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Review Article

The Global Obesity Epidemic is Related to Stroke, Dementia and Alzheimer's disease

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Abstract

The global epidemic in obesity and diabetes has affected individuals in both the developing and developed world with the global death rate (63%) related to chronic diseases with 35% attributed to cardiovascular disease and stroke, 21 % to cancer and 12 % to chronic respiratory disease. The interest in connections between the global stroke epidemic, dementia and Alzheimer's disease (AD) has increased with hypertension, smoking, diabetes, obesity, poor diet, physical inactivity, atrial fibrillation, excessive alcohol consumption, abnormal lipid profile and psychosocial stress/depression implicated in their pathogenesis. The connection between stroke and AD is possibly related to the low adiponectin and high density lipoprotein (HDL) cholesterol levels that are found in hypertensive, obese, diabetic and AD individuals. In obesity adipocyte dysfunction may be related to the down regulation of the AD gene Sirtuin 1, overexpression of the amyloid precursor protein (APP) and mitochondrial apoptosis with relevance to the renin-angiotensin system (RAS) that is associated with accelerated aging, NAFLD, stroke and AD. The unresolved finding of low plasma HDL and adiponectin in the metabolic syndrome may involve the stress hormone angiotensin II (Ang II) with vascular disturbances. Increased levels of adipocyte Ang II are possibly linked to the low plasma HDL contents in stroke and AD individuals. In obese and diabetic individuals the release of stress factors and diet control the activation of the RAS with increased levels of Ang II that are possibly implicated in the dyslipidemia associated with hypertension, cardiovascular disease, stroke and AD related dementia.

ABBREVIATIONS

HDL: High Density Lipoprotein; Ang II: Angiotensin II; RAS: Renin Angiotensin System; ACE: Angiotensin Converting Enzyme; AD: Alzheimer's Disease; NAFLD: Non Alcoholic Fatty Liver Disease; Sirt 1: Sirtuin 1; PPAR: Peroxisome Proliferator Activated Receptor; APP: Amyloid Precursor Protein; NO: Nitric Oxide; PGC-1alpha: Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1-Alpha; NF-Kb: Nuclear Factor Kappa B; AGE: Advanced Glycation End Products; BBB: Blood Brain Barrier

INTRODUCTION

Interests in various genes that are involved in the pathogenesis of Alzheimer's disease (AD) has escalated with the increase in neurodegenerative diseases in developing and developed countries. Apo E is the most common gene associated with late onset AD with neurodegeneration that appears after the age of 65 years. In humans the apo E gene is located on chromosome 19q13.2 [1] and expresses a 299 amino acid protein with three

isoforms such as $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ resulting from the substitution of a cysteine with an arginine residue at codons 112 and 158 [2,3]. In various countries individuals with apo E4 gene are at increased risk for AD and individuals with the apo E2 protective against AD when compared with apo E3 individuals. Other late onset AD genes have been reported and include SORL1, CLU, CR1, PICALM and TREM2 and indicate that variation of genes may increase the risk for AD. Other epigenetic and environmental factors may be involved in the development of neurodegeneration and AD since a number of individuals with the apo E4 gene do not develop AD. A major environmental factor that induce early senescence in various populations is high fat or high cholesterol diets that are associated with low plasma high density lipoprotein (HDL) levels and elevated low density lipoprotein cholesterol levels in AD populations [4,5]. AD related dementia has escalated with the global obesity epidemic that has been associated with early cellular senescence, insulin resistance and non alcoholic fatty liver disease (NAFLD) in the developing and developed world [6-8]. The interests in the rise in obesity, insulin resistance and

AD related dementia has prompted research that may identify the inducing factors that may be responsible for the low plasma adiponectin and elevated angiotensin II (Ang II) levels that are possibly linked to the global NAFLD with low HDL, hypertension and hypercholesterolemia that are connected to early brain senescence associated with the global stroke epidemic and AD [9-19].

