamics and toxic Aβ formation [3,4]. Divalent cations such as magnesium [7] may neutralize and stabilize LPS in the outer membrane but LPS in the presence of monovalent cations forms highly negatively-charged aggregates [7]. Research studies support that LPS and lipids with highly charged or bulky head groups can promote highly curved membrane architectures due to electrostatic and/or steric repulsions [8]. It is now clear that LPS can act on plasma lipid membranes in a receptor independent interaction to phase separate into small, cholesterol and SM-rich domains (lipid rafts) in contrast to a fluid, phosphatidylcholine-rich phase [2,8]. The interactions of cholesterol, apolipoprotein E (apo E) and Aβ [9] are secondary events in cell membranes compared to the rapid cell phospholipid dynamics associated with phospholipids such as 1-palmitoyl-2-oleolyl-phosphatidylcholine (POPC). The common pattern of naturally occurring phospholipids in cells occurs with a saturated chain at the glycerol-1-phosition and an unsaturated chain at the 2-position that confers cells and lipoproteins to have unique metabolic handling with the rapid transfer of phospholipids from the lipoproteins/cells to the liver for metabolism [10]. Phospholipids such as dipalmitoyl phosphatidylcholine (DPPC), dimyristoylphosphatidylcholine (DMPC) and dioleoylphosphatidylcholine (DOPC) are poorly transported from lipoproteins to the liver with delayed metabolism [10]. Aβ oligomers and apo E have been shown to be sensitive to DPPC or DOPC membranes with monomer Aβ favoured by the POPC structures [11-13].

LPS acts on the blood brain barrier (BBB) with BBB disruption or via receptors with the induction of a neuroinflammatory response [14-16]. LPS corrupts Aβ transport across the BBB with increased influx, decreased efflux and increased neuron production of Aβ by induction

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of LRP-1 [17,18]. The effects of LPS on the BBB involve complete inhibition of the Aβ dynamics important to the peripheral hepatic clearance of Aβ. In peripheral cells, neurons and astrocytes membrane-bound and soluble proteins have been shown to bind LPS such as LPS binding protein, toll-like receptor (TLR) and CD14 receptor [19]. Activation of the TLR-4 by LPS is central to neuroinflammation that involves mouse and human astrocytes [3] with lipid rafts that sequester CD14 (GPI-linked protein) involved in TLR-4 endocytosis [20]. In AD the CD14 receptor is referred to as the LPS receptor that is involved in the phagocytosis of the Aβ peptide [18]. The insertion of LPS into neuron membranes [8,21-24] disturbs the handling of the dynamic nature of phospholipids that is essential to neuron endocytic Aβ metabolism by the insertion of the ganglioside GM1 which is a ceramide-oligosaccaride. GM1-cholesterol is found in lipoproteins, astrocytes and neurons with relevance to GM1-cholesterol as the seed for Aβ oligomerization [25-28]. LPS that disrupts the BBB corrupts the astrocyte-neuron crosstalk (Figure 1) with defective abeta clearance from neurons [3].

Lipidomics is now an important tool in lipid biochemistry involved in the characterization of plasma and cell analysis of various lipid species. In aging and AD cell membrane changes that lead to unstable membrane alterations that possibly involve the role of LPS and magnesium deficiency [7] that promote Aβ aggregation and fibril formation [29] with LPS now involved in the poor interpretation of extensive lipidomic analysis in various plasma and cells from AD individuals. LPS and its corruption of the peripheral sink Aβ hypothesis involves the corruption of phospholipid transport between lipoproteins/cells and the liver with impaired Aβ efflux across the BBB and disturbed Aβ homeostasis associated with abnormal phospholipid dynamics relevant to the metabolism of neuronal Aβ and the progression of AD. LPS has been shown to involve cholesterol efflux with effects on liver X-receptor-ATP binding cassette transporter 1 (LXR-ABCA1) interactions [4]. Monitoring dietary fat intake to reduce LPS [19] has become important with absorption of fat relevant to plasma LPS levels and non-alcoholic fatty liver disease (NAFLD). LPS effects on the release of cellular alpha-synuclein may determine membrane phospholipid and cholesterol metabolism relevant to altered cellular ceramide and sphingomyelin content [4]. LPS binds to phospholipid transfer protein (PLTP) with preference for transport by PLTP instead of vitamin E, phospholipid and Aβ transport between cells [3,4,30,31]. LPS has been shown to neutralize apo E with relevance to apo E-PLTP transport of phospholipids and Aβ [19]. Inhibitors of PLTP in plasma should be checked in various populations with relevance to drugs that have a core benzazepine core structure that inhibit PLTP [32,33].

