Early Diagnosis of Neuron Mitochondrial Dysfunction May Reverse Global Metabolic and Neurodegenerative Disease

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Received: 9 December 2015 Accepted: 5 January 2016 Published: 15 January 2016

Abstract

The rise in obesity and diabetes in various countries have reached epidemic proportions [1]with the inability of the brain to regulate body weight and energy balance in the early part of life and related to neurodegenerative disease in these countries. Neurons in the brain become sensitive to Western diets with alterations in neurons that lead to brain circuitry disorders or feeding signals [2]. In insulin resistance and neurodegenerative diseases the astrocyte-neuron interaction is defective in the brain [3] and consumption of a Western diet does not allow neurons to metabolize glucose and fatty acids but instead leads to mitochondrial apoptosis and programmed neuron death. In the periphery in global communities liver steatosis can be reversible with hepatocyte mitochondria still able to metabolize fatty acids and glucose after consumption of a healthy low calorie diet but in the brain neuron mitochondria may not continue with mitochondrial biogenesis but continue to undergo apoptosis with neuron death. Networks between various brain cells involve membrane and nuclear lipid signals with diets involved in the regulation, transmission and communication between various brain cells. The three main types of glial cells are the astrocytes, oligodendrocytes and microglia with astrocytes involved with the maintenance of endothelial cells in brain capillaries and the blood brain barrier (BBB) to prevent toxic substances and their entry into the brain with the prevention of mitochondrial apoptosis in neurons. Astrocytes have been shown to be important to neuron lifespan and survival [4,5] with diets and lifestyle involved with epigenetic modification that disrupt astrocyte signalling [3] involved in the maintenance of neurons in individuals in global populations. Nutritional diets that prevent epigenetic alterations include DNA methylation, covalent histone modification and non-coding RNAs that are involved in gene activation and repression with chromatin structure modifica

Index terms—

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3 Editorial

The rise in obesity and diabetes in various countries have reached epidemic proportions [1] with the inability of the brain to regulate body weight and energy balance in the early part of life and related to neurodegenerative disease in these countries. Neurons in the brain become sensitive to Western diets with alterations in neurons that lead to brain circuitry disorders or feeding signals [2]. In insulin resistance and neurodegenerative diseases the astrocyte-neuron interaction is defective in the brain [3] and consumption of a Western diet does not allow neurons to metabolize glucose and fatty acids but instead leads to mitochondrial apoptosis and programmed neuron death. In the periphery in global communities liver steatosis can be reversible with hepatocyte mitochondria still able to metabolize fatty acids and glucose after consumption of a healthy low calorie diet but in the brain neuron mitochondria may not continue with mitochondrial biogenesis but continue to undergo apoptosis with neuron death.

Networks between various brain cells involve membrane and nuclear lipid signals with diets involved in the regulation, transmission and communication between various brain cells. The three main types of glial cells are the astrocytes, oligodendrocytes and microglia with astrocytes involved with the maintenance of endothelial cells in brain capillaries and the blood brain barrier (BBB) to prevent toxic substances and their entry into the brain with the prevention of mitochondrial apoptosis in neurons. Astrocytes have been shown to be important to neuron lifespan and survival [4,5] with diets and lifestyle involved with epigenetic modification that disrupt astrocyte signalling [3] involved in the maintenance of neurons in individuals in global populations. Nutritional diets that prevent epigenetic alterations include DNA methylation, covalent histone modification and non-coding RNAs that are involved in gene activation and repression with chromatin structure modifications associated withintact circadian regulation critical for the increased survival of astrocytes and neurons. Atherogenic diets that stimulate bacterial lipopolysaccharides (LPS), mycotoxin and xenobiotics into the central nervous system may induce various cellular stresses with the induction of mitochondrial apoptosis induced neurodegenerative diseases.

The increased global susceptibility to insulin resistance associated with brain aging and neurodegenerative diseases now indicate neuron vulnerability to senescence or apoptosis [6]and require early plasma biomarker diagnosis that may assist with reversal of neuron senescence to healthy neurons that may be interpreted from lipidomic tests, genomic tests and proteomic tests [7]. The information provided from these tests now are relevant to the early diagnosis of neuron senescence and linked to mitochondrial biogenesis versus mitochondrial apoptosis that determine the lifespan of neurons. The tests may further assist in novel and important Alzheimer's disease therapeutics that reverse amyloid beta oligomers damage to neuronsin diabetes related neurodegenerative disease and Alzheimer's disease [8].

