2016

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10.5539/jfr.v5n6p45
Martins, I. J. (2016). Food quality induces a miscible disease with relevance to Alzheimer's disease and Neurological diseases. Journal of Food Research, 5(6), 45.
https://doi.org/10.5539/jfr.v5n6p45

Journal of Food Research; Vol. 5, No. 6; 2016
ISSN 1927-0887 E-ISSN 1927-0895
Published by Canadian Center of Science and Education

Food Quality Induces a Miscible Disease with Relevance to Alzheimer's Disease and Neurological Diseases

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Received: August 30, 2016 Accepted: September 12, 2016 Online Published: October 14, 2016

doi:10.5539/jfr.v5n6p45 URL: http://dx.doi.org/10.5539/jfr.v5n6p45

Abstract

Food and nutrition guidelines for the handling and processing of fresh fruit, bread, and vegetables are essential and fresh produce may require cold preservation procedures to prevent minimal bacterial and fungi contamination of food. Bacterial lipopolysaccharides (LPS) corrupt lipoprotein and amyloid beta (Aβ) metabolism in diabetes, Alzheimer's disease (AD) and various neurological diseases. In the developing world the increased plasma LPS levels induce non-alcoholic fatty liver diseases and interfere with albumin and Aβ interactions with spontaneous Aβ oligomer formation in the cerebrospinal fluid and brain that leads to neuron apoptosis by inactivation of Starling's equation that is responsible for the maintenance of hydrostatic and oncotic pressure with relevance to fluid balance. In the developing world increased levels of LPS, mycotoxin and xenobiotics lead to irreversible neurological diseases by inhibition of Starling's equation for maintenance of oncotic/osmotic pressure that lead to neuron senescence or apoptosis. In the developed world nutrigenomic diets are required that prevent Sirtuin 1 gene repression and maintain neuron survival that links the brain and peripheral hepatic monomer Aβ metabolism. The maintenance of blood-cerebrospinal fluid capillary transport of albumin and monomer Aβ is relevant to stabilization of neurons not only in Alzheimer's disease but also in Type 3 diabetes and various neurological diseases. Healthy diets reverse the inhibition of brain to peripheral Aβ transport that is sensitive to Starling's equation for regulation of central nervous system hydrostatic and oncotic pressure with the prevention of diabetes, various neurological diseases and Alzheimer's disease.

Keywords: diet, lipopolysaccarides, albumin, Starling equation, amyloid beta, neurologic disease, Alzheimer's disease, diabetes

1. Introduction

The gene-environment interaction may indicate a population's risk to chronic disease progression with effects of diet that may override genomic expression in populations. In the developing and developed world the United States of America may be a good example of populations that include Caucasians, African Americans, Hispanics, Native Americans, Pacific Islanders or Asians for assessment for neurological diseases. Neurological diseases include Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, autism and neurodevelopmental disorders, neuromuscular disorders/peripheral neuropathies and neurobehavioural disorders. Neurodegeneration is referred to as the accelerated aging of neurons leading to alterations in shape, size and stability of neurons in these neurological diseases.

Interests in premature aging, food and nutrition science may assist in the understanding of diets involved with brain astrocyte aging essential for neuronal survival (Martins & Creegan, 2014; Rodr ǵuez-Arellano *et al*, 2016). Neurons and various cells in the body synthesize amyloid beta a monomeric 4 kd peptide that is extremely susceptible to self-aggregation as toxic oligomer species (Yun et al, 2007) and spontaneous fibril formation and transport of the monomeric amyloid beta (Aβ) species from the brain across the blood brain barrier to the plasma compartment is required for rapid metabolism to the liver (Martins, 2015).

In AD and various other neurological diseases such as a miscible chronic disease that involves Type 3 diabetes (Martins, 2015) may lead to early aging with neuron senescence and associated with food quality and safety (Martins, 2015). Interest in the calorie sensitive gene Sirtuin 1 (Sirt 1) (Herskovits & Guarente, 2014; Tang & Chua, 2008, Guarente, 2007, Hansen & Connolly, 2008) have accelerated with relevance to food and nutrition with its downregulation associated with neuron senescence, circadian rhythm abnormalities with relevance to defective Aβ metabolism in various neurological diseases. Sirt 1 is a 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. Nutritional regulation (calorie restriction) of Sirt1 is involved in neuron proliferation with effects on cellular cholesterol closely linked to Aβ clearance in AD (Martins, 2015).

