Advances in Aging and Health Research

Dr. Ian James Martins
In the current global epidemic, chronic diseases such as non-alcoholic fatty liver disease (NAFLD), diabetes, and neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease have become of major concern to the developed and developing world. Appetite regulation is involved in the aging process with the repression of anti-aging genes connected to insulin resistance and neurodegenerative diseases. Interests in the gene-environment interactions indicate that the anti-aging genes are connected to the metabolism of bacterial lipopolysaccharides (LPS), drugs, and xenobiotics. In the developing world, relevance to gram-negative bacteria and increased plasma bacterial lipopolysaccharides (LPS) outer membrane endotoxins bind to cell membranes and interfere with cholesterol and amyloid beta (Aβ) interactions with repression of anti-aging genes to mediate accelerated neuron death. Biotherapeutics and nutritional biotherapy have become important to reverse these global chronic diseases. Biotherapeutics that involve Indian spice therapy require reassessment with relevance to insulin therapy, immunotherapy, antimicrobial therapy, and drug therapeutics. Combined insulin and Indian spice therapy interferes with human insulin biological activity relevant to the prevention of uncontrolled intracellular glucose levels and mitochondrial apoptosis. Magnesium therapy reverses cell senescence associated with various chronic diseases such as cardiovascular disease, diabetes, and Alzheimer’s disease. Factors such as stress, core body temperature, and food quality influence biotherapeutics with prevention of NAFLD, diabetes, and neurodegenerative diseases.

Aging is associated with increased oxidative stress that alters cellular chro-
matin structure, DNA methylation with histone modifications. These epigenetic alterations lead to nuclear changes associated with mitochondrial apoptosis that is a major defect in the global chronic disease epidemic. The variability in longevity between individuals in different communities implicate various nutritional and environmental factors involved in transcriptional dysregulation that lead to cell damage that accumulates with age and contributes to mitophagy, insulin resistance and programmed cell death. In the current global chronic disease epidemic the identification of anti-aging genes are necessary for the understanding of transcriptional regulation for gene expression, DNA repair and telomere maintenance in peripheral cells and neurons. These anti-aging genes are linked to appetite, longevity and mitochondrial biogenesis with relevance to the prevention of the global chronic disease epidemic and age related diseases.
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Dr. Ian James Martins is an Editor/Reviewer for Open Acess Pub/MDPI journals and various other international journals. Advisory Board Member for Photon Journal. Fellow of International Agency for Standards and Ratings (IASR). Conferred with the RICHARD KUHN RESEARCH AWARD-2015 ENDOCRINOLOGY AND METABOLISM. Chief Editor for International Journal of Diabetes Research (2014-2018), Research and Reviews: Neuroscience (2016-2018) and Journal of Diabetes and Clinical Studies (2017-2018). BIT Member (BIT Congress. Inc) with an \textit{h-index of 64}, (ResearchGate STATS \textit{(h-index27)}, Scopus Author ID: 7103152779/Mendeley STATS \textit{(h-index 21)}, UWA Research Repository \textit{(h-index16}). Scientist for The Science Advisory Board (USA) and an Academic with Academia.edu. The citations past 27 years have accumulated to >4584. Ian James Martins - Semantic Scholar \url{https://www.semanticscholar.org/author/Ian-James-Martins/5258067}. Semantic Scholar profile for \textit{Ian James Martins}, with fewer than 50 highly influential citations \textbf{RESEARCHGATE ANALYSIS}: Ian J Martins\textit{Ph D}Centre of Excellence for Alzheimer’s Disease... \url{https://www.researchgate.net/profile/Ian_Martins2} under Ian James Martins’ name places publication RG score (> 96\%) of international SCIENTISTS. \textbf{ORCID CONNECTING RESEARCHER}: Editorial Team \url{www.macrothink.org/journal/index.php/jfs/about/editorialTeamBio/13511}. Prestigious Recognition of Lifetime Membership by International Agency for Standards and Ratings as Fellow for Diabetes, Medical Science (Nutrition). Winner (World Academic Championship -2017) in Diabetes and Medical Science (Nutrition).Certificates from various international conferences have been
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received in relation to anti-aging, health and disease. Keynote addresses at the International Conference on Biomedicine and Pharmacotherapy 2018, Global Experts Meetings on Diabetes, Hypertension, Metabolic Syndrome 2018, Immunology World 2018, Laboratory Medicine 2018, Innovate Pharma 2017, Innovate Neurology 2017, World Diabetes and Endocrinology Summit-2017 and Pharmacology and Ethnopharmacology 2016. Chair/Co-chair Sessions on Laboratory management, Cytogenetics, Clinical Microbiology, Diagnostic Laboratory Medicine etc, 13th International Conference on Laboratory Medicine and Pathology, Berlin, Germany, June 25-26, 2018, Chairing Sessions on Vaccinology, Immunopathology, Immunotherapy, Immune Proteomics, Cancer and Tumour Oncology, 7th World Congress on Immunology, Amsterdam, Netherlands, April 19-20, 2018, Chair, Pipeline 1: Biotherapeutics for Diseases, Bit's 2nd International Congress of Biotherapy-2018 (Programme Committee Member), Chair, Innovate Conferences 2017, Chair/Co-Chair at congress World Gene Convention-2016 (Shanghai, China, Pharmacology and Ethnopharmacology 2016 (Chicago, USA), Annual World Congress of Diabetes-2014 (Haikou, China), World Gene Convention-2014 (Haikou, China). Research Activity Statistics have been provided by Publons with comparison to other researchers. Ian James Martins is now in the 98th percentile as assessed for Publons users by merit. Dr Ian Martins is a reviewer for approx. 47 journals over the past 5 years.
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Chapter 1. Sirtuin-1 Mediates the Obesity Induced Risk of Common Degenerative Diseases: Alzheimer’s Disease, Coronary Artery Disease and Type 2 Diabetes

Ian James Martins¹,², Andrea. C. Wilson¹,², Wei Ling Florence Lim¹,², Simon. M. Laws¹,²,³, Stephanie. J. Fuller³, Ralph Nigel Martins¹,²,³

¹Centre of Excellence in Alzheimer’s Disease Research and Care School of Medical Sciences, Edith Cowan University, Perth, Australia
²School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Perth, Australia
³McCusker Alzheimer’s Research Foundation, Hollywood Medical Centre, Perth, Australia

Abstract: Obesity, especially at mid-life, is a major risk factor for atherosclerosis, insulin resistance and the metabolic syndrome, which in turn contribute to coronary artery disease (CAD), Type 2 diabetes and Alzheimer’s disease (AD). The rise in overweight and obesity in all societies is prompting intense research into the causes and effects of the condition. Obesity disrupts many body systems including glucose and lipid metabolism, circadian rhythms and liver function. It also causes or increases inflammation and oxidative stress. Within cells,
the endoplasmic reticulum (ER) appears to be particularly susceptible to such metabolic disruption. Sirtuin 1 (Sirt1) and leptin have received attention recently as they are central regulatory factors for the body’s metabolic pathways which interact at particular levels, for example lipid and Abeta metabolism. This mini-review discusses recent findings concerning obesity, lipid metabolism and the role of Sirtuin 1 and how all influence the ER. A greater understanding of obesity and its effects on metabolic control systems of the body are required, to develop pharmacological, dietary and lifestyle changes that will reduce the incidence of CAD, Type 2 diabetes and AD.

**Keywords:** Obesity; Sirtuin 1, Alzheimer’s Disease, Cardiovascular Disease, Diabetes

## 1. Introduction

Obesity is associated with an increased risk for athero-sclerosis, contributing to the onset of coronary artery disease. Obesity is also well-known to be associated with Type 2 diabetes, insulin resistance and hyperlipoproteinemia. In fact, obesity and the metabolic syndrome have become major public health issues as they have reached epidemic proportions in Western populations [1]. Obesity is now recognized as an important risk factor for AD and cognitive decline [2]-[10]. For example, in a study of 8534 individuals from the Swedish Twin Registry, it was found that both overweight and obesity at midlife increase the risk of dementia, AD, and vascular dementia [11] [12], and in an 18 year follow up study of overweight women, a higher incidence of dementia (particularly AD) was found in these women relative to controls [13]. Obesity and overweight, as measured by body mass index and skin fold thickness, has been strongly associated with AD and dementia, independent of the development of diabetes and cardiovascular disorders [6].
2. Obesity and Adiposity

Obesity is defined as having a body mass (BMI) index of >30 (BMI = weight in kg/[height in m]²), whereas overweight is defined as having a BMI from 25 to 30. Obesity is a medical condition in which excess body fat has accumulated to such an extent that it is likely to have adverse effects on life expectancy and leads to increased health problems. Adiposity is the body fat tissue content, and as the degree of adiposity increases, the level of adiposity can be defined as being overweight or obese by measures such as the BMI.

3. Midlife Obesity

Being overweight or obese in early life or middle adult life leads to hyperinsulinemia which may lead to diabetes later in life. Therefore the timing and the development of adiposity is critical to the understanding how it is associated with the pathogenesis of AD (Figure 1).

Figure 1. Obesity as a mechanism for induction of Alzheimer’s disease.
In a recent longitudinal study of 1149 individuals, mid-life obesity was found to be a significant risk factor for AD in later life [14]. Abnormally high levels of the Abeta peptide are believed to be involved in AD pathogenesis, and in our own recent studies, we have found a strong positive correlation between body fat and blood plasma Abeta levels in cognitively normal individuals aged between 23 to 65 [15].