The understanding of the biological mechanisms between obesity and stroke have increased to prevent the associated dementia as the major global brain disorder where multiple aspects of brain function effect the individuals cognition and behaviour. These include personality changes such as loss of insight, loss of empathy for others, poor self-care, emotional explosiveness, and impulsiveness. Early interventions related to the disturbed biological mechanisms that involve the renin angiotensin system (RAS) in obesity [20,21] and stroke may delay or prevent the induction of insulin resistance, dyslipidemia and hypertension that may result in vascular dementia and complicate AD that occurs late in life. In the current global stroke epidemic links with obesity involve adiposity which is the body fat tissue content and its increase is measured by body mass index (BMI). Obese individuals are defined as having a BMI of >30 ($\text{BMI} = \text{weight in kg/m}^2$ [height in m] whereas overweights are defined as having a BMI from 25 - 30 kg/m^2 and ideal lean individuals to have a BMI of 25 kg/m^2 . The connections between the adipose tissue and the liver in the induction of NAFLD involve RAS and have become important to the rapid progression of various other diseases [22] such as diabetes, cardiovascular disease and stroke that are associated with AD related dementia.

ADIPOCYTE SENESCENCE AND RAS ARE INVOLVED WITH STROKE AND AD RELATED DEMENTIA

In the current obesity and diabetes epidemic the anti-ageing gene sirtuin 1 (Sirt1) is implicated as a NAD(+) dependent class III histone deacetylase (HDAC) protein that targets transcription factors to adapt gene expression to metabolic activity, insulin resistance and inflammation in chronic diseases [23,24]. Interests in Sirt 1 have increased since it may override the effects of late onset genes with its cellular expression important in the processing of amyloid precursor protein (APP) which generates the AD peptide amyloid beta in neurons with links to stress response that limits lifespan with accelerated neurodegenerative disease [25,26]. Diet and nutrigenomics are involved in Sirt1 regulation of DNA repair with transcription factors regulated by Sirt1 in obesity closely connected to the nuclear hormone receptors such as peroxisome proliferator activated receptor (PPAR), liver X receptor, pregnane X receptor, farnesoid X receptor involved in liver metabolic homeostasis with roles in lipid metabolism in adipose tissue. Sirtuins are involved in gluconeogenesis in the liver, fat mobilisation from white adipose tissue, cholesterol metabolism, and energy metabolism.

In adipose tissue, Sirt1 triggers fat mobilisation by inhibiting peroxisome proliferator activated receptor gamma (PPAR-gamma) [27], and in the pancreas, Sirt1 repression of the uncoupling protein 2 increases insulin secretion and also influences mitochondrial biogenesis and inflammation. Furthermore implicating the effects of dysregulated Sirt 1 on adipocyte differentiation and senescence [28-32] and regulation

of gene expression and secretion of adiponectin [33-35]. Sirt1 dysregulation is clearly involved in adiposity with adipocyte size negatively correlated with adiponectin levels, adipose tissue ceramide metabolism and HDL levels [36-40]. Adiponectin is mainly secreted from the adipose tissue into the bloodstream and inversely correlated with body fat in adults. Adiponectin self-associates into larger structures from trimers to form hexamers or dodecamers with the high-molecular weight form biologically more active with regard to glucose homeostasis. Adiponectin like leptin may be involved in appetite control with effects in the brain with the plasma levels regulated by dietary fat intake [41]. Adiponectin is involved in the metabolic syndrome, NAFLD and reverse cholesterol transport with effects on hepatic HDL and apolipoprotein A-I synthesis [39,42-45]. Adipocytes from obese and diabetic individuals are associated with increased adipocyte APP gene expression and plasma amyloid beta levels that implicate adiponectin and Sirt1 dysregulation in midlife obesity to AD [46-50]. Excess calorie consumption leads to hepatic Sirt1 downregulation that causes NAFLD with the excess fatty acid and cholesterol transported to the adipose tissue with effects on the release of adipokines (adiponectin, leptin) and cytokines (tumor necrosis factor alpha, interleukin-6 and C-reactive protein levels, Ang II) [51] that are implicated in cardiovascular disease, kidney disease and hypertension associated with early brain senescence and AD related dementia. The dysregulated release of adipokines has also been connected to advanced glycation end products (AGE) formation in obesity [52].

