Insulin resistance and Cholesterol dyshomeostasis involve α-Synuclein and Amyloid beta interactions in Neurodegenerative diseases

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INTRODUCTION

Epidemiological studies indicate that diabetes, Parkinson's disease (PD) and Alzheimer's disease (AD) are closely linked with dysregulated cholesterol pathways that involve molecular genetics, cell biology and insulin resistance in the pathogenesis of these diseases. In Parkinson's disease the α-synuclein protein is an amyloidogenic protein shown to bind to cholesterol. The binding of AD amyloid beta (Aβ) has been associated with cholesterol in membranes with the regulation of Aβ metabolism closely connected to plasma cholesterol levels. Interests in proteins and their interactions with membrane lipids in neurodegenerative diseases have accelerated with the existence Aβ and α-synuclein pathologies in individuals with neurodegeneration. The peripheral sink Aβ hypothesis (**REF 1**) is closely associated with the anti-aging gene Sirtuin 1, bacterial lipopolysaccharides (LPS) (**REF 2**) and cholesterol regulation possibly connected to the metabolism of Aβ and α-synuclein protein in diabetes and neurodegenerative diseases. **REF 1**: Martins IJ. Diabetes and Cholesterol Dyshomeostasis Involve Abnormal α-Synuclein and Amyloid Beta Transport in Neurodegenerative Diseases. Austin Alzheimers J Parkinsons Dis. 2015;2(1): 1020-28.**REF 2:** Martins IJ. Bacterial Lipopolysaccharides and Neuron Toxicity in Neurodegenerative Diseases. Neurol Neurosurg. 2018; 1(1): 1-3.

METHODS AND RESULTS

The role of molecular genetics with relevance to neurological diseases now involves the gene Sirtuin 1 (Sirt 1) that determines circadian rhythm, insulin resistance and protein aggregation in various neurodegenerative diseases (**REF 3**). In a previous model (**Figure 1**) for the peripheral sink amyloid beta clearance pathway the membrane cholesterol content was critical for the metabolism of amyloid beta and amyloid beta oligomerization. The role of Sirt 1 in the regulation of membrane cholesterol flux within cells indicates its essential role in amyloid beta aggregation. In Parkinson's disease the α-synculein protein (**REF1**) is an amyloidogenic protein shown to bind to cholesterol (tilted peptide 67-78/isooctyl chain) with membrane cholesterol levels that determine amyloid beta and alpha-synuclein interactions (**Figure 1**). The peripheral sink amyloid beta clearance model has been revised with Sirt 1 regulation of heat shock proteins (HSP) involved in amyloid beta aggregation (**REF 4**) and the promotion of alpha-synuclein aggregation. **REF 3**: Martins IJ. Nutritional and Genotoxic Stress Contributes to Diabetes and Neurodegenerative Diseases such as Parkinson's and Alzheimer's Diseases. - Frontiers in Clinical Drug Research -CNS and Neurological Disorders. Volume 3 Editor: Atta-ur-Rahman Pp. 158-192 (35**REF 4:** Martins IJ. Calorie Sensitive Anti-Aging Gene Regulates Hepatic Amyloid Beta Clearance in Diabetes and Neurodegenerative Diseases". EC Nutrition ECO.01 (2017): 30-32.

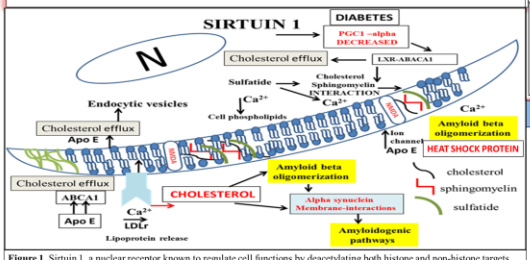


Figure 1. Sirtuin 1, a nuclear receptor known to regulate cell functions by deacetylating both histone and non-histone targets when down regulated is associated with circadian abnormalities and with poor glucose and cholesterol metabolism linked to abnormal heat shock protein-amyloid beta metabolism in Alzheimer's disease with increased α-synuclein aggregation in Parkinson's disease

