

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

Ian James Martins^{1-3*}

¹Centre of Excellence in Alzheimer's Disease Research and Care, School of Medical Sciences, Edith Cowan University, 270 Joondalup Drive, Joondalup, Australia

²School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Nedlands, Australia

³McCusker Alzheimer's Research Foundation, Hollywood Medical Centre, 85 Monash Avenue, Suite 22, Nedlands, Australia

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 ($A\beta$) peptide with the promotion of toxic $A\beta$ oligomer formation. The common pattern of naturally occurring phospholipids such as 1-palmitoyl-2-oleoyl-phosphatidylcholine in cells confers cells with the rapid transfer of $A\beta$ and phospholipids. Phospholipids such as dipalmitoylphosphatidylcholine (DPPC), dimyristoylphosphatidylcholine (DMPC) and dioleoylphosphatidylcholine (DOPC) are poorly transported with delayed metabolism of $A\beta$ oligomers. LPS can alter cells with POPC cell membrane characteristics by insertion of itself and promotion of ganglioside GM1-cholesterol as the seed for $A\beta$ oligomerization. LPS modification of cell membrane fluidity in neurons involves the phospholipid transfer protein that affects vitamin E, phospholipid and $A\beta$ metabolism. Healthy diets that contain olive oil, canola oil and vegetable oil promote membrane fluidity and $A\beta$ metabolism but in the developing world increased LPS levels interfere with healthy diets and their regulation of phospholipid and $A\beta$ dynamics. Unhealthy diets that contain palmitic acid should be avoided that promote DPPC cell membrane contents with poor phospholipid and $A\beta$ metabolism. Nutritional therapy may improve metabolic disease and Alzheimer's disease by the delay of LPS toxic induced $A\beta$ interactions that involve various proteins such as albumin ($A\beta$ 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 phosphatidylcholine 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 ($A\beta$) peptide into the disordered phase and alter cells phospholipid dynamics [6] in cell membranes with the promotion of non-brownian $A\beta$ dynamics and toxic $A\beta$ 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 $A\beta$ [9] are secondary events in cell membranes compared to the rapid cell phospholipid dynamics associated with phospholipids such as 1-palmitoyl-2-oleoyl-phosphatidylcholine (POPC). The common pattern of naturally occurring phospholipids in cells occurs with a saturated chain at the glycerol-1-position 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]. $A\beta$ oligomers and apo E have been shown to be sensitive to DPPC or DOPC membranes with monomer $A\beta$ 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 $A\beta$ transport across the BBB with increased influx, decreased efflux and increased neuron production of $A\beta$ by induction

***Corresponding author:** Ian James Martins, Centre of Excellence in Alzheimer's Disease Research and Care, School of Medical Sciences, Edith Cowan University, 270 Joondalup Drive, Joondalup, Australia, Tel: +61863042574; E-mail: i.martins@ecu.edu.au

Received June 07, 2016; Accepted July 02, 2016; Published July 10, 2016

Citation: Martins IJ (2016) Bacterial Lipopolysaccharides Change Membrane Fluidity with Relevance to Phospholipid and Amyloid Beta Dynamics in Alzheimer's Disease. J Microb Biochem Technol 8: 322-324. doi: [10.4172/1948-5948.1000304](https://doi.org/10.4172/1948-5948.1000304)

Copyright: © 2016 Martins IJ. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

of LRP-1 [17,18]. The effects of LPS on the BBB involve complete inhibition of the A β dynamics important to the peripheral hepatic clearance of A β . 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 A β 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 A β metabolism by the insertion of the ganglioside GM1 which is a ceramide-oligosaccharide. GM1-cholesterol is found in lipoproteins, astrocytes and neurons with relevance to GM1-cholesterol as the seed for A β 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 A β 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 A β hypothesis involves the corruption of phospholipid transport between lipoproteins/cells and the liver with impaired A β efflux across the BBB and disturbed A β homeostasis associated with abnormal phospholipid dynamics relevant to the metabolism of neuronal A β 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 A β 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 A β [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]. Nutritional therapy [9,19,34] that improves the survival of the species by the release of proteins that delay LPS toxic A β interactions and involve various proteins such as albumin (A β self-association) may be involved with reduced toxic effects of LPS associated A β 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 A β metabolism. Bacterial LPS can insert 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 A β . 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 A β 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 A β 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 A β oligomerization. LPS modification of cell membrane fluidity in the liver and neurons interfere with apo E-PLTP actions that effect vitamin E, phospholipid and A β 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.