Microbiological spoilage of food in the developing world has become important with unsafe food that contains harmful bacteria (WHO/Food safety, 2015). Microbiological contamination of food can occur at the place of production or at the market place and home. Unsafe gram negative bacteria may reside in unpasteurized milk, undercooked meat and fresh fruits and vegetables that are poorly distributed or stored. Delayed transport of food products may allow temperature related modification of food production, storage and distribution with high bacterial/fungal contamination (Hymery, et al, 2014; Makun, 2013; Leff & Fierer, 2013; Howel, 1912). Many publications in the developed world indicate that hypercholesterolemia is connected obesity, Type II diabetes and neurological diseases and numerous studies have linked defective high density lipoprotein (HDL) metabolism to cardiovascular disease and neurodegeneration (Hottman et al. 2014). Food quality and food science has now become important to determine the effects of ingested food that contain microbiological contamination on defective HDL cholesterol metabolism and the induction of non alcoholic liver disease (NAFLD) that has reached epidemic levels in the world (Younossi et al. 2016).

Lipopolysaccarides (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). 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. LPS can rapidly insert into cell membranes with a preference for insertion and partition into cholesterol/sphingomyelin domains in cell membranes (Martins, 2015; Ciesielski et al, 2012). LPS has been associated with repression of the anti-aging gene Sirt 1 with relevance to metabolic diseases, NAFLD, diabetes and Alzheimer's disease (Martins, 2015; Martins, 2015; Martins, 2016; Martins, 2016; Martins, 2016).

Dietary fat increase plasma endotoxins such as LPS into the blood plasma (Feingold et al, 1992;Miele, et al, 2013; Le Roy et al, 2013; Alisi, et al, 2012; Duseja, et al, 2014) that bind to LPS binding proteins, lipoproteins and cell receptors (Fenton & Golenbock, 1998). Lipoproteins such as chylomicron that are produced after taking a meal high in fats contain the LPS binding protein (LBP) that bind LPS and are essential for interactions of LPS to apo B containing cholesterol-rich lipoproteins (chylomicron remnants, very low density lipoproteins, high density lipoproteins). Interest in LPS in relation to dyslipidemia has escalated with relevance to the neutralization of apo E by binding of LPS (amphipathic α-helix organization) and the toxic effects of LPS are neutralized in the body by rapid transport to the liver for metabolism (Martins, 2015). Increased plasma LPS elicit hepatic release of cytokines and acute phase proteins (APP) and lipoproteins such as HDL that contain apo E and apolipoprotein AI (apo AI) may classically be involved in the modulation of the inflammatory response that involve the liver and immune cells (Martins, 2015).

Interactions between HDL and lipoproteins (chylomicrons, very low density lipoproteins, low density lipoproteins) with relevance to cholesterol transport that involve lipid transfer proteins such as cholesterol ester transport proteins and phospholipid transport proteins has become important with relevance to LPS and its interactions with phospholipid and cholesterol transport to lipoproteins and cell membranes (Martins, 2015; Martins, 2016). Interactions between LPS and apo AI have also been reported with effect on LPS on inflammatory responses and diminished by apo AI function with detrimental effects on HDL and reverse cholesterol transport (Henning et al, 2006;Wang et al, 2008; Gupta et al, 2005). Therefore LPS has detrimental effects on HDL metabolism and reverse cholesterol transport that involve neutralization of apo E and apo AI with the induction of dyslipidemia and NAFLD.

2. Amyloid Beta Metabolism Is Defective in Alzheimer's Disease and Neurological Diseases and Associated with Chronic Diseases

The role of cholesterol in modulating the expression of amyloid precursor protein (APP) and the levels of cell Aβ have been reported. The cholesterol receptors low density receptor related protein 1 (LRP-1) and low density

lipoprotein receptor (LDL r) act on the blood brain barrier (BBB) and regulate the transport of Aβ from the brain to the periphery (Martins, 2015). In chronic diseases such as obesity and diabetes excessive food intake may increase plasma LPS levels with interference with Sirt 1's circadian regulation (Martins, 2016) of Aβ metabolism by corruption of peripheral plasma Aβ metabolism in both Alzheimer's disease and various neurological diseases (Erickson et al, 2012). In various neurological diseases the transport of Aβ is corrupted with several reports of BBB disorders associated with neurodegenerative diseases (Rosenberg, 2012; Kanwar, et al, 2012).

