Commentary

Appetite Regulation and the Peripheral Sink
Amyloid beta Clearance Pathway in Diabetes and Alzheimer’s Disease

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First Published October 03, 2018

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Major interests in senescence and neurodegenerative diseases [1,2] have raised concerns with relevance to appetite regulation and the inactivation of the peripheral sink amyloid beta (Aβ) clearance pathway. Appetite control is now critical to neuron survival [3] with the peripheral sink Aβ clearance pathway and epigenetic alterations linked to neurodegeneration [3]. The release of Aβ (MWT 4 kd) monomers from neurons is associated with the Aβ clearance from the brain and determined by the apolipoprotein E mediated efflux of Aβ [4] across the blood brain barrier to the periphery with rapid uptake by the liver [5]. The activation of the peripheral sink amyloid beta clearance pathway to reduce brain Aβ levels has been studied by various laboratories [6-8]. Cellular senescence and toxic Aβ aggregation in diabetes and neurodegenerative diseases have become of major concern with the recent discovery of the Sirtuin 1 (Sirt 1) gene that is now the major gene involved in senescence [9] and global chronic disease in man [10,11]. Dietary interventions are now critical to appetite regulation and senescence with high calorie diets, bacterial lipopolysaccharides (LPS), low zinc levels, mycotoxins [12] and low magnesium levels [13] associated with Sirt 1 repression and programmed cell death [3]. Sirt 1 is a nicotinamide adenine dinucleotide (NAD +) dependent class III histone deacetylase (HDAC) that targets transcription factors to adapt gene expression to metabolic activity and the deacetylation of nuclear receptors indicate its critical involvement in insulin resistance and brain Aβ accumulation [14].

In the developing world the increased plasma LPS levels are now associated with antibiotic resistance [15] with LPS associated with Sirt 1 repression [16] in neurons with inactivation of the circadian rhythm relevant to toxic Aβ aggregation [5]. Diets that contain LPS/patulin are associated with Sirt 1 inactivation, cellular senescence and delayed hepatic Aβ clearance in diabetes and neurodegenerative diseases (Figure 1). Caffeine consumption should be carefully controlled with relevance to Aβ aggregation and accelerated brain aging [17]. Indian spice consumption [18] as a biotherapeutic to prevent toxic
Aβ aggregation and the treatment of Alzheimer’s disease should be revised with excessive curcumin and piperine associated with Sirt 1 transcriptional dysregulation, toxic Aβ aggregation and hyperglycemic mitochondrial apoptosis [18].

Figure 1: Appetite control is critical for activation of the peripheral sink amyloid beta clearance pathway in diabetes and neurodegenerative diseases. Sirt 1 transcriptional regulation and fat consumption determine the intact adipose tissue-liver interaction that is essential to prevent inactivation of the hepatic amyloid beta clearance with the induction of toxic amyloid beta aggregation and mitochondrial apoptosis.

Heat shock protein metabolism is now connected to Sirt 1 regulation, mitochondrial apoptosis and insulin resistance [22]. Insulin therapy with relevance to Aβ and Alzheimer’s disease now needs to include HSP metabolism to prevent mitochondrial apoptosis. Sirt 1 repression is associated with defective HSP metabolism and linked to Aβ aggregation and mitophagy in diabetes. Diabetes and core body temperature defects have been reported with inactivation of the heat shock gene Sirt 1 relevant to neuron apoptosis and inactivation of the peripheral sink Aβ pathway [22]. Sirt 1 and heat shock transcription factor 1 are associated with endoplasmic reticulum stress and misfolded proteins associated with mitochondrial apoptosis [22]. Brain stimulation technologies and heat therapy [23] need to be carefully controlled to prevent heat shock gene inactivation relevant to diabetes and Alzheimer’s disease.
The major defect in the peripheral sink Aβ pathway is relevant to the adipose tissue and liver crosstalk in man with defective interplay between the two tissues [24,25] that leads to impaired hepatic Aβ metabolism (Figure 1). In humans this defective adipose tissue-liver interaction is involved in programmed cell death relevant to several chronic diseases. Adipose tissue regulates Aβ production [26-28] and controls plasma Aβ aggregation. The excessive adipose tissue production of Aβ is responsible for the assembly of Aβ proteins into higher-order structures [29,30] that are fundamental to structural biology and Alzheimer’s disease and to the understanding species longevity. In humans compared with various species the adipose tissue-liver interaction determines Aβ structures and immune dysregulation [22,31,32] that determines species aging and lifespan. The impaired adipose tissue-liver Aβ metabolism may be regulated by drug, caffeine, Indian spices, LPS, mycotoxins [12] and environmental xenobiotics [10] with increased sensitivity to longevity in various species when compared to man.

Appetite control and the peripheral sink Aβ clearance pathway (Figure 1) are of particular relevance to chronic kidney disease and neurodegenerative disease [33] with appetite dysregulation and Aβ aggregation related endoplasmic reticulum stress [34] and mitochondrial apoptosis. A blood test for the peripheral sink amyloid beta clearance pathway is now under evaluation with the measurement of plasma Sirt 1 and HSP 70 levels [22] critical to determine neuron death [35]. A major interest in measurement of Sirt 1 expression with relevance to the control of the adipose tissue-liver interaction may supersede various tests that determine species longevity. Plasma Sirt 1 levels in diabetes and Alzheimer’s disease need to be compared to determine nuclear Sirt 1 expression defects in Alzheimer’s disease [36] are primary with secondary plasma Sirt 1 alterations in diabetes, obesity and non alcoholic liver disease (adipose tissue-liver defects) [19].

Conclusion

The peripheral sink amyloid beta clearance pathway in diabetes and Alzheimer’s disease is defective. Appetite control and intact Sirt
1 are critical to prevent inactivation of the peripheral sink amyloid beta clearance pathway. Factors such as drugs, caffeine, Indian spices, LPS, mycotoxins and environmental xenobiotics determine longevity in various species when compared to man. Sirt 1 and circadian regulation of the adipose tissue-liver interaction are essential to determine toxic antigenic Aβ structures with immune dysregulation connected to diabetes and Alzheimer’s disease.

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 (NHMRC 595312 & NHMRC 595300).

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