4. Diet and Risk of Alzheimer’s Disease

Epidemiological studies have shown that people of similar ethnic origins yet living in different environments can have significantly different risks of dementia [16] [17]. Nigerians living in Africa have a much lower incidence of AD when compared with African Americans living in the US [16]. Similar results were obtained with Japanese people living in Japan when compared with Japanese Americans living in the US [17]. These differences were believed to be mostly due to dietary differences. Diet and dietary fat intake are now considered particularly important when comparing the lifestyles of populations screened for AD [18]. In support of obesity and caloric intake influencing AD risk, for example, one study has found that the more saturated fat consumed in a meal the greater the risk for developing AD and senile dementia [19]. In other studies of humans and other animals, it has been found that feeding diets high in saturated fats results in learning and memory impairments. High caloric intake of saturated fat has also been associated with greater cerebral Abeta amyloid deposition [19]. In contrast diets containing chronically high levels of polyunsaturated fatty acids result in better learning when compared with diets containing saturated fat [20].

Cholesteryl esters can be hydrolysed in lysosomes following which fatty acids become available for oxidative metabolism, in particular to carbon dioxide
As a result, the metabolism of dietary lipids can be assessed using a stable isotope breath test \[21\] and using such a test, the clearance and metabolism of cholesterol-rich dietary lipoproteins in obese individuals has been found to be markedly lower than normal, indicating that the ingested fat was poorly cleared and metabolised from the blood plasma. Obese individuals have high triglyceride levels and low HDL levels with an increase in small LDL particles \[22,23\]. In animal models of AD, strong correlations between high fat/high cholesterol diets and increases in brain Abeta levels and HDL cholesterol levels and lower LDL cholesterol levels have been shown. For example, increased cerebral Abeta deposition as well as increased memory impairment has been shown in AD model transgenic mice fed high fat diets, and although exercise \[24\] and environmental enrichment \[25\] have been shown to reverse these effects to some extent, when translating to clinical situations, one major recommendation would always be to reduce saturated fat intake. Longitudinal studies have shown that people with an overall lower calorie intake also have a reduced incidence of AD later in life \[13\].

In obese individuals, there are several abnormalities in free fatty acid (FFA) metabolism \[26\] \[27\]. There is an increase in FFA release from adipose tissue to the blood plasma which impairs the uptake of glucose by muscle \[26,27\]. Furthermore, the rate of lipolysis is accelerated in visceral adipose tissue and the increase in circulating FFA results in dyslipidemia, hyperinsulinemia and hyperglycemia \[28\].

Essential fatty acids such as cis-linolenic acid (LA) and alpha-linolenic acid are essential for humans, and the metabolism of these fatty acids is altered in obesity and other diseases \[29\] \[30\]. In AD individuals the composition of phospholipid fatty acids is also altered \[31\] with increases in saturated fatty acids (14:0, 16:0, 18:0) and decreases in polyunsaturated fatty acids being found \[31\]. These alterations in phospholipid fatty acid composition may be associated
with the high saturated fatty acid intake at midlife in AD individuals [32].

5. Leptin and Obesity

Leptin is a 16-kDa hormone that plays a key role in regulating energy intake and energy expenditure. It acts on the hypothalamus to influence appetite and metabolism. Leptin regulates lipid homeostasis and has also been shown, in vitro and in vivo, to have important effects on Abeta levels via apolipoprotein E-dependent pathways [33]. It is secreted by adipose tissue and levels are usually directly proportional to the levels of body fat. Therefore, obese individuals have elevated leptin levels that is related to their increased adipose tissue mass [33]. It appears that obese people are resistant to the effects of leptin, in much the same way that people with type 2 diabetes are resistant to the effects of insulin [34].

6. Insulin and Obesity

Insulin modulates cognition and other aspects of normal brain function. The insulin resistance syndrome is characterized by chronic high levels of insulin, reduced insulin activity and reduced brain insulin levels. Insulin resistance together with obesity can lead to increases in cardiovascular risk factors such as dyslipidemia, hypertension and Type 2 diabetes [35]. Insulin resistance is also associated with age-related memory impairment and an increased risk of Alzheimer’s disease. High insulin levels are known to increase the levels of Abeta and inflammatory changes that are linked to age and obesity [35,36]. For example, AD-model mouse studies have shown that inducing type 2 diabetes caused an increase in Abeta production and Abeta neuropathology, impaired insulin receptor signal transduction, and a significant potentiation of cognitive deterioration compared to non-diabetic control AD mice [37]. It has been suggested
that the higher levels of brain Abeta in such mice may be due to result from the high insulin completely consuming insulin-degrading enzyme (IDE) activity–IDE can degrade both insulin and Abeta but has a preference for insulin thus resulting in elevated Abeta [38]. Preventing or correcting insulin abnormalities may reduce the risk of age related memory impairment and AD.

High fat diets are known to interfere with glucose tolerance and insulin sensitivity and yet such detrimental effects depend greatly on the type of fat consumed [39-41]: saturated and trans-fatty acids increase insulin resistance whereas monoand polyunsaturated fats decrease resistance and protect against the disease.

7. Sirtuin 1

The sirtuin proteins, also known as silent information regulators, are class III histone deacetylases (HDAC). Sirtuin 2 was the first to be identified: it was found to be a mediator of replicative lifespan in budding yeast. It was then shown to modulate longevity in worms and flies. These protective actions are believed to result from the beneficial regulation of stress management and energy homeostasis [42]-[56]. Sirtuins are now known to regulate several cell functions by deacetylating both histone and non-histone targets.

The mammalian homologue, Sirtuin 1 (Sirt1), seems to have evolved complex systemic roles in cardiac function, DNA repair and genomic stability. Sirt1 has been shown to play a central role in metabolic homeostasis. It is involved in gluconeogenesis in the liver, fat mobilisation from white adipose tissue, cholesterol metabolism, insulin secretion from the pancreas and energy metabolism in general [57]. For example, Sirt1 deacetylates and activates the transcriptional co-activator PGC1-alpha and the transcription factor FoxO1 in the liver, to promote gluconeogenesis. In adipose tissue, Sirt1 triggers fat mobilisation by
inhibiting peroxisome proliferator-activated receptor gamma (PPAR-gamma), and in the pancreas, Sirt1 repression of the uncoupling protein 2 (UCP2) increases insulin secretion [58]. Sirt1 also influences mitochondrial biogenesis, inflammation (cytokine release) and amyloidosis [42]-[56].

Calorie restriction has been shown to extend life span. In fact, it has been shown to extend the median and maximum life span of numerous organisms including yeast, flies, worms, fish, and rodents and mammals. It is now believed that this may be mediated partly due to the increase in Sirt1 activity which is induced by calorie restriction. For example, increased Sirt1 activity mediates mitochondrial biogenesis, which in turn may reduce the production of reactive oxygen species, a possible cause of aging and AD pathogenesis [59]. The involvement of Sirt1 in insulin regulation as well as cholesterol, fatty acid and glucose homeostasis has been linked to obesity, diabetes and cardiovascular disease. As these diseases are all thought to increase risk of AD, this provides further reason to believe that activating Sirt1 by calorie restriction may reduce the risk of AD (Figure 2) [60].

Figure 2. Anti-aging protein Sirtuin 1 controls peripheral cholesterol & lipid homeostasis and brain amyloid beta metabolism; ER = endoplasmic reticulum, UPR = unfolded protein response, VLDL = very low density lipoprotein, HDL = high density lipoprotein, PPAR = peroxisome proliferators-activated receptor.
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The concept that diet can regulate adipocyte plasma leptin (16 kda protein) as well as Sirt1 levels is supported by reports that high fat diets can lead to leptin resistance and low Sirt1 levels in rats and humans [57] [61]-[64]. Brain Sirt1 expression is increased by caloric restriction and fasting has been shown to increase brain Sirt1 protein content specifically in the hypothalamus. It also appears that the effect of Sirt1 on energy balance is mediated through central melanocortin signalling [58].

Recent studies suggest a functional relevance of SIRT1 in normal brain physiology, neurogenesis and neurological function [42]-[56]. In one important study for example, Sirt1 was found to downregulate micro-RNA known as miR-134. MiR-134 has been shown to down-regulate cAMP response binding protein (CREB) and brain-derived neurotrophic factor (BDNF), thus reducing synaptic plasticity. Sirt1 can prevent this miR-134-induced downregulation, thereby promoting synaptic plasticity [53]. Since 2005, miRNAs have been linked to complex metabolic processes in mammals, and changes to miRNAs can occur in many metabolic abnormalities and disease conditions. For example obesity, hyperlipidemia (elevated levels of blood lipids), and insulin resistance have been shown to be associated with aberrant expression of multiple essential miRNAs in pancreatic islets of Langerhans and peripheral tissues, including adipose tissue. Furthermore, in obese patients and experimental models of obesity such as 3T3-L1 preadipocytes and adipocytes from leptin deficient mice (ob/ob: mouse model of insulin resistance and obesity) and diet-induced obese mice, miRNAs normally induced during adipogenesis are downregulated. In particular, miR-143, miR-103 and miR-107, known to regulate adipocyte differentiation, are down-regulated in the ob/ob mice, possibly through an inflammatory pathway [65].