Sirt 1 is also responsible for alpha-synuclein metabolism with alpha-synuclein important to interactions with cholesterol in cell membranes relevant to Aβ metabolism (Martins, 2015). Albumin has been shown to bind Aβ and LPS with levels of LPS being reported to decrease in plasma albumin levels. The plasma, CSF and the brain Aβ's self aggregation properties can be determined by the levels of albumin and vitamin E levels with the circadian variations of CSF protein (Nilsson, et al, 1992) under the influence of Sirt 1. CSF in neurological and AD individuals contain apo E with essential involvement in amyloid beta clearance and metabolism (Hesse *et al.*, 2000; Cruchaga *et al.*, 2012). LPS is involved with the neutralization of apo E and the induction of NAFLD (Martins, 2015; Harte *et al.*, 2010; Miele *et al.*, 2013) with lower CSF albumin levels and inactivated apo E associated with defective CSF transport of amyloid beta relevant to accelerated amyloid beta aggregation in the CSF. The interest in CSF Aβ metabolism in diabetes (Kobessho, et al, 2008; Manschot, et al, 2008) and neurological diseases has accelerated with neurological disease now linked primarily to dietary LPS plasma levels, insulin resistance and accelerated Aβ aggregation.

Research in the role of LPS in the peripheral sink Aβ hypothesis (Martins, 2015) has escalated with the improved understanding of the LPS effects on astrocytes and neurons in the brain and effects on the transport across the blood brain barrier (BBB). LPS has been associated with impaired Aβ efflux across the BBB with the downregulation of the (LRP-1) that has previously been shown to be critical to the Aβ efflux from the brain (Lee *et al.*, 2008). The effects of systemic LPS on disturbed Aβ homeostasis are relevant to Aβ generation (Lee *et al.*, 2008; Llewellyn *et al.*, 2010). Activation of inflammation in astrocytes by LPS corrupt the important role of astrocytes in the metabolism of neuronal Aβ (24) with the development of AD. In the brain the CD14 receptor is referred to as the LPS receptor and involved with Aβ metabolism (Martins & Creegan, 2014). LDL receptor deficiency was associated with astrocytosis with increased amyloid deposition and implicate LPS and interactions with the LDLr in astrocyte-neuron Aβ metabolism (Martins, 2015; Martins & Creegan, 2014).

The Starling equation (Starling, 2016) indicates the movement of fluid across membranes by calculation of hydrostatic and oncotic pressure that involve the blood: CSF barrier and CSF: blood brain barrier (Feingold et al, 1992;Miele, et al, 2013; Le Roy et al, 2013; Alisi, et al, 2012; Duseja, et al, 2014). In the Starling equation as shown below the reflection coefficient (sigma) is a correction factor that indicates changes in the oncotic pressure as a result of protein changes in the CSF compartment. Cappillary membranes do not allow large molecular weight proteins to pass into the CSF compartment but albumin and monomeric Aβ has access to the CSF compartment to maintain the oncotic pressure.

The adapted Starling equation () reads as follows:

$$J_v = K_f([P_c - P_i] - \sigma[\pi_c - \pi_i])$$

where:

J_v is the net fluid movement between compartments.

$[P_c - P_i] - \sigma[\pi_c - \pi_i]$ is the net driving force,

- P_c is the capillary hydrostatic pressure
- P_i is the interstitial hydrostatic pressure
- π_c is the capillary oncotic pressure
- π_i is the interstitial oncotic pressure
- K_f is the filtration coefficient – a proportionality constant
- σ is the reflection coefficient