The interests in high fat diets and the renin angiotensin system (RAS) [53-55] have become important to hypertension/stroke therapy with the regulation of the increased synthesis by the liver and adipose tissue of angiotensinogen [56,57] that is converted to Ang I by the action of renin released by the kidney. Ang II is a major stress hormone peptide [58] that is converted from Ang I by the angiotensin converting enzyme (ACE) present in various tissues such as the lung, kidney and adipose tissue. ACE inhibitors have been used as the major antihypertensive drugs with effects on vasoconstriction, kidney sodium reabsorption and blood pressure reduction. Ang II is involved in adipogenesis with connections to RAS expression in the adipose tissue [59-61] that promotes oxidative stress/inflammation with induction of senescence and chronic disease in various tissues [22] and associated with the development of cognitive decline and dementia [62]. Ang II has been shown to regulate plasma adiponectin [63-65] and apolipoprotein A-I levels with relevance to the reverse cholesterol transport and HDL in chronic and vascular diseases. Furthermore adiponectin has been shown to inhibit vascular inflammation by regulation of the RAS [66-69] and inhibition of the RAS has been indicated to increase adiponectin levels [70] that alter tumor necrosis factor alpha, interleukin-6 and C-reactive protein levels [71]. Furthermore interactions between leptin and Ang II was associated with vasoconstriction [72,73] and effects of Ang II on adiponectin release was related to down regulation of Sirt 1 [74] with the Sirt 1 longevity gene involved with the down regulation of the Ang II Type 1 receptor [75]. The Ang II and adiponectin interaction are closely linked with Ang II and Sirt 1 receptors and indicate their important roles in insulin resistance, ceramide, HDL metabolism and endothelial dysfunction in obesity, diabetes and cardiovascular disease [36,37,76-80]. In obese individuals

having a BMI between 25 - 30 kg/m² the induction of senescence possibly involves mitochondrial disorders early in life in tissues such as the adipose tissue, liver and brain with the role of Ang II and adiponectin closely involved in organ lifespan in various communities. The role of Sirt1 in apoptotic pathways that induce NAFLD, endothelial dysfunction, hypertension and brain ischemic damage has been reported with dietary and stress related Sirt 1 regulation of the endothelial nitric oxide (NO) synthase as an intervention in neuroprotection and prevention of vascular related diseases with cerebral damage in human stroke [81-88]. In various tissues Ang II may downregulate Sirt 1 activity and adiponectin release that may promote senescence by dysregulation of mitochondrial biogenesis [89] in the adipose tissue, liver, heart and brain.

ADIPONECTIN AND RAS ARE INVOLVED WITH ASTROCYTE-NEURON SENESCENCE AND BBB DISEASE

The main cell types characterizing the CNS are essentially neurons and glial cells with glial cells involved in communication, repair and function to support neuron communication and survival. 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). Astrocytes are involved in a number of biological processes that include brain RAS, lipid homeostasis, steroid, and xenobiotic metabolism [6]. Stress related disorders and the metabolic syndrome that involve stroke, dementia and AD implicate adiponectin and its receptors that involve neuron and astrocytes [90-93] with RAS, hypertension and premature brain ageing (Figure 1). In obesity leptin resistance associated with increased ceramide levels [94,95], hypertension and disease of the BBB are linked [96,97] and ageing involves brain abnormalities, BBB disruption with neuroinflammation and oxidative stress to the brain [98,99]. Increased adipocyte dysfunction in various countries with NAFLD and low adiponectin levels are now linked to accelerated brain ageing with induction of adipocyte senescence [100,101] associated with an increase in peripheral leptin, Ang II and AGE with increased oxidative stress and activation of the brain RAS [102,103] that involves the neurons, astrocytes, endothelial cells, oligodendrocytes and microglia. AGE levels are linked with the suppression or downregulation of Sirt 1 with elevated levels of AGE [104,105] associated with astrocyte dysfunction [6] increased neurotoxicity and acute ischemic stroke [106-110]. Treatment of AD with drugs is intertwined with the role of obesity, hypertension [111,112] and adiponectin [77-80] with dietary interventions that reduce insulin resistance [113], inflammatory markers, endothelial dysfunction associated with the brain angiotensin system [114-116] and the ageing process. Stress related disorders induce adiponectin and Ang II imbalances [117,118] that link to Sirt 1 dysregulation, NO disorders and endothelial dysfunction [119,120] with BBB disease and increased risk for stroke. Increased peripheral Ang II can cross the BBB [121,122] with central effects on neurons within the brain with increased BBB permeability [123-126] to various apoptotic lipids such as ceramide [6] and AGE that further compromise the astrocyte-neuron interactions. The connections between diabetes, [127] RAS and AD has become important