8. Sirtuin 1 and the Amyloid Precursor Protein (APP) of Alzheimer’s Disease

The maintenance of Sirt1 expression by calorie restriction has the effect of
regulating lipid metabolism and energy expenditure, which in turn helps regulate the production of many other proteins [54] [55] [57] [66]. In obesity however, Sirt1 levels are reduced and increased plasma Abeta, leptin and body fat have all been shown to correlate with increased adipose tissue size (AT). It has also been shown that Abeta precursor protein (APP) production is upregulated in adipocytes, and that plasma Abeta levels correlate with these increased levels of APP [67]. The increased plasma Abeta is proposed to be due to obesity influencing peripheral Abeta clearance, as obesity-induced Sirt1 dysregulation is strongly associated with liver steatosis and decreased Aβ clearance by the liver [15] [33] [57] [66]-[69]. Under conditions of calorie restriction on the other hand, Aβ content in the brain is attenuated, and this effect can be reproduced in mouse neurons in vitro by manipulating cellular SIRT1 expression/activity, ultimately promoting the nonamyloidogenic α-secretase processing of the APP, which precludes the generation of Abeta [70]. In particular, the over-expression of SIRT1 in the hippocampus has been shown to provide protection against neurodegeneration in a mouse model of Alzheimer’s disease [71], and the over-expression of SIRT1 in the brains of AD-model transgenic mice has been shown to reduce brain Abeta production and amyloid deposition in these mice, due to the induction of the α-secretase enzyme ADAM-10 [72]. In the arcuate nucleus of the hypothalamus, there are two types of neurons that play vital roles in regulating feeding and energy expenditure: the anorexigenic proopiomelanocortin (POMC) neurons and the orexigenic agouti-related peptide (AgRP) neurons. Sirt1 is expressed in both sets of neurons [51] [73].

Alterations in circadian rhythms have been demonstrated in both obesity and AD, and alterations in Sirt1 expression and leptin levels have been associated with this disruption to the daily light/dark cycle. Obese individuals are highly susceptible to circadian desynchrony, especially if on a high fat and cholesterol diet which disrupts normal tissue Sirt1 regulation of cholesterol homeostasis [69] [74]-[76]. PPARgamma, also known for its extensive roles in glucose and lipid
metabolism is now emerging as a critical factor in the regulation of circadian networks and it exhibits a circadian expression pattern that is magnified by consumption of a high-fat diet [77]. PPARgamma has been implicated in the pathology of several diseases including obesity, diabetes, atherosclerosis, and cancer, and PPARgamma agonists have been used successfully in the treatment of dyslipidemia and hyperglycemia. In support of Sirt1’s role in circadian rhythms, a recent epidemiological study of Sirt1 and circadian locomotor output cycles kaput (CLOCK) genetics found that subjects carrying minor alleles at SIRT1 and CLOCK loci displayed a higher resistance to weight loss compared with homozygotes for both major alleles, suggesting links between the circadian clock and Sirt1 function [73].

Other genetic studies are uncovering strong links between obesity and SIRT1 gene polymorphisms. For example, in a Japanese study, the A allele of SIRT1 polymorphism rs7895833, G allele of rs7069102, and T allele of rs2273773 were found to pose a high risk for obesity in men. Furthermore, the A allele of rs7895833 in women, and the G allele of rs7069102 and C allele of rs2273773 in men, were found to carry a high risk for hypertension [78]. In later studies by the same group, SIRT1 polymorphisms, rs7069102 and rs2273773, were found to be associated with abnormal cholesterol metabolism and coronary artery calcification, respectively, especially in males [79]. Another recent study of French caucasian adults found a strong association between high BMI and the SIRT1 SNPs rs3395786 and rs11599176, whereas 4 SNPs studied in BMI-discordant siblings of Swedish families were found to be associated with lower BMI [80]. In another study of the SIRT1 gene, a common SNP in a novel p53-binding sequence in the human SIRT1 promoter was found to affect nutrient-sensitive SIRT1 expression, and thus could have a significant impact on SIRT1-mediated changes in human metabolism and physiology that are induced by calorie restriction [81]. In contrast, a German study genotyped 1573 long-lived individuals (centenarians and nonagenarians) and matched younger controls, looking at
five SIRT1 single nucleotide polymorphism polymorphisms on longevity [82]. Such genetic studies are providing a greater understanding of metabolic differences between people and why some individuals may be more susceptible than others to obesity and related metabolic disturbances.

9. Obesity, the Endoplasmic Reticulum and Alzheimer’s Disease

Common medical conditions that can occur in middle age, such as diabetes, visceral obesity, and atherosclerosis cause considerable stress to the body. Obesity and atherosclerosis are regarded as states of chronic low-grade inflammation. At the cellular level, inflammatory mediators and lipid accumulation can evoke chronic stress, in particular affecting the endoplasmic reticulum (ER). It has recently been shown that the ER responds to metabolic stress through a well-coordinated molecular response. This involves the transcriptional activation of a variety of genes, the attenuation of protein synthesis, the degradation of ER-localised misfolded proteins, and sometimes the onset of apoptosis [83]. Disturbances in liver metabolism are known to be key components in the development of fatty liver, insulin resistance, and atherosclerosis. It has been shown that SIRT1 helps to regulate lipid homeostasis by positively regulating peroxisome proliferators-activated receptor alpha (PPARalpha), a nuclear receptor that mediates the adaptive response to fasting and starvation. This was demonstrated in liver-specific SIRT1 knockout mice, which when challenged with a high fat diet, developed hepatic steatosis, hepatic inflammation, and endoplasmic reticulum stress [46]. In these mice, PPARalpha signalling was shown to be impaired and fatty acid beta-oxidation was decreased. In other studies, the overexpression of SIRT1 in the liver of diet-induced insulin-resistant low-density lipoprotein receptor-deficient mice and of genetically obese ob/ob mice attenuates hepatic steatosis and ameliorates systemic insulin
resistance. These beneficial effects were associated with decreased mammalian target of rapamycin complex 1 (mTORC1) activity, inhibited unfolded protein response (UPR) and enhanced insulin receptor signaling in the liver, leading to decreased hepatic gluconeogenesis and improved glucose tolerance. These studies suggest that SIRT1 acts as a negative regulator of UPR signalling in Type II diabetes, and supports the concept that SIRT1 can attenuate hepatic steatosis, reduce insulin resistance, and restore glucose homeostasis, largely through the inhibition of mTORC1 and ER stress [84]. In other recent studies of Sirt1 and diabetes, SIRT1 in HepG2 cells has been shown to regulate ER stress by increasing expression of oxygen-related protein 150 (ORP150), an inducible ER protein thought to be a molecular chaperone involved in Ca²⁺ metabolism, again supporting the concept that SIRT1 can ameliorate insulin resistance via the regulation of ER stress [85].

10. Conclusions

The potential influence of associations between obesity and Alzheimer’s disease pathogenesis has been of great interest in recent research. High caloric intake and the consumption of a diet rich in saturated fat have both been associated with obesity, Type II diabetes, cardiovascular disease and Alzheimer’s disease. Sirt1 appears to play a central role in many metabolic changes that have been implicated in many of these conditions, as well as in AD pathogenesis. Recent studies of Sirt1 and ER function suggest Sirt1 provides considerable protection against metabolic stress via ER regulation.

Several studies have suggested that in early to midadult life, exercise and dietary interventions [86] [87] such as calorie restriction may prevent obesity as well as reduce or prevent amyloid deposition in the brain, due to the resultant chronic activation of Sirt1 in tissues such as the brain and the liver. When con-
sidering diet, omega −3 fatty acids are important for brain development, and fish consumption has been associated with decreased cognitive deficits and a reduced risk for AD [88] [89]. A diet low in saturated fats and cholesterol, yet rich in fruit, vegetables, and omega −3 fatty acids may provide essential micro-nutrients and antioxidants. Pharmaceutical treatments and/or other therapies centered around Sirt1 regulation might provide promising therapies in the treatment of metabolic diseases including obesity. Studies have already provided support for this theory—for example, the activation of Sirt1 by the polyphenol resveratrol and several synthetic pharmacologic activators has been shown to protect against high-fat diet induced obesity and other metabolic derangements. This is supported by studies which have found that transgenic mice over-expressing SIRT1 are leaner than controls, have a higher metabolism, and have lower serum levels of cholesterol, insulin, and glucose. Thus, calorie restriction, regular exercise, and/or drug treatment in obesity or other disease state may maintain or restore normal SIRT1 gene function. The evidence suggests that this would ultimately stabilise lipid metabolism and cause significant weight loss, reduce obesity and related disorders, as well as reduce or delay the development of Alzheimer’s disease.

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Chapter 2. The Acceleration of Aging and Alzheimer’s Disease through the Biological Mechanisms Behind Obesity and Type II Diabetes

Ian James Martins\textsuperscript{1,2}, Wei Ling Florence Lim\textsuperscript{1,3}, Andrea C. Wilson\textsuperscript{1,3}, Simon M. Laws\textsuperscript{1,2,3}, Ralph Nigel Martins\textsuperscript{1,2,3}

\textsuperscript{1}Centre of Excellence in Alzheimer’s Disease Research and Care, School of Medical Sciences, Edith Cowan University, Joondalup, Australia
\textsuperscript{2}School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Perth, Australia
\textsuperscript{3}McCusker Alzheimer’s Research Foundation, Hollywood Medical Centre, Perth, Australia

Abstract: The incidence of diabetes is predicted to increase to 21% by 2050. Currently, one third of US adults are obese and over 11% of these individuals have diabetes. Due to the growing need for therapeutic intervention to control and/or stabilize this increase in the incidence of diabetes in Western communities, gaining a comprehensive understanding of the association between obesity and Type 2 diabetes has become increasingly important to diabetes research. The increased cell senescence associated with diabetes has been associated with the limited ability of cells to divide, with indication of telomere shortening and genomic instability of the cells. Obese individuals have shorter telomeres suggesting an inverse relationship between adiposity
and telomere length. The implication that Type 2 diabetes has on biological aging is of particular interest since telomere shortening in obesity and diabetes has been associated with an early risk for dementia and even progression to Alzheimer’s disease (AD). Lifestyle, nutrition and longevity are closely related and cellular senescence has been associated with telomere shortening and connected to longevity. Diet, cholesterol lowering drugs and exercise that control food intake and glucose tolerance in aging and diabetic individuals, via connections between liver circadian clocks and the suprachiasmatic nucleus in the brain, also have been shown to alter telomere lengths. Lifestyle interventions, such as diets low in fat and exercise, target the rise in obesity and associated telomere shortening by delaying or preventing the onset of Type 2 diabetes. The implementation of these anti-aging therapies early in life may prevent calorie overload and activation of calorie sensitive genes such as Sirtuin 1 (Sirt1). This may maintain telomere length and the control of obesity, which is linked to cardiovascular disease, diabetes and accelerates aging and AD.