The reflection coefficient correction factor will change when LPS arrives into the plasma/ CSF compartment by a reduction in albumin and spontaneous aggregation of Aβ (**Figure 1**) with complete corruption of the peripheral clearance Aβ pathway (Martins, 2015) relevant not only to Alzheimer's disease but also to diabetes and various neurological diseases. LPS will change membrane fluidity (Martins 2015; Martins, 2016) with effects on the filtration coefficient of the Starling equation at the blood:CSF barrier and CSF:blood brain barrier with corruption of the influx and efflux of Aβ (Martins, 2016). LPS effects on brain membrane fluidity (**Figure 1**) supersede phospholipid and monomer Aβ membrane interactions with the promotion of non-Brownian Aβ

dynamics in the plasma, CSF and brain (Martins, 2015; Martins, 2016). Effects of LPS on Aβ transport involve alpha synuclein with effects on membrane fluidity that involve cholesterol (Martins, 2015) and Aβ oligomers in the CSF and brain with LPS involved in the transformation of membranes in capillaries that override the filtration coefficient that determines protein (albumin/Aβ) transport in the CSF and brain (**Figure 1**).

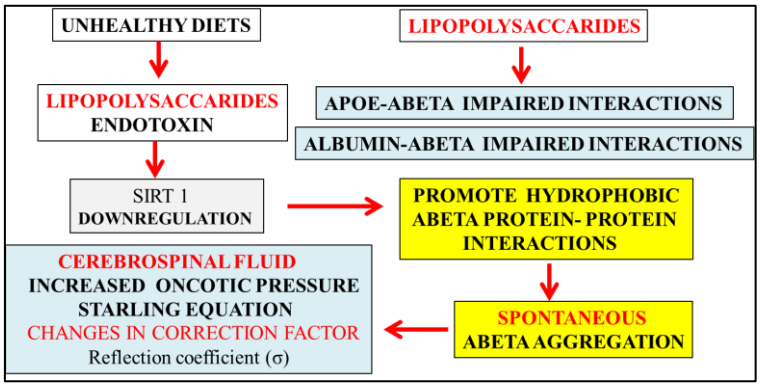

Figure 1. Unhealthy diets increase LPS levels with effects in the cerebrospinal fluid that promote amyloid beta aggregation with corruption of membrane fluidity (blood:CSF barrier and CSF:blood brain barrier) and do not allow the passage of essential proteins such as albumin into the CSF. LPS effects on Starling equation is associated with increased oncotic pressure and associated with defects in the brain transport of amyloid beta from the CNS via the cerebrospinal fluid into the plasma for metabolism by the liver.

The effects of bacterial LPS to chronic disease may be linked to developing or third world countries associated with poor hygiene standards and poor food storage and corruption of Starling Law may lead to irreversible autonomous disease associated with central nervous system fluid balance dyshomeostasis (Feingold et al, 1992;Miele, et al, 2013; Le Roy et al, 2013; Alisi, et al, 2012; Duseja, et al, 2014). LPS in these developing countries repress Sirt 1 expression and completely inactivate the brain from the periphery with a defect in Aβ metabolism. In these developing countries mycotoxin (Martins, 2015) and xenobiotics levels (Martins, 2013) found in food and water may be elevated and may further induce CSF Aβ aggregation and elevated oncotic pressure diseases (Martins, 2013). Sirt 1 is a calorie sensitive gene and in the developed world nutrigenomic diets (Sirt 1 upregulation) may be appropriate to reverse circadian rhythm abnormalities with effects on improved peripheral amyloid beta metabolism with decreased CSF amyloid aggregation and improvements in calculations for the Starling equation by CNS albumin and amyloid beta transport with relevance to fluid transport to the brain (Starling, 2016; Buishas et al, 2014). Dietary intake in the developing and developed world in various chronic and neurologic diseases need dietary modifications with lifestyle changes to allow reversal of defective Aβ metabolism and physiological fluid balances that are essential for neuron survival and reversal of accelerated aging.

3. Food Quality and the Nature of Diet Maintains Post-Prandial Lipid and Amyloid Beta Metabolism Relevant To Diabetes and Neurological Diseases

The consumption of the very low carbohydrate and low fat diets (Martins, 2015) are required to prevent LPS absorption and prevent LPS repression of the anti-aging gene Sirt 1 that is now linked to the defective gene-environment interactions involved in defective liver cholesterol metabolism (post-prandial) associated with insulin resistance, NAFLD disturbed brain Aβ transport in various neurological diseases. Furthermore, healthy diets that maintain LPS and protein interactions with proteins such as albumin, lactoferrin and transferrin and other acute phase proteins/glycoasminoglycans delay LPS induced Aβ toxic oligomer formation connected to neuron number important to thinking and intelligence (Martins, 2016).