Acknowledgement

This work was supported by grants from Edith Cowan University, the McCusker Alzheimer's Research Foundation and the National Health and Medical Research Council.

References

1. Akhtar S, Sarker MR, Hossain A (2014) Microbiological food safety: a dilemma of developing societies. *Crit Rev Microbiol* 40: 348-359.
2. Ciesielski F, Griffin DC, Rittig M, Moriyón I, Bonev BB (2013) Interactions of lipopolysaccharide with lipid membranes, raft models - a solid state NMR study. *Biochim Biophys Acta* 1828: 1731-1742.
3. Martins IJ (2015) Unhealthy diets determine benign or toxic amyloid beta states and promote brain amyloid beta aggregation. *Austin J Clin Neurol* 2: 1060-66.
4. Martins IJ (2015) Diabetes and cholesterol dyshomeostasis involve abnormal a-synuclein and amyloid beta transport in neurodegenerative diseases. *Austin Alzheimers J Parkinsons Dis* 2: 1020-1028.

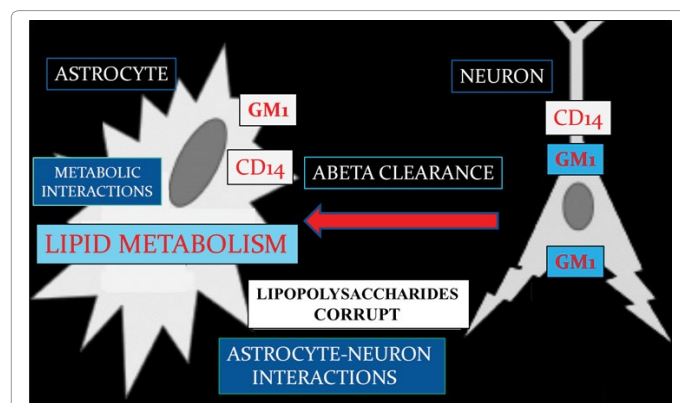


Figure 1: Bacterial LPS interfere with neuron phospholipid and amyloid beta dynamics with the promotion of toxic amyloid beta formation. LPS effects in the periphery are relevant to disruption of the peripheral clearance of amyloid beta by the liver that involve LPS and ganglioside GM1-cholesterol that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