METHODS AND RESULTS

Literature searches of the databases indicate that Sirt 1 regulation of immune responses (**REF 5, REF 6**) are connected to mitochondrial apoptosis in neurodegenerative diseases. Nutritional biotherapy is essential for activation of Sirt 1 and control of neuron mitophagy. Toxic protein aggregation has become of major concern to various neurological diseases with Sirt 1 important not only to HSP–amyloid beta aggregation and alpha-synuclein aggregation but also to cellular prion and tau protein homeostasis (**REF 2**) **Figure 2**. Literature reviews indicate that the critical repressor of Sirt 1 is bacterial lipopolysaccharide (LPS) (**REF 7**) with LPS linked to neuron toxicity in neurodegenerative diseases (**REF2**). LPS are endotoxins and essential components of the outer membrane of gram negative bacteria and consist of covalently linked segments, surface carbohydrate polymer, core oligosaccharide and acylated glycolipid that can bind to cell membranes to alter membrane interactions (**REF 8**). Sirt 1 regulation of hepatic drug metabolism (**REF 9**) may be regulated by LPS with connections to toxic protein aggregation in neurodegenerative diseases.

REF 5: Heat Shock Gene Inactivation and Protein Aggregation with Links to Chronic Diseases. Diseases. 2018, 6;39:1-5.

REF 6: Appetite Control and Biotherapy in the Management of Autoimmune Induced Global Chronic Diseases. J Clin Immunol Res. 2018; 2(1): 1-4.

REF 7: The Future of Genomic Medicine Involves the Maintenance of Sirtuin 1 in Global Populations. Int J Mol Biol . 2017. 2(1): 00013.

REF 8: Bacterial Lipopolysaccharides Change Membrane Fluidity with Relevance to Phospholipid and Amyloid Beta Dynamics in Alzheimer's Disease. J Microb Biochem Technol. 2016; 8: 322-324.

REF 9: Sirtuin 1, a Diagnostic Protein Marker and its Relevance to Chronic Disease and Therapeutic Drug Interventions". EC Pharmacology and Toxicology 6.4 (2018): 209-215.

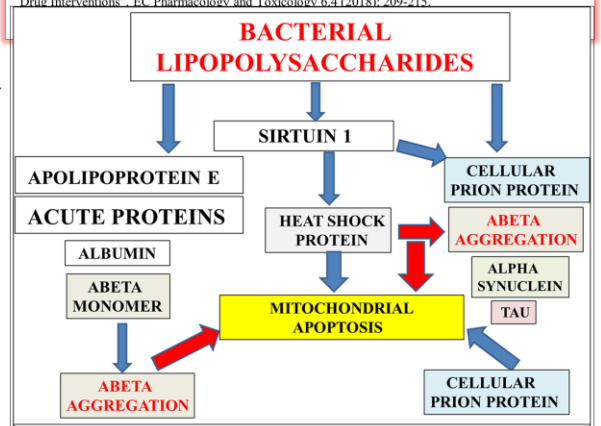


Figure 2. LPS neutralize various proteins and repress the nuclear receptor Sirt 1 relevant to protein aggregation and mitochondrial apoptosis. The effects of LPS on mitophagy may be mediated by acute phase proteins, albumin, cellular prion protein or amyloid beta aggregation. Under core body temperature disturbances heat shock proteins induce amyloid beta/cellular prion alpha synuclein protein aggregation and induce neuronal mitophagy

CONCLUSIONS

1. Diabetes, Parkinson's disease and neurodegenerative diseases require the nuclear receptor Sirtuin 1 activation essential for the prevention of neuron mitophagy.

2. Healthy diets are required to maintain therapeutic drug metabolism for the treatment of neurodegenerative diseases.

3. Plasma LPS levels need to be assessed to prevent protein aggregation in the brain with neuron mitophagy responsible for accelerated neuron death in Parkinson's disease and neurodegenerative diseases.