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Calorie Sensitive Anti-Aging Gene Regulates Hepatic Amyloid Beta Clearance in Diabetes and Neurodegenerative Diseases

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COLUMN ARTICLE

Diet and lifestyle has become important to the maintenance of mitochondrial biogenesis that has become of major concern to chronic diseases. The anti-aging gene Sirtuin 1 (Sirt 1) is regulated by diet with high calorie diets involved in its downregulation. Under post-prandial conditions with increased fatty acids and glucose consumption the Sirt 1 regulation of suprachiasmatic nucleus (SCN) involved in the regulation of brain and liver amyloid beta metabolism [1] is reset with circadian rhythm alterations related to cholesterol efflux disturbances, amyloid beta aggregation and mitochondrial apoptosis [2-5]. Individuals with apolipoprotein E4 (apo E4) are more susceptible to mitochondrial apoptosis [6] when compared with apo E3 and related to the reduced liver amyloid beta clearance. Defective Sirt 1 in diabetes and Alzheimer's disease [1] involve hypercholesterolemia and amyloid beta aggregation with induction of mitophagy and programmed cell death (Figure 1).

Heat shock proteins (HSP) are now linked to obesity, cardiovascular disease, adiposity and Alzheimer's disease [7-9]. Stress and calorie consumption are sensitive to hepatic heat shock protein (HSP 60,70,90) metabolism with relevance to Sirt 1 and its involvement in HSP 70 metabolism and mitochondrial biogenesis [9,10-15]. Sirt 1 repression involves HSP interaction with amyloid beta relevant to endoplasmic reticulum stress with induction of mitochondria induced programmed cell death [9,14]. High calorie diets that repress Sirt 1 involve HSP-insulin receptor [9] interactions with relevance to insulin resistance and mitochondrial apoptosis. Sirt 1 defects interfere with liver X receptor-ATP binding cassette transporter proteins involved in cholesterol efflux [16] and supersede apo E3 regulation of cholesterol/amyloid beta metabolism with elevated HSP 70 interactions involved in defective mitochondrial apoptosis [17].

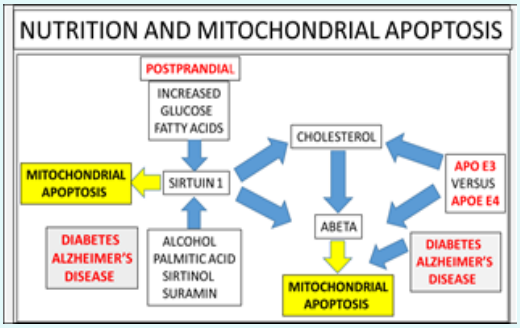

Figure 1: Diet and lifestyle changes in diabetes and neurodegenerative diseases have become of critical importance to prevent mitochondrial apoptosis. In various genetic and cell biology studies cholesterol and apo E (apo E3 vs apo E4) have been shown to be essential for amyloid beta (abeta) metabolism in cultured cells and in genetically engineered animals. In apo E4 individuals defective amyloid beta metabolism induces mitochondrial apoptosis. In various post-prandial studies, high fat/sugar diets downregulate the nuclear receptor Sirt 1 in diabetes and neurodegenerative diseases with the induction of mitochondrial apoptosis. Sirt 1 defects override apo E3 isoform control of cholesterol and amyloid beta metabolism with the induction of mitochondrial apoptosis.

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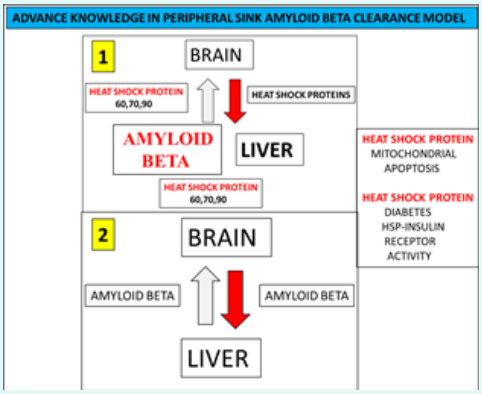

Figure 2: The peripheral sink amyloid beta model (Panel 2) shows the rapid hepatic clearance of neuron amyloid beta transported from the brain to the liver (1). In Panel 1 Sirt 1 nuclear receptor repression indicates brain HSP-abeta interactions interfere with the efflux of amyloid beta from the brain and in the liver HSP-abeta complexes induce endoplasmic reticulum-mitochondria programmed cell death [17].

Inhibitors of Sirt 1 induce mitochondrial apoptosis, hypercholesterolemia and amyloidosis [18]. Advances in the peripheral sink amyloid beta clearance model indicates rapid brain to liver transport of amyloid beta (Figure 2, Panel 2) now involves the heat shock protein 70 (HSP70) [9] (Figure 2, Panel 1). Induction of HSP from cells has become of major interest and experiments in the nematode *C. elegans* used for toxicological studies indicate caffeine doses that induce HSP release [19]. *C. elegans* sirtuins have similar homology to human Sirt 1 [20] with relevance to effects of caffeine on Sirt 1 circadian dysregulation [18,21] with corruption of the peripheral sink clearance pathway. LPS is involved in Sirt 1 repression and apo E neutralization [22,23] and shown to induce HSPs [9] with relevance to mitochondrial apoptosis and corruption of the peripheral sink amyloid beta clearance pathway (Figure 2).

CONCLUSION

Advances in the peripheral sink amyloid beta clearance model identify the calorie sensitive anti-aging gene Sirt 1 as the defective gene in the hepatic clearance of amyloid beta in diabetes and neurodegenerative diseases. High calorie diets, LPS and caffeine induce HSP dysregulation that determines the defective hepatic amyloid beta clearance from the central nervous system and plasma with relevance to mitochondrial induced hepatocyte and neuron apoptosis.

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Keywords: *Nutrition; Sirtuin 1; Mitochondria; Heat Shock Protein; Amyloid Beta; Cholesterol; Diabetes; Alzheimer's Disease*

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