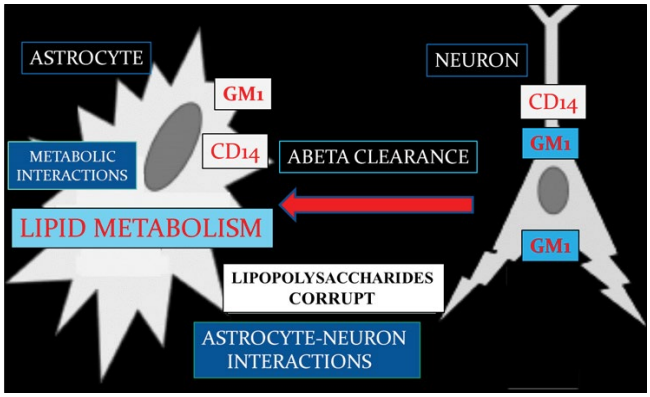

Figure 1: Bacterial LPS interfere with neuron phospholipid and amyloid beta dynamics with the promotion of toxic amyloid beta formation. LPS effects in the periphery are relevant to disruption of the peripheral clearance of amyloid beta by the liver that involve LPS and ganglioside GM1-cholesterol that corrupt the astrocyte-neuron interactions.

Nutritional therapy [9,19,34] that improves the survival of the species by the release of proteins that delay LPS toxic Aβ interactions and involve various proteins such as albumin (Aβ self-association) may be involved with reduced toxic effects of LPS associated Aβ oligomerization. Unhealthy diets such as high fat and cholesterol have been shown to increase plasma LPS levels and induce hypercholesterolemia, inflammation and NAFLD in man and mice [35-39]. Unhealthy diets that contain palmitic acid (dairy, coconut oil, palm oil) should be avoided that change cell membrane fluidity since they promote DPPC cell membrane contents with poor Aβ metabolism. Bacterial LPS can insertion into cell membranes the liver and brain with the increased induction of NAFLD and neurodegeneration.

Healthy diets such as olive oil maintain POPC cell phospholipids that confers cells with the rapid metabolism of cholesterol and Aβ. Unhealthy diets without LPS but high in cholesterol and fat (palmitic acid) may induce increased liver and neuron membrane cholesterol/DPPC lipid rafts with delayed metabolism of Aβ oligomers. Unhealthy diets that contain palmitic acid or LPS can also downregulate the nuclear receptor Sirtuin 1 (Sirt 1) [3,4,34,40] with abnormal membrane fluidity and increased cell cholesterol levels associated with alteration in phosphatidylcholine, sphingomyelin and cholesterol ratios in cholesterol/SM-rich domains. Alcohol can stimulate LPS absorption from the intestine with alcohol involved with Sirt 1 downregulation [41,42]. Sirt 1 inhibitors such as suramin and sirtinol [43] inhibit hepatic Sirt 1 with reduced clearance of LPS and increased plasma LPS levels. Alteration by LPS of liver and brain cholesterol and phospholipid dynamics promotes toxic Aβ oligomer formation with the development of AD.

Conclusion

In the developing world the rise in plasma LPS levels has become of major concern to health and nutrition. LPS can corrupt healthy diets with POPC cell membrane characteristics by insertion of itself or promotion of ganglioside GM1-cholesterol as the seed for Aβ oligomerization. LPS modification of cell membrane fluidity in the liver and neurons interfere with apo E-PLTP actions that effect vitamin E, phospholipid and Aβ metabolism. Nutritional therapy intervention such as low fat and cholesterol diets prevent the absorption of LPS and maintain liver and brain membrane fluidity in metabolic disease and Alzheimer's disease with reduced toxic effects of LPS to astrocyte-neuron crosstalk in the brain.

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