**Keywords:** Telomere, Sirtuin 1, Lifestyle, Nutrition, Diabetes, Obesity, Alzheimer’s Disease

### 1. Background

Age-related diseases are becoming a major concern as the world’s population grows older due to advances in medical technology, health and nutrition. Dementia accounts for a large proportion of age-related diseases and is characterised clinically by deterioration in cognitive processing, including memory. Alzheimer’s disease (AD) is the most common form of age-related dementia. The insulin-resistance syndrome has in many studies been associated with diabetes and AD. The social and economic consequences of this disease present a signif-
icant challenge to society, and it is imperative that strategies to prevent or delay the onset of diabetes are developed to prevent the proportion of the age related group with cardiovascular dysfunction progressing towards AD. AD is a neurodegenerative disease which presents clinically with key clinical symptoms including progressive decline in memory. Risk factors for AD include old age, family history of dementia, APOE 4 genotype, Down’s syndrome, obesity and type 2 diabetes.

Epidemiological studies clearly suggest that human obesity is associated with the increased risk for atherosclerosis, contributing to the early onset of coronary artery disease and diabetes. The susceptibility of humans to obesity is far higher compared with other species [1]. Amongst mammals, humans have been reported to have the highest level of fat than any other species as genes and environmental factors predispose humans to obesity [2]. In an editorial by Testa and Ceriello published in 2007, the increased cell senescence associated with diabetes was associated with the limited ability of cells to divide with indication of cellular alteration in genes and genomic instability of the cells [3]. Human obesity may complete the pathogenetic loop between cell senescence and diabetes through telomere shortening and an association with an increased risk for atherosclerosis. This in turn contributes to the early onset of coronary artery disease and diabetes.

Visceral obesity in particular increases the risk of atherosclerosis owing to both insulin resistance and dyslipoproteinemia and this global rise in obesity is possibly linked to telomere disease. Obesity has been closely linked to diabetes [4] [5] and the association of obesity and telomere shortening has now been reported [6]. In particular, telomere length, high density lipoprotein (HDL) cholesterol [7] and other risk factors for atherosclerosis that could be exacerbated by obesity-associated telomere dysfunction include hypertension and hyperlipidemia (particularly hypertriglyceridemia). These are also risk factors for AD.
Circadian desynchrony and hyperphagia are also related to obesity and anti-aging, circadian proteins, such as sirtuins are known to regulate several cell functions by deacetylating both histone and nonhistone targets. Sirtuins are NAD(+)dependent class III histone deacetylase (HDAC) proteins that target transcription factors to adapt gene expression to metabolic activity. Sirtuin 1 (Sirt1) is linked to life span, obesity and cardiovascular disease with effects on liver steatosis, inflammation, food intake, energy metabolism, cognition, mitochondrial biogenesis, neurogenesis, glucose/cholesterol metabolism and amyloidosis [8]-[22]. Regulation of Sirt1 by calorie restriction in extending life span has been recognized. Novel dietary activators of Sirt1 are required and designing compounds that have therapeutic potential for the control of telomere shortening, clock circuitry and generation of Aβ for the treatment of AD is the focus of several research groups [23]-[26].

Obesity in humans is seen to be associated with decreased life span in man and is an excellent model for the assessment of cell senescence, inflammation, diabetes and AD [27]-[31]. The understanding of alterations in genes/genomic stability and the environment in the aging brain has been the subject of various anti-aging programs as well as the mechanisms involved in anti-aging strategies related to low fat diets and reversing brain aging. The association between diabetes and neurodegenerative diseases (AD and Parkinson’s disease) have related the majority of the genes to cholesterol metabolism, cytokines and inflammation. Environmental factors such as diet and circadian desynchrony have become important in Western countries since interests in the global increase in obesity is possibly linked to diabetes, timing of food consumption, metabolic activity and alterations in adipose tissue leading to a release of adipokines (leptin and adiponectin). These adipokines increase with age and are associated with age related pathological alterations in cytokines associated with neuroinflammation [32] [33].
The mechanism linking obesity with diabetes is unclear but the global epidemic indicates that most patients with type 2 diabetes are obese; over a third (34%) of US adults are obese and about 11% of these individuals have diabetes [4]. The incidence of diabetes is predicted to increase to 21% by 2050 [5]. The understanding of mechanisms which connects these two diseases has become important to diabetes research since therapeutics to control and stabilize the increase in the incidence of diabetes in Western communities is required. As lipids and proteins accumulate in cells, the cells become impaired and can no longer divide, decreasing the lifespan of the cell resulting in cell telomeres that have eroded or shortened with cell senescence. The telomere is a repeating sequence of DNA at the end of a chromosome (TTAGGG)n [34] [35]. Aging results in a progressive loss of telomere repeats and with telomere shortening the cell ceases to replicate with alterations in lipid and protein metabolism with eventual cell death [34] [35]. Obese individuals have shorter telomeres and an inverse relationship has been found with adiposity and telomere length [6] [36] [37]. The pathogenetic loop between obesity and diabetes has recently been related to Sirt1 which is involved in cellular senescence. The genomic instability and telomere dysfunction observed in obesity is now closely associated with the pathogenesis of diabetes, dyslipidemia and cardiovascular disease. Diabetes, genetic and environmental factors have been reported to stress telomeres [38] through telomere shortening (Figure 1).

Sirt1 and cell senescence has been closely linked to telomere biology and global DNA repair which provides mechanistic explanations for SIRT1 functions, in protection from DNA damage, and thus genomic stability [39] [40].
Sirt1 has been closely linked to telomerase which is a ribonucleoprotein (RNP) complex responsible for the elongation of telomeres to maintain genomic integrity. Telomerase is composed of the telomerase reverse transcriptase (TERT) and telomerase RNA components (TERC). These factors regulate the catalytic activity of telomerase [41]. Telomerase protects cells from apoptosis via the maintenance of genomic integrity by stabilizing telomeres and adding DNA, in mediating cell survival and anti-apoptotic functions against various cytotoxic stresses [42] [43]. Telomerase is closely connected to telomere length maintenance and control of genes involved in growth and cell proliferation [44].

Anti-aging strategies that target telomere shortening in diabetes is of particular interest to biological aging since telomere shortening has been associated as an early risk for dementia [45] [46]. Age-related changes in AD lead to neuronal apoptosis and therapy to delay the onset and even progression of Alzheimer’s disease are urgently required. Nutrition related to low fat diets and drugs that reduce intestinal absorption of fat with modulation of adipose tissue Sirt1 activity may improve the adipocyte brain crosstalk that may be assessed as a possible treatment of neuronal diseases that afflict diabetic and AD individuals. Sirt1 is essential for neurogenesis and calorie restriction activates Sirt1 with effects on...
longevity by modulation of phosphoinositide 3 kinase pathway that determines life span [47]-[49]. The role of Sirt1 in brain metabolic regulation and synaptic plasticity has been shown and maintenance of Sirt1 expression by calorie restriction regulates lipid metabolism and energy expenditure [19]. Age associated cardiovascular changes have been strongly associated with alterations in Sirt1 [8]-[11] and genetic as well as experimental evidence of its control of lifespan is of interest to the areas of diabetes, neurodegeneration and AD. Telomere and telomerase activity has now taken an important place in AD therapeutics, using telomere length and telomerase activity in the determination of neuronal populations in these individuals [50] [51]. Sirt1 and its role in AD is of interest with reviews that indicate that Sirt1 is closely connected to Abeta production, telomere maintenance and stem cell aging [39] [40] [52] [53]. Interests in Sirt1 control of telomerase is of interest to diabetes and AD with recent publications suggesting telomerase inhibition is involved with abeta cell apoptosis. In AD, transgenic mice telomere length has also shown to be associated with amyloid pathology with indications that Sirt1 expression and activity is essential to neuronal population maintenance and prevention of AD.

3. Lifestyle, Diet and Drug Connections to Diabetes and Alzheimer’s Disease

The estimate in global deaths due to diabetes was estimated to be 5.2% of all deaths in 2009 [54]. In poorer countries, mortality related to diabetes was 2% - 3%, in countries such as the USA, Canada and the middle east the mortality was approx. 8% and for individuals between 35 - 64 years between 6% - 27% of the deaths were attributable to diabetes [55]. In 2011, the largest number of people with diabetes were in India, China, United States of America and the Russian Federation and mortality in 2011 reached 8.2% of the global population [55]. Nutrition and longevity are closely related and cellular senescence has been as-
associated with telomere shortening as well as the life span of the organism [34,35]. Apart from nutrition, minor alcohol consumption has been shown in midlife to shorten telomeres and accelerate aging in older individuals [56,57]. Diet, cholesterol lowering drugs and exercise may improve telomere lengths. This may provide the classical evolutionary conserved environment to suit anti-inflammatory processes which control of food intake and circadian rhythm and promote normal liver and brain, lipid and protein homeostasis, ultimately preventing glucose intolerance and diabetes.

Sirt1 (nutrient sensitive gene) is closely linked to food intake and the prevention of diabetes, which is linked to amyloidosis and may offer a potential therapy for AD treatment (Figure 2, [58] [59]). Interests in high fat intake and the consumption of fat at specific times of the day requires further investigation as a mechanism for diabetes and AD induction. Drugs that reduce intestinal absorption of fat will modulate the tissue anti-aging protein Sirt1, improving the adipocyte brain crosstalk that should be assessed as a possible treatment of neuronal diseases such as AD.