Figure **??**: Downregulation of the calorie sensitive gene Sirtuin 1 is important to mitochondrial biogenesis with Sirt 1/pr53 regulation of other anti-aging genes such as Klotho, p66shc, Foxo3a and the anti-aging transcription factor PGC1-alpha involved in mitochondrial function. Plasma protein analysis for the diagnosis of neuron mitochondrial function has become important with neurodegeneration closely linked to the global diabetic epidemic, NAFLD and various chronic diseases. Proteins such as apelin, angiotensin II, gelsolin, heat shock proteins, thrombospondin 1, transforming growth factor beta, tumour necrosis factor alpha, insulin like growth factor 1, fibroblast growth factor 21, adiponectin, GDF11 and hepatocyte growth factorare involved with mitochondrial survival and may involve p53 regulation of mitochondrial function in metabolic and neurodegenerative diseases.

Genomic analysis now indicate that the antiaging gene Sirtuin 1 (Sirt 1) regulates other anti-aging genes that are now critical to mitochondrial biogenesis and neuron proliferation [8]. Sirt 1's regulation of mitochondria involve p53 regulation and include other anti-aging genes (Figure **??**) that synthesize the Klotho anti-aging protein, p66shc longevity protein and transcription factors such as Forkhead box O3(FOXO3a) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1 apha) that are essential for the maintenance of mitochondrial function in cells [9][10][11]. In Figure **??** the plasma proteome analysis of various proteins may now indicate the diagnosis of neuron apoptosis versus neuron survival from the determination of plasma proteins that are relevant to mitochondrial biogenesis versus mitochondrial apoptosis. The plasma proteome analysis for neuron survival that involve mitochondrial health include proteins such as apelin, angiotensin II, gelsolin, heat shock proteins (HSP 70, HSP 60), thrombospondin 1 (TSP-1), Transforming growth factor beta (TGF beta), Tumour necrosis factor alpha (TNF alpha), Insulin like growth factor 1 (IGF-1), Fibroblast growth factor 21 (FGF21), adiponectin, GDF11 and hepatocyte growth factor (HGF). Dysregulated crosstalk between the adipose tissue and the liver [10] alter the release of these proteins with low and defective transport of these proteins to neurons in the brain relevant to increased mitochondrial senescence versus mitochondrial biogenesis.

The gene-environment interaction identifies Sirt 1 in many global populations as the defective gene involved in the defective nuclear-mitochondria interactions in the adipose tissue and the liver relevant to the mitochondrial theory of aging [12][13][14].Sirt 1 (nicotinamide adenine dinucleotide dependent class III histone deacetylase) targets transcription factors such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC 1-<alpha>), p53, pregnane X receptor (PXR), peroxisome proliferator-activated receptor (PPAR) to adapt gene expression to mitochondrial function with relevance to metabolic activity, insulin resistance and inflammation. Sirt 1 is involved in chromatin remodelling with effects on the nuclear and mitochondria interactions that determine neuron proliferation via mitochondrial biogenesis by deacetylation of PGC 1 alpha

and p53 transcription factors that are important to mitochondrial DNA homeostasis [15][16][17][18][19]. Sirt 1's regulation of circadian clocks regulate mitochondrial function that determine neuron synaptic plasticity in various neurological diseases [10,[20][21][22][23][24] ??25] ??26] ??27] ??28] ??29] ??30] ??31] ??32] ??33] ??34]. Major commercial interests in simple proteome tests that can be conducted in any routine laboratory may now indicate from plasma proteome analysis the proliferation of mitochondria with relevance to neuron survival and prevention of programmed cell death. In the current global non alcoholic fatty liver disease (NAFLD) epidemic the various proteins are important to neuron mitochondrial biogenesis and alterations in these proteins in the blood plasma may be involved in mitochondrial apoptosis and determine early neuron cell death. Sirt 1 and Sirt 3 are both involved with neuron mitochondria function with Sirt 1's important role in circadian regulation of Sirt 3's regulation of mitochondrial function ??35, ??6].However with the aging process various plasma proteins are now relevant to mitochondrial health by the regulation of Sirt 1/p53 expression (Figure ??) that may involve astrocyte regulation of mitochondrial biogenesis versus apoptosis that determine synaptic dysfunction and neurodegeneration ??37] ??38] ??39].

HGF has also been shown to be important to neuron and axon survival with relevance to HGF in p53 transcriptional regulation and mitochondrial biogenesis ??40] ??41] ??42] ??43] ??44] ??45] ??46] ??47] ??48] ??49] [76,77] with its connections to Sirt 1/IGF-1/GH regulation by diet and nutrition [78]. TNF alpha [79] is particularly sensitive to mitochondrial induced neuronal apoptosis and with TGF beta [80] overide Sirt 1'scontrol of circadian regulation with relevance to mitochondrial related neuron apoptosis [81,82].