In obesity and diabetes the LPS level in the blood plasma are elevated and related to hyperglycemia and NAFLD (Harte *et al.*, 2010; Miele *et al.*, 2013). In the developing and developed world dairy products such as French cheese and yoghurt (Arslan *et al.* 2011; Coton *et al.*, 2011; Hickey *et al.*, 2015) should be consumed as recommended by food safety practices. Gram negative bacteria such as E Coli and Pseudomonas aeruginosa (Arslan *et al.* 2011) can be involved in the fermentation and food spoilage that release LPS into the intestine. Diets that are high in fat and cholesterol stimulate LPS absorption (Huang, *et al.*; 2007 Lee, 2013) with increased risk for NAFLD (Harte *et al.*, 2010; Miele *et al.*, 2013). Dairy foods such as cheese and yogurt may involve many variables that include the milk preparation and temperature (storage, light, time). Modern technologies that involve freezers with safe storage time and lifetime in the food industry do not allow for microbiological

contamination (gram negative bacteria) in the developed world compared with the developing world.

The potent effects of apple and cheese spoilage produces the mycotxon patulin that can be concentrated in the brain and liver with the corruption of the apo E mediated clearance of Aβ induced by patulin with relevance to post-translational modification of proteins (Martins, 2015). Ochratoxin A (OTA) is found in the rind and inner part of the cheese, coffee and in alcohol (beer, wine) and can lead to increased OTA to the brain with neuron apoptosis. Alcohol (apple cocktail, beer, wine) promotes the intestinal absorption of LPS and myoctoxin and alcohol is a Sirt 1 inhibitor with relevance to corruption of the brain and peripheral regulation of Aβ metabolism. Stress and lifestyle changes may induce an apelinergic dysfunction (Martins, 2015) with individuals in the developing world more susceptible to CSF Aβ aggregation associated with the absence of the brain to peripheral links in hepatic Aβ metabolism.

Activators of Sirt 1 (nutrigenomic diets) are required such as leucine, pyruvic acid and magnesium (Martins, 2016) that maintain hepatic and brain Sirt 1 activity to prevent delayed hepatic cholesterol and brain Aβ metabolism with relevance to Type 3 diabetes and NAFLD (Martins, 2016). Excessive phosphatidylinositol doses (gm/day) (Martins, 2015) need to be administered to individuals in the developing world to reverse plasma, CSF and brain Aβ aggregation with phosphatidylinositol doses important to therapeutic effects on membrane stability and fluid filtration. Central acting CNS drugs to maintain oncotic/osmotic pressure in diabetes and various neurological diseases need to be consumed with excellent food quality to prevent LPS/mycotoxin/xenobiotic ill effects (Martins, 2015; Martins, 2016). LPS/mycotoxin contamination can be associated with the packing, storage, transportation, handling, and processing of fresh produce to the final destination needs to be assessed carefully.

4. Conclusion

In the developing and developed world the induction of NAFLD, diabetes, neurological diseases and Alzheimer's disease is now connected to the handling and processing of food and may require cold preservation procedures to prevent minimal bacterial and fungi contamination. The peripheral sink clearance Aβ pathway that is critical to maintain neuron survival is inactivated by increased plasma/CSF contents of LPS and mycotoxin with complete nullification of Starling's equation for hydrostatic and oncotic pressure regulation in the brain with relevance to the developing world. The brain and peripheral links to hepatic Aβ metabolism is now very important not only to Alzheimer's disease but to various neurological diseases, Type 3 diabetes, NAFLD. In the developing world the gene-environment effects may not include the participation of the anti-aging gene Sirt 1 that is responsible for the maintenance of CSF circadian rhythm, neuron proliferation and peripheral Aβ metabolism. LPS downregulates Sirt 1 and corrupts the Starling forces by interference with capillary membrane fluidity and the regulation of albumin levels relevant to toxic Aβ and alpha-synuclein formation in the CSF and brain. Peripheral Aβ metabolism is now relevant to diabetes and various neurological diseases and reversal of neurological diseases/Alzheimer's disease in the developed world now involves a healthy diet that promotes the rapid Aβ transport from the brain to the CSF for rapid metabolism to the liver.

Acknowledgements

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

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