Figure 2. High fat and high cholesterol diets affect Sirt1 control of circadian rhythms with liver steatosis and effects on peripheral and brain amyloid beta metabolism.
In recent years, the world diabetes epidemic now includes younger individuals and has become of concern because of the risk for telomere shortening and non-alcoholic liver disease (NAFLD) [60]. In Western countries, accelerated aging is associated with NAFLD and has reached epidemic levels, with 40% of the community with the disease and up to 20% of these individuals developing hepatic fibrosis and cirrhosis [61] [62]. Individuals with longer lifespan have been shown to be diabetes free and increased mortality was attributed to increases in obesity [61]. Age related pathologies, such as NAFLD, that have been linked to Type 2 diabetes and AD, indicate association between insulin resistance, oxidative stress and telomere shortening [63]. Hepatocyte senescence, telomere shortening, nuclear size alterations and telomere foci have been closely associated to NAFLD and indicate mitochondrial dysfunction and lack of cell cycle progression beyond the cell cycle G1/S phase [64]-[68]. Interests in telomere shortening and insulin resistance indicate that the suprachiasmatic nucleus (SCN), which closely regulates peripheral clocks such as the liver (NAFLD) and adipose tissue (increased adiposity), is abnormal with relevance to the pathophysiology of disease [62] progression in obese, diabetic and AD individuals [69]-[72].

Drug therapies that target the brain have not been successful in preventing amyloid deposition but drugs that target the periphery may be promising by lengthening peripheral cell telomeres, lowering plasma fat and cholesterol and activating adipose tissue, liver and brain metabolic activity. Interest in Sirt1 modulation of various proteins that regulate cellular inflammation, glucose and cholesterol homeostasis are relevant to diabetes and neurodegeneration. Regulation of this calorie-restricted gene, Sirt1, as an important control that targets obesity, diabetes and brain aging by suppression of inflammation as well as maintenance of neuroprotective mechanisms that facilitate normal food intake and vitamin E transport to the central nervous system essential for growth of neurons has been the interest of anti-aging research studies. Designing com-
pounds for the regulation of Sirt1 to extend life span has been recognized and activators of Sirt1 in order for telomere maintenance have been reported. The use of melatonin, which is involved in telomere maintenance and circadian clock control [40], is relevant for the treatment of diabetes and AD as compared with other circadian rhythm drugs such as the benzodiazepines or non-benzodiazepines.

The relationship between telomere erosion and apoE4 is closely associated [23] with the role of apolipoprotein E and its connections with inflammation/cytokines [73] [74] as an important control of telomere attrition in the periphery and the brain. The connections between dyslipidemia and inflammation have been reported in diabetes, where inflammation in the blood plasma and altered cytokines have been associated with changes in lipid metabolism (increased triglyceride and low HDL) and in the brain, alterations in the light/dark cycle [75]. Drugs involved with telomere lengthening are possibly involved in the adaptation of the organism to the environment and require regulation of liver glucose and cholesterol and are controlled by dietary fat and cholesterol intake (Figure 2, [76]-[78]). The mechanism by which the ε4 allele promotes AD risk could be associated with diabetes and telomere shortening as well as with abnormal regulation of food intake, explaining the hyperphagia associated changes in diabetes and AD [79]-[81].

4. Nutritional Science and Drugs Delay Obesity and Severity of Diabetes Linked to Aging and Alzheimer’s Disease

Biological aging is closely connected to telomere length and control of cellular senescence. Each time a cell replicates and divides the telomere loses some of its length. Eventually the telomere runs out and the cell can no longer divide
and rejuvenate, triggering a poor state of cell health that contributes to disease risk and eventual cell death. Telomere length is epigenetically regulated and affected by nutrients, alcohol, drugs, genetics and the environment (Figure 3).

It is interesting to note that telomere shortening would be accelerated by synergistic effects of mixing alcohol and fats such as palmitic acid with increased genomic instability and DNA breakdown. The effective function of telomeres require methylation, which uses nutrients like methionine, an essential amino acid that serves as a methyl donor and is involved with the biosynthesis of other nutrients. Improper conversion is associated with production of homocysteine and atherosclerosis, methylsulfonylmethane, sulphur, choline, and trimethylglycine, as building blocks and allow regulation of genes by appropriate telomeres. Vitamins such as vitamin B12, folic acid, and vitamin B6 play multiple roles in genomic stability as well. Foods that are important include protein, eggs, cottage cheese, dairy, red meat, chicken, legumes, duck, nuts, and seeds. Antioxidants and vitamins C, D and E are essential and maintain genomic stability as well as telomeres. A lack of antioxidants leads to increased free radical damage and more risk for damage to telomeres. Minerals, such as magnesium, are needed by many enzymes involved with DNA replication and repair and total

Figure 3. Potential anti-aging therapies (left) delay the aging process by telomere maintenance and control of DNA damage.
magnesium intake should be between 400 mg - 800 mg per day. Zinc is intimately involved with DNA as well as DNA repair. The lack of zinc causes an excessive amount of DNA strand breakage and telomere depletion. Inflammation and stress shorten telomeres and omega 3 fatty acids (eicosapentaenoic acid/docosahexaenoic acid) are important as basic nutrients to preserve telomeres. Nutrients such as quercetin, green tea catechins, grape seed extract, curcumin, and resveratrol also help maintain telomeres, with both grape seed extract and curcumin showing the ability to generate longer telomeres. In addition, resveratrol and calorie restriction activate Sirt1 with prevention of telomere attrition.

Drug evaluation and differences in therapeutic effects of various drugs may indicate that the telomere length of tested rodents or diseased individuals may be related to genetic, diet and environmental conditions. Drugs such as statins have been shown to control telomere/telomerase in peripheral leukocytes from individuals with cardiovascular disease [82] [83] and have provided potential anti-aging therapy for diabetes and AD. Statins, however, are not Sirt1 activators and Sirt1 activators are primarily in control of telomere length and attrition. The close association of hyperphagia with diabetes and AD indicate that fat consumption (calorie excess) may have marked effects on telomeres/telomerase activation [42] [43]. Experimental drugs in mice, such as an acyl coA cholesterol acyltransferase (ACAT) inhibitor Avasimibe, that prevents fat absorption (calorie excess) have shown clear effects on body weight, liver and brain growth in mice consuming high fat diets (Abstract AD/PD Italy, 2013) possibly as a Sirt1/telomerase activator. Interests in telomerase activation have increased with the recent findings of TA-65 (purified from the root of Astragalus membranaceus/legume), a small molecule activator of telomerase involved in glucose regulation [84]. In contrast, various drugs that are Sirt1 inhibitors should be assessed with various diets since telomere shortening and attrition by Sirt1 inhibitors will lead to degenerative diseases such as obesity, diabetes, cardiovascular disease and AD. Lifestyles changes such as diet and exercise early in
the life of obese or diabetic individuals may prevent circadian alterations and calorie overload. Continued Sirt1 activation and the maintenance of peripheral (liver) and CNS (brain) cell telomeres with prevention of obesity linked to diabetes may decrease accelerated aging and the risk of AD.

5. Conclusion

The biological mechanism behind the global epidemic of obesity and Type 2 diabetes has become important to Alzheimer’s research since therapeutic interventions with the potential to control and stabilize their increased incidence in Western society may also have the potential to delay the acceleration in aging and AD. The increased cell senescence associated with obesity and diabetes has indicated an increase in telomere shortening and genomic instability of the cells from these individuals. Stabilization of biological aging is of particular interest in obesity and diabetes and the delay of telomere shortening in these individuals may result in a decrease in dementia and even a delay in the progression to (AD). Lifestyle, nutrition and longevity are closely connected to life span of obese and Type 2 diabetic individuals and therapeutics such as cholesterol lowering drugs, exercise and diets low in fat, target the rise in obesity and associated telomere shortening by delaying or preventing the onset of Type 2 diabetes. Implementing these anti-aging therapies early in life may prevent calorie overload and activation of calorie sensitive genes, such as (Sirt1), that may maintain telomere length and the control of obesity, which is linked to cardiovascular disease, diabetes and accelerates aging and AD.

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Chapter 2. The Acceleration of Aging and Alzheimer’s Disease through the Biological Mechanisms Behind Obesity and Type II Diabetes


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Chapter 3.

LPS Regulates Apolipoprotein E and Aβ Interactions with Effects on Acute Phase Proteins and Amyloidosis

Ian James Martins\textsuperscript{1,2,3}

\textsuperscript{1}Centre of Excellence in Alzheimer’s Disease Research and Care School of Medical Sciences, Edith Cowan University, Joondalup, Australia
\textsuperscript{2}School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Nedlands, Australia
\textsuperscript{3}McCusker Alzheimer’s Research Foundation, Holywood Medical Centre, Nedlands, Australia

Abstract: Interactions between apolipoprotein E (apo E) and amyloid beta (Aβ) are associated with the peripheral clearance of Aβ and are important to the development of neurodegenerative diseases. Interests in acute phase proteins (APP) as biomarkers for the early progression of Alzheimer’s disease indicate that the peripheral Aβ metabolism is perturbed and the role of nutritional diets are important to reduce APPs to maintain peripheral Aβ clearance with relevance to hepatic cholesterol homeostasis and brain amyloidosis. The role of nutriproteomic diets that reverse the effects of high fat diets are associated with the reduction in APPs, cholesterol homeostasis and improved clearance of Aβ. Nutritional diets that reduce the increase in plasma endotoxins (gut microbiota) such as lipopolysaccarides (LPS) reduce the effects of LPS on cell membranes and increase the cellular uptake of Aβ by interactions with apo E. LPS alter hepatic lipid metabolism with an increase hepatic cytokines and APPs.
in plasma. Interactions between apo E and Aβ are altered by LPS with increased binding of LPS to apo E with effects on electrostatic alterations in Aβ oligomers. The role of LPS in neurodegenerative diseases includes the effects of LPS on alpha-synuclein metabolism with relevance to Parkinson’s disease and Alzheimer’s disease.