Adiponectin levels are closely connected to mitochondrial biogenesis with Sirt 1 regulation important toadiponection gene expression [83][84][85][86][87]. Plasma TSP1 levels have become important to mitochondrial apoptosis with levels of LPS involved in TSP1 regulation and Sirt 1 repression [7]. TSP1effects on CD47 receptor to prevent mitochondrial biogenesis and TSP-1 effects on p53 expression override Sirt 1/p53 transcriptional regulation of neuron synapticity and survival [88][89][90][91][92][93]. Sirt 1 regulation of brain derived neurotrophic factor (BDNF) is now important to BDNF induced mitochondrial function and synaptic plasticity [9]. Early analysis of plasma proteins (Figure ??) that determine mitochondrial survival by p53 transcriptional regulation may now be important to Sirt 1 metabolism of toxic oligomers such as amyloid beta and alpha synuclein in neurodegenerative diseases [9,10].

Furthermore plasma lipidomic analysis allow interpretation that in insulin resistance and neurodegenerative diseases the increased plasma ceramides and sphingosine 1 phosphate are associated with increased liver/neuron mitochondrial apoptosis with programmed cell death of neurons associated with Sirt 1 repression. Lipids such as ceramides have been shown to inhibit Sirt 1/p53 transcriptional regulation and induce cell death in neurons or hepatocytes [94,95]. In contrast sphingosine 1 phosphate may act as a Sirt 1 activator by actions on increased PGC1alpha levels with increased mitochondrial biogenesis [96]. Ceramides supersede the effects of various plasma proteins (Figure ??) that have been shown to regulate p53 transcriptional activityto prevent mitochondrial apoptosis with relevance to neuron differentiation with plasma ceramide levels important to mitochondrial related defects in synaptic plasticity and neurodegeneration [3,7]. Nutritional therapy is required to promote the nuclear-mitochondria interaction andprevent mitochondrial apoptosis with improvement in the astrocyte-neuron crosstalk that determines the lifespan of neurons [97]. Diet and nutrition is particularly relevant to neuron Sirt 1 regulation of the circadian rhythm with relevance to mitochondrial biogenesis and the prevention of high glucose induced mitochondrial dysfunction in neurons [98]. The effects of high fat diets that contain palmitic acid induce liver steatosis and steastosis may be reversible but accelerated mitochondrial disease in neurons [99][100][101][102][103] by palmitic acid as a Sirt 1 inhibitor may induce irreversible neurodegenerative disease ??53]. Nutriproteomic diets [7] have become important by the release from the adipose tissue and liver of proteins essential for the maintenance of the nuclear-mitochondria crosstalk in neurons. In the developing world nutritional therapy may be superseded with relevance to xenobiotic induced mitochondrial apoptosis [104] with accelerated synaptic plasticity defects and neurodegeneration. Activators of Sirt 1 such as leucine may be essential for mitochondrial biogenesis [105,106] and with stress disorders the apelinergic system defects [57] may lead to accelerated mitochondrial apoptosis with neuroendocrine disease. Interests in nutritional therapy include Sirt 1 activators such as pyrroloquinoline quinone, resveratroland rutin [107][108][109][110] that specifically stimulate mitochondria biogenesisin the liver and brain compared with ochratoxin A [111] that interferes with mitochondrial respiration.

4 Conclusion

Interests in the early diagnosis of neuron senescence has become a major concern for many global communities with accelerated neurodegeneration involved with the metabolic syndrome and various chronic diseases. The mitochondria in neurons are sensitive to dysregulation with irreversible defects in these mitochondria that result in neuron apoptosis early in life. The plasma proteins such as Apelin, Angiotensin II, Gelsolin, Heat shock proteins (HSP 70, HSP 60), Thrombospondin 1 (TSP-1), Transforming growth factor beta (TGF beta), Tumour necrosis factor alpha (TNF alpha), Insulin like growth factor 1 (IGF-1), Fibroblast growth factor 21 (FGF21), GDF11, Adiponectin and Hepatocyte growth factor (HGF) should be measured early in life to determine mitochondrial damage in brain cells. The importance of the plasma profile is now relevant to assessment by nutritional therapy to reverse and halt neuron loss that is irreversible with relevance to the accelerated neurodegeneration and early

nutritional regulation has become critical to the reversal of the global NAFLD, metabolic syndrome and chronic diseases.

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Figure 1:

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