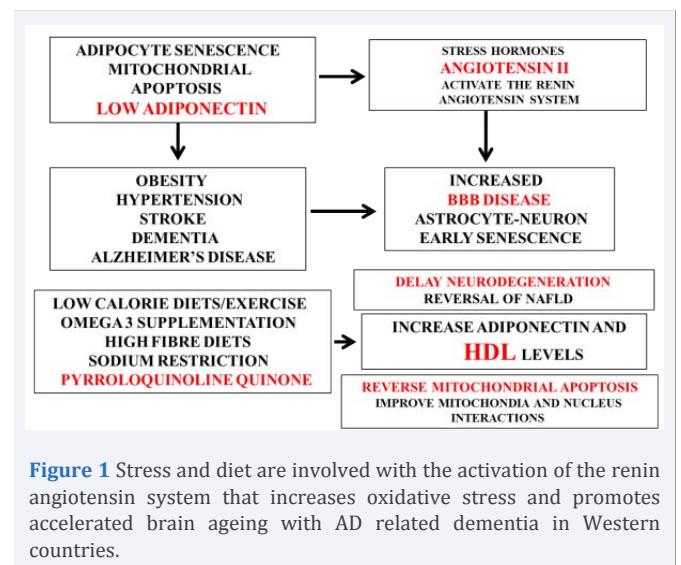


Figure 1 Stress and diet are involved with the activation of the renin angiotensin system that increases oxidative stress and promotes accelerated brain ageing with AD related dementia in Western countries.

with the use of ACE inhibitors and angiotensin II receptor blocker therapy [128]. ACE inhibitors that lead to Ang II inhibition have been studied to reduce a beta plaque in AD triple transgenic mice but do not reduce amyloid beta production in the brain [129-133]. Blockade of the ang II receptor was shown to increase adiponectin levels in the periphery [70] with relevance to stress related disorders that involve the adiponectin receptors and neuronal apoptosis [90].

The increased oxidative stress related to the abnormal RAS in obesity leads to damage to mitochondria in various tissues and corruption of mitochondrial biogenesis. Down regulation of Sirt 1 activity leads to senescence with marked effects on neuron mitochondrial biogenesis that compromise astrocyte neuron interactions [134,135]. The brain cells as a target for accelerated ageing and stroke [136-138] are sensitive to mitochondrial dysfunction with increased ceramide [139,140] and advanced glycation end products [141] connected to nuclear apoptosis in neurons with accumulation of proteins that are associated with diseases such as AD and Parkinson's disease (Figure 1). Stress and nutrient effects on stress responsive Sirt 1 is linked to mitochondrial biogenesis by deacetylation of the peroxisome proliferator-activated receptor gamma coactivator-1-alpha (PGC-1alpha) [142-146] associated with decreased amyloid beta production [147-150] and NO homeostasis. An effect of Ang II on mitochondrial senescence has been reported with the regulation of PGC-1alpha and NO generation by Ang II receptors in mitochondria [151-153]. Adiponectin has been shown to enhance mitochondrial division by activation of the PGC-1alpha master regulator of mitochondrial biogenesis [154,155]. The obesity epidemic in various communities is involved low HDL and the induction of mitochondrial senescence in various organs [156,157] with low adiponectin and increased Ang II levels that are possibly implicated in the AD mitochondrial cascade hypothesis [158,159] with astrocyte mitochondrial function essential for neuron survival. Involvement of nuclear factor kappa B (NF-kB) in the ageing process and mitochondrial apoptosis, have also implicated PGC-1alpha and Ang II in NF-kB activation and Sirt 1 in NF-kB inhibition with promotion of neuroprotection [160-166].