**Keywords:** Lipopolysaccharides, Apolipoprotein E, Amyloid Beta, Acute Phase Protein, Diet

### 1. Introduction

In the aging populations in Western communities Alzheimer’s disease (AD) has increased and the prevalence in the next 30 years may reach 20 - 30 million people. Diets such as nutriproteomic diets have become important to the reversal of neurodegeneration with the aging process related to unhealthy diets such as high fat diets that are closely linked to amyloidosis in rodents and man [1] [2]. The role of nutriproteomic diets has become critical to prevent accelerated brain aging with high fat diets involved in the induction of metabolic dysfunction. Monitoring the plasma reveals an array of acute phase proteins [3] with respective charges that may interact with electrostatic oligomers of Aβ and assist in the understanding of accelerated aging in Western communities. Healthy diets that prevent the induction of APP have become important to prevent non-alcoholic fatty liver disease (NAFLD) linked to obesity, diabetes and AD (Figure 1).

The understanding of apo E mediated hepatic Aβ [3] clearance has become important with lipid-protein interactions implicated in the metabolism of Aβ in the periphery and the central nervous system [3]. The kinetics and interactions that determine the binding of apo E to Aβ and the role of lipoproteins that possibly determine interactions between apo E and Aβ has become important to the
Figure 1. Nutriproteomic diets reduce the hepatic release of cytokines and APPs that are involved in peripheral inflammation associated with the increase in hepatic Aβ metabolism. In aging and AD nutriproteomic diets maintain hepatic cholesterol metabolism (3) with the decrease in brain inflammation/Aβ plaque density.

prevention of neurodegeneration. Apo E is important in lipid metabolism with multiple roles in cell biology and is involved in the understanding of how apo E4 promotes risk of neurodegeneration. The cellular uptake of the apo E/Aβ complex has become important to early aging and AD with the interaction between these peptides determined by the nature of associated lipids, inflammatory markers (APP) that indicate relevance to NAFLD and neurodegeneration. Atherogenic diets promote abnormal hepatic cholesterol homeostasis and exist as the primary cellular mechanism involved in the peripheral aggregation and clearance of Aβ (Figure 1) [3]. Atherogenic diets that contain high fat contents have been discouraged in various communities with the role of these fat diets in the transport of gut microbiota [4] that increase plasma endotoxins such as lipopolysaccarides (LPS) in the blood plasma [4]. LPS has been associated with metabolic diseases and diabetes [4] and the importance of the cellular Aβ has increased with relevance to the binding of LPS (amphipathic α-helix organization) to apo E [5]-[9] and the influence of LPS on Aβ release
or generation in cells [10]-[12]. Peptides have been designed with $\alpha$-helix organization to neutralize lipopolysaccharide endotoxins [13]-[15] with relevance to the binding of apo E to $\alpha\beta$. Furthermore, LPS alter hepatic lipid metabolism with an increase hepatic cytokines and APPs in plasma that are involved in LPS inactivation [16]-[23] associated with $\alpha\beta$ dyshomeostasis [3]. Lipoproteins such as chylomicrons that are produced after a high fat diet contain the LPS binding protein (LBP) that bind LPS and essential interactions of LPS to apo B containing cholesterol-rich lipoproteins [4] clearly implicate dietary fat and LPS in peripheral $\alpha\beta$ metabolism in diabetes with relevance to neurodegenerative diseases.

2. LPS Neutralize Apo E Binding to Membrane Lipids with Effects on Peripheral $\alpha\beta$ Metabolism

LPS are endotoxins and essential components of the outer membrane of all Gram-negative bacteria [24] [25]. LPS from bacteria share common features in their basic architecture and consists of three covalently linked segments [26], a surface carbohydrate polymer (O-specific chain), a core oligosaccharide featuring an outer and inner region and an acylated glycolipid (termed Lipid A). The O-specific chain shows the most diversity and Lipid A anchors the LPS molecule in the Gram-negative outer membrane and is most conserved in bacteria species [26]. Membrane-bound and soluble proteins have been shown to bind LPS such as LBP, toll-like receptor (TLR) and CD14 receptor. In the central nervous system systemic LPS injection initiates the acute phase response and upregulates membrane CD14 receptor that controls TLR4 endocytosis [27] and induces microglial activation that results in neurodegeneration and Parkinson’s disease (PD) [26]-[29]. In AD the CD14 receptor is referred to as the LPS receptor and is involved in the phagocytosis of the $\alpha\beta$ peptide [30]. LPS induction
of APPs are linked to the CD14 receptor with the levels linked to liver inflammation and NAFLD [31]. LPS has been shown to effect hepatic genomic stability [32] with effects on reverse cholesterol transport in macrophages [4] and with macrophage activation [33].

LPS can rapidly insert into cell membranes with a preference for insertion and partition into cholesterol/sphingomyelin domains in cell membranes [34]-[36]. Cholesterol is an essential membrane component and in association with phospholipids, glycosphingolipids such as ceramide or gangliosides, glycerylphospholipids (plasmalogen) and sterols make up the membrane bilayers in cells. Lipid rafts containing sphingomyelin and cholesterol form microdomains in cell membranes for the recruitment of lipid modified proteins such as Aβ oligomers [4] with the binding of these hydrophobic proteins to membranes [3]. The essentiality of cholesterol determines Aβ binding to membranes with the addition of cholesterol important to the binding of Aβ oligomers to cells [3]. LPS may influence membrane cholesterol by binding to cell membranes and lipoproteins and its packing in the membrane allows the increased interaction or displacement of the Aβ peptide. In aging and AD membrane changes that lead to membrane alterations possibly involve the role of LPS in Aβ aggregation and fibril formation. Furthermore, amphipathic helices are critical to binding of peptides to LPS [13]-[15] with the role of apo E that contain these amphipathic helices linked to the binding to LPS that disrupt the role of apo E in the clearance and metabolism of Aβ in aging and AD. Apo E and its role in neutralization of LPS may be linked to its transport of LPS from macrophages to the liver [37] and support its critical role in LPS-lipoprotein (chylomicron, very low density lipoprotein) interactions to prevent inflammatory processes and closely linked to hepatic APP release (Figure 2). LPS has been shown to effect cholesterol efflux by the modulation of the anti-aging protein Sirtuin 1 (Sirt 1) with effects on LXR-ABCA1 interactions [4]. Monitoring dietary fat intake to reduce LPS has become important to metabolic diseases and neurodegenerative diseas-
es such as Parkinson’s disease [26] [38]-[41]. In obese mice altered inflammatory responses were found with LPS administration when compared with control mice with intestinal microbiota and NAFLD closely linked with connections to the systemic inflammation and the metabolic syndrome [42]-[45]. LPS effects on the release of alpha-synuclein [4] from cells in the periphery link the endotoxin to peripheral alpha-synuclein homeostasis (Figure 2) and to cholesterol metabolism with relevance to PD and AD [4]. LPS and cytokines have been shown to stimulate hepatic sphingolipid synthesis with the production of lipoproteins and with altered ceramide and sphingomyelin content [46]. Close connections between ceramide and LPS have been reported in cells [4] with disturbed cellular cholesterol efflux relevant to Aβ homeostasis in diabetes, AD and PD.

Figure 2. LPS increases the hepatic production of cytokines, APPs with marked effects on hepatic cholesterol homeostasis. LPS increases peripheral amyloidosis by interactions with APPs that interfere with the aggregation and deposition of Aβ. LPS stimulates the cellular expression of alpha-synuclein (4) that is linked to cell membrane cholesterol homeostasis and Aβ metabolism.
3. Hepatic Release of Acute Phase Proteins and Cytokines Is Regulated by LPS with Abeta Aggregation

The close connections between LPS and the liver involve the induction of lipoprotein synthesis with close connections between cytokines, apo E and RCT [3]. In addition to marked alterations in lipid metabolism (RCT) hepatic protein synthesis and serum protein levels (APP) are altered and associated with LPS levels (Figure 2). APPs have become important diagnostic markers for early progression of aging and AD [3] since APPs are now involved in important interactions with Aβ oligomers. LPS may prevent the clearance of Aβ by alteration in APP levels and by membrane receptor interactions. LPS may involve increase in hepatic cytokines that are connected to apo E sequestration with poor apo E redistribution from very low density lipoprotein and high density lipoprotein to peripheral membranes. Alterations in peripheral cholesterol homeostasis in neurodegeneration may involve LPS related apo E interactions that determine the peripheral metabolism of Aβ (Figure 2).

The detection of misfolding in proteins associated with APP possibly involve LPS effects on APP with the reversal and the formation of amyloid fibrils determined by the levels of serum amyloid protein P (SAP) and serum amyloid A (SAA) involved in systemic amyloidosis and cholesterol metabolism [3] [21]. Gelsolin is an actin binding protein and is involved with actin filament assembly and Aβ binding [3]. Interactions with apo E are associated with gelsolin related stabiility of misfolded proteins [3]. Gelsolin and SAP have marked effects on LPS neutralization (amphipathic molecules) and compete more effectively than LPB [20] [22]. LPS has been shown to induce hepatic LBP and SAA with implications to peripheral amyloidosis [21]. Transthyretin and clusterin are protective on protein folding with a reduction in amyloid plaque formation [3] with
increased plasma clusterin and transthyretin associated with LPS injections in animals [18]. Alpha 2 macroglobulin binds to Aβ with Aβ metabolism connected to apo E/LRP receptor interactions [3]. Elevated levels of alpha 2 macroglobulin in diabetes may determine Aβ metabolism with LPS effects on alpha 2 macroglobulin homeostasis [47] connected to the peripheral amyloidosis in diabetes.