5. De Almeida, Fedorov A, Prieto M (2003) Sphingomyelin/phosphatidylcholine/cholesterol phase diagram: Boundaries and composition of lipid rafts. *Biophys J* 85: 2406–2416.
6. Zhou X, Yang C, Liu Y, Li P, Yang H, et al. (2014) Lipid rafts participate in aberrant degradative autophagic-lysosomal pathway of amyloid-beta peptide in Alzheimer's disease. *Neural Regen Res* 9: 92-100.
7. Adams PG, Lamoureux L, Swingle KL, Mukundan H, Montañó GA (2014) Lipopolysaccharide-induced dynamic lipid membrane reorganization: Tubules, perforations, and stacks. *Biophys J* 106: 2395-2407.
8. Adams PG, Swingle KL, Paxton WF, Nogan JJ, Stromberg LR, et al. (2015) Exploiting lipopolysaccharide-induced deformation of lipid bilayers to modify membrane composition and generate two-dimensional geometric membrane array patterns. *Sci Rep* 27: 10331.
9. Martins IJ, Gupta V, Wilson AC, Fuller SJ, Martins RN (2014) Interactions between Apo E and amyloid beta and their relationship to nutriproteomics and neurodegeneration. *Current Proteomics* 11: 173-183.
10. Martins IJ, Lenzo NP, Redgrave TG (1989) Phosphatidylcholine metabolism after transfer from lipid emulsions injected intravenously in rats Implications for high-density lipoprotein metabolism. *Biochim Biophys Acta* 1005: 217-224.
11. Peters-Libeu CA, Newhouse Y, Hall SC, Witkowska HE, Weisgraber KH (2007) Apolipoprotein E**dipalmitoyl* phosphatidyl choline particles are ellipsoidal in solution. *J Lipid Res* 48: 1035-1044.
12. Hane F, Drolle E, Gaikwad R, Faught E, Leonenko Z (2011) Amyloid- β^2 aggregation on model lipid membranes: an atomic force microscopy study. *J Alzheimers Dis* 26: 485-494.
13. Drolle E, Gaikwad RM, Leonenko Z (2012) Nanoscale electrostatic domains in cholesterol-laden lipid membranes creates a target for amyloid binding. *Biophys J* 103: L27-29.
14. Ghosh A, Birngruber T, Sattler W, Kroath T, Ratzer M, et al. (2014) Assessment of blood-brain barrier function and the neuroinflammatory response in the rat brain by using cerebral open flow microperfusion (cOFM). *PLoS One* 9: e98143.
15. Banks WA, Gray AM, Erickson MA, Salameh TS, Damodarasamy M, et al. (2015) Lipopolysaccharide-induced blood-brain barrier disruption: Roles of cyclooxygenase, oxidative stress, neuroinflammation, and elements of the neurovascular unit. *J Neuroinflammation* 12: 223.
16. Banks WA, Robinson SM (2010) Minimal Penetration of Lipopolysaccharide across the Murine Blood-brain barrier. *Brain Behav Immun* 24: 102–109.
17. Jaeger LB, Dohgu S, Sultana R, Lynch JL, Owen JB, et al. (2009) Lipopolysaccharide alters the blood-brain barrier transport of amyloid beta protein: a mechanism for inflammation in the progression of Alzheimer's disease. *Brain Behav Immun*. 23: 507-517.
18. Liu Y, Walter S, Stagi M, Cherny D, Letiembre M, et al. (2005) LPS receptor (CD14): A receptor for phagocytosis of Alzheimer's amyloid peptide. *Brain* 128: 1778-1789.
19. Martins IJ (2015) LPS regulates apolipoprotein E and A β interactions with effects on acute phase proteins and amyloidosis. *Advances in Aging Research* 4: 69-77.
20. Zanoni I, Ostuni R, Marek LR, Barresi S, Barbalat R, et al. (2011) CD14 controls the LPS-induced endocytosis of Toll-like receptor 4. *Cell* 147: 868-880.
21. Li Y, Powell DA, Shaffer SA, Rasko DA, Pelletier MR, et al. (2012) LPS remodeling is an evolved survival strategy for bacteria. *Proc Natl Acad Sci U S A* 109: 8716-8721.
22. Clifton LA, Skoda MW, Daulton EL, Hughes AV, Le Brun AP, et al. (2013) Asymmetric phospholipid: lipopolysaccharide bilayers; a Gram-negative bacterial outer membrane mimic. *J R Soc Interface* 10: 89.
23. Pei B, Chen JW (2003) More ordered, convex ganglioside-enriched membrane domains: the effects of GM1 on sphingomyelin bilayers containing a low level of cholesterol. *J Biochem* 134: 575-581.