NUTRITIONAL INTERVENTIONS, DRUGS AND LIFESTYLE CHANGES IMPROVE COGNITION AND BRAIN AGEING

High fat diets with increased leptin levels and low adiponectin levels are associated with increased ageing with increased inflammatory markers, ceramide and APP in both the adipose tissue and the brain. Interventions to increase adiponectin levels and reduce endothelial dysfunction and hypertension [77,79] have been linked to various dietary and lifestyle changes. A search from a number of articles identify methods to increase plasma adiponectin levels (60-80%) and include low-calorie diets with weight loss and high fibre diet intake with exercise [167]. Furthermore the daily intake of fish or omega-3 supplementation increase adiponectin levels by 14-60% with effects on NAFLD reversal that are intimately linked to the prevention of accelerated brain ageing. Dietary fruit intake [168] and unsaturated fat have been shown to be involved in the regulation of adiponectin levels and Ang II levels with adipocyte differentiation and the nature of the fat consumed possibly linked to the plasma forms of adiponectin. Dietary salt intake involved in long term restriction of sodium intake reduce the activation of the RAS and lower peripheral Ang II levels and increase adiponectin levels [169,170] with reduced detrimental effects on mitochondrial apoptosis involved in astrocyte-neuron interactions. Hormones such as testosterone and estrogen may not maintain peripheral adiponectin secretion from adipocytes with other foods such as green tea, coffee and hyolipidemic drugs also involved in the modification of adiponectin levels [171-173]. High fat diets reduce adiponectin levels associated with down regulation of Sirt 1 and insulin resistance with effects on mitochondrial biogenesis on cell nucleus interactions that involves the PGC-1 α and estrogen-related receptor- α [174,175]. Sirt 1 activators are important to prevent neuron senescence by regulation of adiponectin levels and mitochondrial biogenesis. Inhibitors of Sirt 1 such as alcohol, palmitic acid and suramin are involved in cellular senescence with contribution to accelerated ageing by inhibition of mitochondrial biogenesis, cell mitosis and progression to chronic diseases [23,24]. Sirt 1 and senescence involve the poor regulation of NO that possibly generates peroxynitrite with induced cell damage associated with obesity, diabetes, stroke and neurodegenerative diseases such as AD [176-179]. Lifestyle changes that reduce stress such as exercise has been shown to increase adipose tissue mitochondrial biogenesis possibly by upregulation of Sirt 1 and associated with the release of increased amounts and sizes of adiponectin into the plasma. Diets with xenobiotics should be avoided to reduce oxidative stress and prevent mitochondrial and nuclear apoptosis [8]. Nutritional diets supplemented with the nutrient pyrroloquinoline quinone may assist in stimulating mitochondrial biogenesis to prevent and reverse mitochondrial apoptosis and has become important as therapy to delay brain ageing with an increase in cognition and prevention of hypertension and stroke with AD related dementia in obese and diabetic individuals.

CONCLUSION

The global obesity epidemic with accelerated ageing provide strong connections to the global stroke epidemic and AD

related dementia. Poor diet and lifestyle changes in response to stress are associated with early senescence with increased ceramide, AGE, increased Ang II, low adiponectin and HDL levels. In obese and diabetic individuals activation of the RAS that involves the adipose tissue that leads to increased oxidative stress, insulin resistance with mitochondrial apoptosis. These findings may assist in the understanding of the connections between the low HDL and neuron apoptosis that are strongly implicated in the pathogenesis of late onset AD (4,5) in Western countries.

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