The APP C-reactive peptide (CRP) that has been shown to be increased in obesity and has been closely related to BBB permeability and disruption [3]. Increases in CRP in obesity is associated with the release of SAA [3]. These APPs induce systemic inflammation and hypercholesterolemia with induction of blood brain barrier (BBB) disturbances and release into the brain of APP may involve LPS binding to CRP [48] [49] with the regulation of brain amyloidosis. LPS induced the expression of alpha-synuclein [4] [50] has been associated with the permeability in the BBB [49] and involve cholesterol homeostasis (Figure 2). Nutriproteomic diets are essential to prevent the rise in APPs such as CRP and SAA as associated with aging [51]. Diets that reduce APPs are connected to the rapid clearance of plasma LPS with the prevention of LPS transport across the BBB to the CNS connected to brain cholesterol homeostasis and neurodegeneration.

The peripheral clearance of Aβ and its relationship to high fibre diets [52] has now become of particular interest to neurodegenerative diseases such as PD and AD. Nutriproteomic diets (Figure 1) that are low in fat and glucose activates the liver and brain anti-aging protein Sirt 1 [53]-[55] and accelerates Aβ and cholesterol metabolism. Nutriproteomic diets such as high fibre diets/low protein diets [3] increase adiponectin levels [54] [56] [57] that facilitate rapid transport of LPS from the brain across the BBB to the liver with LPS removal connected to the reduced inflammatory effects of APP, increased adiponectin levels and prevention of NAFLD [54] [58]. Functional foods (yoghurt) that contain prebiotic and probiotics may reduce gram negative bacteria in the intes-
tine [59] [60]. However, diets high in fat (yoghurt, cream, cheese) and alcohol stimulate the rapid transport of LPS (gram negative bacteria) across the intestinal tract that corrupt hepatic membrane receptor interactions and peripheral Aβ homeostasis. High fibre diets (fatty acids and phytosterols) have become important to the peripheral Aβ homeostasis with effects of nutritional therapy by phytosterols (ABCA1 pathways) relevant to rapid LPS transport mediated by ABCA1 in macrophages and the liver [4] [52] [61]. Furthermore polysaccharides found in food colloids [62] [63] and yoghurt may increase polysaccharides in plasma and involve pathological polysaccharide-protein interactions with membrane fouling [64] relevant to mimicking similar to bacterial LPS cell membrane interactions.

4. Conclusion

Interactions between apo E and Aβ have become important and associated with the peripheral clearance of Aβ and the development of neurodegenerative diseases. Accelerated aging is connected to high fat diets with the release of increased LPS from the intestine into the blood plasma closely linked to abnormal hepatic cholesterol metabolism, increased cytokine release with amyloidosis. LPS directly interact with apo E and apo B in lipid particles with marked effects on LPS mediation in the inflammatory process and hepatic cholesterol homeostasis. LPS rapidly transfer to cholesterol and sphingomyelin domains in membranes with abnormal membrane interactions with Aβ oligomers. Dietary fat increases LPS levels that neutralizes apo E, increases alpha-synuclein levels and prevents the rapid peripheral clearance of Aβ with the promotion of accelerated aging. APPs directly interact with Aβ oligomers and the role of LPS on these interactions has become important to the increased inflammation in aging populations in Western communities. The nature and amount of dietary fatty acid, cholesterol and carbohydrate have become important to assess LPS effects...
on hepatic APP and cytokine production associated with inflammation and the reduced peripheral clearance of Aβ. Healthy nutriproteomics diets that prevent the LPS induction of APP prevent NAFLD linked to obesity, diabetes and AD.

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**Abbreviations**

LPS, Lipopolysaccharides, Apo E, Apolipoprotein E, Aβ, Amyloid beta, APP, Acute phase protein, Sirt 1, Sirtuin 1, AD, Alzheimer’s disease, PD, Parkinson’s disease, NAFLD, Non alcoholic fatty liver disease, LBP, LPS binding protein, SAP, Serum amyloid protein P, SAA, Serum amyloid A, CRP, C-reactive peptide, BBB, Blood brain barrier.

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Chapter 3. LPS Regulates Apolipoprotein E and Aβ Interactions with Effects on Acute Phase Proteins and Amyloidosis

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Chapter 4.

Anti-Aging Genes Improve Appetite Regulation and Reverse Cell Senescence and Apoptosis in Global Populations

Ian James Martins$^{1,2,3}$

$^1$Centre of Excellence in Alzheimer’s Disease Research and Care, School of Medical Sciences, Edith Cowan University, Joondalup, Australia
$^2$School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Nedlands, Australia
$^3$McCusker Alzheimer’s Research Foundation, Holywood Medical Centre, Nedlands, Australia

Abstract: Appetite regulation by nutritional intervention is required early in life that involves the anti-aging gene Sirtuin 1 (Sirt 1) with Sirt 1 maintenance of other cellular anti-aging genes involved in cell circadian rhythm, senescence and apoptosis. Interests in anti-aging therapy with appetite regulation improve an individual’s survival to metabolic disease induced by gene-environment interactions by maintenance of the anti-aging genes connected to the metabolism of bacterial lipopolysaccharides, drugs and xenobiotics. Interventions to the aging process involve early calorie restriction with appetite regulation connected to appropriate genetic mechanisms that involve mitochondrial biogenesis and DNA repair in neurons. In the aging process as the anti-aging genes are suppressed as a result of transcriptional dysregulation chronic disease ac-
CELERATIONS AND CONNECTED TO INSULIN RESISTANCE, NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND NEURODEGENERATIVE DISEASES SUCH AS PARKINSON’S DISEASE AND ALZHEIMER’S DISEASE. INTERESTS IN THE GENE ENVIRONMENT INTERACTION INDICATE THAT THE ANTI-AGING GENE SIRT 1 THAT REGULATES FOOD INTAKE HAS BEEN REPRESSED EARLY IN THE AGING PROCESS IN VARIOUS GLOBAL POPULATIONS. THE CONNECTIONS BETWEEN SIRT 1 AND OTHER ANTI-AGING GENES SUCH AS KLØTHO, P66SHC (LONGEVITY PROTEIN) AND FORKHEAD BOX PROTEINS (FOXO1/FOXO3A) HAVE BEEN ASSOCIATED WITH PROGRAMMED CELL DEATH AND ALTERATIONS IN THESE ANTI-AGING GENES REGULATE GLUCOSE, LIPID AND AMYLOID BETA METABOLISM THAT ARE IMPORTANT TO VARIOUS CHRONIC DISEASES.

KEYWORDS: ANTI-AGING GENES, APPETITE, ENVIRONMENT, NUTRITION, SENESCENCE

1. Introduction

The hypothalamus is involved with many biological functions and includes appetite and body weight control, feeding, emotion, memory, thermoregulation, fluid balance and insulin regulation [1]-[3]. The hypothalamic nuclei that are involved in food intake include the arcuate nucleus, the paraventricular nucleus, the lateral hypothalamic area, the ventromedial nucleus and dorsomedial nucleus. Arcuate nucleus neurons at the bottom of the hypothalamus near the third ventricle have direct contact with peripheral satiety factors like leptin and insulin. Neurons in the hypothalamus are responsible for various connections to other brain regions and one of the important functions of the hypothalamus is control of the daily light dark cycle. The suprachiasmatic nucleus (SCN) that coordinate the neuronal, humoral systems and the circadian rhythms activate the arcuate nucleus that releases neuropeptide Y (NPY) and agouti related protein (AgRP) that control physiological functions (body) temperature, melatonin release, glucocorticoid secretion and behavioural functions (feeding and
memory). The SCN and peripheral oscillators are altered by food availability with calorie restriction important in the maintenance of the SCN and the synchrony of the peripheral clocks. The neurons in the hypothalamus (appetite centre) are sensitive to apoptosis and become senescent early in life with relevance to global chronic diseases such as non-alcoholic fatty liver disease (NAFLD), obesity and diabetes.

In neurodegenerative diseases such as Parkinson’s disease (PD) and Alzheimer’s disease (AD) neurons in specific regions of the brain become apoptotic later in life but may not involve the neurons in the appetite centre. Neurodegenerative diseases such as PD and AD have become the cornerstone of brain research with appetite dysregulation and insulin resistance now closely connected to these diseases. Early neuron transcriptional dysregulation that involves the SCN leads to food intake disorders and it cannot be excluded that neurons in the appetite centre are defective early in life in global populations with appetite dysregulation associated with neurodegenerative diseases such as PD and AD. Appetite dysregulation is connected to the anti-aging gene Sirtuin 1 (Sirt 1) that is connected to the circadian rhythm with effects on the endocrine and metabolic systems that involve diseases of the adipose tissue, heart, liver, pancreas and brain [4]-[6]. Neuron apoptosis and survival [7]-[10] is determined by Sirt 1 and other anti-aging genes and interventions that prevent down regulation of anti-aging genes may allow appetite regulation with prevention of other chronic diseases. The rise in NAFLD in global populations [11] [12] has required early intervention with connections to the severity of diseases such as obesity, diabetes and neurodegenerative diseases. Interests in the calorie restriction with stabilization of anti-aging genes have accelerated in recent years to delay and prevent programmed cell death linked to the various chronic diseases (Figure 1). Interventions such as diet and lifestyle in chronic diseases such as obesity, diabetes and cardiovascular disease involve abnormal post-prandial lipid metabolism [13] [14]. Diet is strongly associated with insulin and insulin like growth
factor-1 (IGF-1) with cell senescence (mitochondrial apoptosis) and genotoxic stress linked to the global NAFLD and neurodegeneration [15]-[21].