24. Nikolaeva S, Bayunova L, Sokolova T, Vlasova Y, Bachteeva V, et al. (2015) GM1 and GD1a gangliosides modulate toxic and inflammatory effects of E. coli lipopolysaccharide by preventing TLR4 translocation into lipid rafts. *Biochim Biophys Acta* 1851: 239-247.
25. Yanagisawa K1 (2005) GM1 ganglioside and the seeding of amyloid in Alzheimer's disease: endogenous seed for Alzheimer amyloid. *Neuroscientist* 11: 250-260.
26. Šachl R, Amaro M, Aydogan G, Koukalová A, Mikhalyov II, et al. (2015) On multivalent receptor activity of GM1 in cholesterol containing membranes. *Biochim Biophys Acta* 1853: 850-857.
27. Frey SL, Chi EY, Arratia C, Majewski J, Kjaer K, et al. (2008) Condensing and fluidizing effects of ganglioside GM1 on phospholipid films. *Biophys J* 94: 3047-3064.
28. Nicastro MC, Spigolon D, Librizzi F, Moran O, Ortore MG, et al. (2016) Amyloid β -peptide insertion in liposomes containing GM1-cholesterol domains. *Biophys Chem* 208: 9-16.
29. Martins IJ (2016) Magnesium therapy prevents senescence with the reversal of diabetes and Alzheimer's disease. *Health* 8: 694-710.
30. Desrumaux C, Pisoni A, Meunier J, Deckert V, Athias A, et al. (2013) Increased amyloid- β^2 peptide-induced memory deficits in phospholipid transfer protein (PLTP) gene knockout mice. *Neuropsychopharmacology* 38: 817-825.
31. Martins IJ, Hopkins L, Joll CA, Redgrave TG (1991) Interactions between model triacylglycerol-rich lipoproteins and high-density lipoproteins in rat, rabbit and man. *Biochim Biophys Acta* 1081: 328-338.
32. Luo Y, Shelly L, Sand T, Reidich B, Chang G, et al. (2010) Pharmacologic inhibition of phospholipid transfer protein activity reduces apolipoprotein-B secretion from hepatocytes. *J Pharmacol Exp Ther* 332: 1100-1106.
33. Rakonczay Z (2003) Potencies and selectivities of inhibitors of acetylcholinesterase and its molecular forms in normal and Alzheimer's disease brain. *Acta Biol Hung* 54: 183-189.
34. Martins IJ (2015) Unhealthy nutrigenomic diets accelerate NAFLD and adiposity in global communities. *J Mol Genet Med* 9: 1-11.
35. Huang H, Liu T, Rose JL, Stevens RL, Hoyt DG (2007) Sensitivity of mice to lipopolysaccharide is increased by a high saturated fat and cholesterol diet. *J Inflamm (Lond)* 4: 22.
36. Ghosh SS, Righi S, Krieg R, Kang L, Carl D, et al. (2015) High fat high cholesterol diet (Western Diet) aggravates atherosclerosis, hyperglycemia and renal failure in nephrectomized LDL receptor knockout mice: Role of intestine derived lipopolysaccharide. *PLoS One* 10: e0141109.
37. Kim KA, Gu W, Lee IA, Joh EH, Kim DH (2012) High fat diet-induced gut microbiota exacerbates inflammation and obesity in mice via the TLR4 signaling pathway. *PLoS One* 7: e47713.
38. Pendyala S, Walker JM, Holt PR (2012) A high-fat diet is associated with endotoxemia that originates from the gut. *Gastroenterology* 142: 1100-1101.
39. Erridge C, Attina T, Spickett CM, Webb DJ (2007) A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. *Am J Clin Nutr* 86: 1286-1292.
40. Martins IJ (2016) Anti-aging genes improve appetite regulation and reverse cell senescence and apoptosis in global populations. *Advances in Aging Research* 5: 9-26.
41. Wang HJ, Zakhari S, Jung MK (2010) Alcohol, inflammation, and gut-liver-brain interactions in tissue damage and disease development. *World J Gastroenterol* 16: 1304-1313.
42. Lieber CS, Leo MA, Wang X, Decarli LM (2008) Effect of chronic alcohol consumption on hepatic SIRT1 and PGC-1 α in rats. *Biochem Biophys Res Commun* 370: 44-48.
43. Martins IJ (2016) Drug therapy for obesity with anti-aging genes modification. *Ann Obes Disord* 1: 1001.