Figure 1. Anti-aging strategies involve the maintenance of appetite regulation and insulin resistance that are connected to the anti-aging genes that are suppressed early in life. Appetite dysregulation accelerates abnormal post-prandial lipid metabolism and NAFLD in global populations and early intervention is required to prevent the severity of diseases such as obesity, diabetes and neurodegenerative diseases. Appetite maintenance improves the endocrine and metabolic system that is connected to blood brain barrier (BBB) disease and various organs diseases.

Interest in genomics that leads to the identification of novel genetic pathways assists in the treatment of various chronic diseases with the new knowledge that may delay early programmed cell death pathways in cells. Nutritional interventions that are controlled by the consumption of a low calorie diet indicate the maintenance of connections between Sirt 1 and other anti-aging genes such as Klotho, p66Shc (longevity protein) and FOXO1/FOXO3a that have been connected to the cell death by effects on glucose, lipid and amyloid beta metabolism. These anti-aging genes in neurons are involved in transcriptional regulation with effects that are important to SCN control of food intake and to the sur-
vival and stability of neurons. High fat diets that induce cell senescence are linked to cell transformation and are associated with liver cell dysfunction (NAFLD), adipogenesis disorders (obesity) and other organ diseases (Figure 1). The severity of endocrine and metabolism disorders are associated with poor neuron survival with early neuron transformation that leads to appetite dysregulation with overeating linked to metabolic disease. Major advances in the early diagnosis of diseases such as NAFLD and neurodegenerative disease associated with obesity and diabetes are required. Diagnostic blood assays such as plasma cholesterol measurements may not determine early senescence and programmed cell death [22] and extensive blood testing that is now underway in global populations may not be relevant to liver cell or neuron apoptosis (neurodegenerative diseases). The role of diets that control the absorption of bacterial lipopolysaccharides (LPS) are critical to prevent NAFLD and neurodegeneration [23] and the repression of anti-aging genes are possibly linked to LPS with the acceleration of appetite dysregulation and chronic diseases. The effects of LPS may also interfere with IGF-1 mediated expression of anti-aging genes with IGF-1/p53 transcriptional regulation linked to Sirt1 regulation of cell survival in aged and stressed cells [15]-[21]. To improve appetite dysregulation and prevent overeating that is linked to gene-environment effects (stress) on metabolic disease the maintenance of the apelinergic pathway [24] early in life is essential. Nitric oxide (NO) is involved in appetite regulation and NO disturbances have been reported in various chronic diseases [25]. Diets that are high in NO override cell NO maintenance that is controlled by Sirt1 relevant to endocrine, metabolic disease and thrombosis [24]-[27]. The effects of stress and xenobiotics (environment) are associated with cell NO disturbances that prevent the reversal of cell senescence (Figure 2). The nutritional diets that maintain the anti-aging genes and NO cell homeostasis possibly involve Sirt1/IGF-1 [29]-[36] with the effects of dietary LPS involved in the NO dyshomeostasis, neuron senescence and apoptosis.
Figure 2. The acceleration of chronic diseases involve NO disturbances linked to stress, consumption of unhealthy diets and xenobiotics (gene-environment interactions). Endocrine and metabolic diseases are linked to appetite dysregulation with NO disturbances that involve defective apelinergic pathways. Nutritional diets maintain the anti-aging genes and NO cell homeostasis with the importance of Sirt1/IGF-1 interactions in NO homeostasis, neuron senescence and apoptosis. Sirt1 is involved with the circadian rhythm and platelet apoptosis with relevance to thrombosis and embolism.

Zinc deficiency and chronic disease has become important with zinc levels relevant to hormone bioactivity [3], Sirt1 activity [28] and IGF-1 functions [37] [38]. Zinc supplementation has become important to LPS toxicity with relevance to inflammation in various global populations [39] [40]. Appetite regulation has been associated with various neuropeptides such as brain derived neurotrophic factor (BDNF) and NPY, hormones such as insulin, adiponectin, leptin and various intestinal peptides [3] [41]-[43]. The role of zinc and Sirt1 that involved in the regulation of the anti-aging genes has become important since repression of these genes do not maintain the action of the various neuropeptides, hormones and intestinal factors involved in appetite regulation with relevance to chronic diseases. Anti-aging therapy that maintains appetite regulation improves an individual’s survival against autonomous disease induced by the environment (bacterial lipopolysaccharides, drugs, xenobiotics) in various communities.
Diets that are nutritional activate cellular anti-aging genes with the prevention of cell senescence and apoptosis. Appetite regulation maintains the autonomic innervation of the liver by the brain with the maintenance of rapid post-prandial lipid metabolism [13] [14] and the prevention of diseases of the adipose tissue, heart, and pancreas.

2. Repression of Anti-Aging Genes Determine Food Intake Regulation, Insulin Resistance and Neurodegenerative Disease

Overnutrition in chronic disease is involved with central nervous system dysregulation of neuropeptides with abnormal peripheral hormone signalling from the pancreas (insulin), adipose tissue (leptin and adiponectin) and gastrointestinal tract (neuropeptides) involved in chronic diseases. The increases in global chronic disease in the past 20 years have indicated that insulin resistance and organ suicide are closely connected. The role of the mitochondria in organ function is critical with increased mitochondrial apoptosis with accelerated aging. The role of anti-aging genes in organ disease has become of central interest to maintain mitochondria functions and the identification of longevity genes that determine their function is critical to the maintenance of chronic diseases. The association between senescence and chronic disease now indicate that the anti-aging genes have been suppressed (autonomous disease) and insulin resistance, IGF-1 levels and neuropeptide disturbances are closely connected to mitochondria aging and cell senescence. Defective anti-aging genes are associated with glucose dysregulation with inhibition of insulin signalling involved with mitochondrial apoptosis. In SCN neurons within the brain the anti-aging genes that are involved with appetite regulation become altered by altered gene expression and abnormal posttranscriptional regulation closely connected to appetite dysregulation. The SCN synchrony between neurons is essential to maintain circadian rhythms and
disturbances between neurons are associated with autonomous neuron disease linked to the anti-aging gene repression and liver dysfunction.

The gene that is involved in the regulation of food intake is Sirtuin 1 (Sirt 1) that is linked to life span, obesity and cardiovascular disease with effects on NAFLD, inflammation, energy metabolism, cognition, mitochondrial biogenesis, neurogenesis, glucose/cholesterol metabolism and amyloidosis. 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 is involved in the deacetylation of the nuclear receptors with its critical involvement in insulin resistance. Sirt 1 is also involved in telomerase reverse transcriptase and genomic DNA repair with its involvement in telomere maintenance that maintains chromosome stability and cell proliferation. Sirt1 is essential for neurogenesis and calorie restriction activates Sirt1 with effects on longevity by modulation of phosphoinositide 3 kinase pathways and age associated cardiovascular changes. Tissue nuclear receptors undergo deacetylation of histone and non-histone targets by Sirt 1 that targets transcription factors peroxisome proliferator-activated receptor-gamma coactivator (PGC-1 alpha), p53, pregnane x receptor (PXR) to adapt gene expression to metabolic activity, insulin resistance and inflammation. Sirt 1 is linked to glucose regulation with the involvement of Forkhead box protein O1 (FOXO1) deacetylation (apoptosis) that involve p53 transcriptional dysregulation and peroxisome proliferator activated receptor (PPAR) gamma nuclear receptor. Furthermore Sirt 1/p53 interactions may regulate adipocytokines and immune responses that may be important to NAFLD, obesity and neurodegeneration. Interests in calorie restriction, appetite regulation and neurodegeneration that involve Sirt 1 mediated regulation of other anti-aging genes involve p53 and FOXO deacetylation that has attracted interest in relation to autonomous disease of the brain and liver. In these tissues Sirt 1 is an important gene involved in maintenance of the mitochondria and deacetylation of the transcriptional factor FOXO3a that represses
Rho-associated protein kinase-1 gene expression with activation of the non amyloidogenic $\alpha$-secretase processing of the amyloid precursor protein and reduction of amyloid beta ($A\beta$) generation in neurons. Sirt 1 is also involved with hepatic cholesterol regulation with effects on liver nuclear receptors involved with cholesterol flux and metabolism. Overnutrition is associated with the repression of Sirt 1 and other anti-aging genes (Figure 3) such as Klotho, p66Shc (longevity protein) and FOXO1/FOXO3a that is now connected to autonomous diseases of the brain and liver with SCN disturbances induced by Sirt 1 repression and IGF-1 dysregulation involved in programmed cell death relevant to various chronic diseases such as obesity, diabetes, PD and AD.

![Diagram of Sirt 1 regulation](image)

Figure 3. The anti-aging gene Sirt 1 is associated with transcriptional regulation and linked to insulin resistance, cancer and NAFLD. Sirt 1 regulation of p53, PGC1-alpha, PXR, PPAR, AMPK, FOXO1 involve nutrient, xenobiotic metabolism with relevance to DNA repair and the immune system. Transcriptional regulation of Sirt 1/p53 interactions are associated with alpha synuclein and amyloid beta interactions with the abnormal p53 transcriptional regulation of the anti-aging genes (Sirt 1, Klotho, p66Shc (longevity protein), FOXO1/FOXO3a) associated with IGF-1 and cancer.

### 2.1. Klotho

The klotho (KL) gene is composed of 5 exons and encodes a type-I single
pass transmembrane protein (1014-amino acid-long), short intracellular domain (10-amino acid-long). The extracellular domain is composed of two domains, termed KL1 and KL2, with weak homology. Klotho knockout mice have a short life span with increased oxidative stress associated with atherosclerosis, osteoporosis, infertility, and cognitive decline. The gene for the mammalian KL has two transcripts encode a long type I transmembrane protein and a short secreted protein that is released from the cell membrane and found in the serum and cerebrospinal fluid (CSF) [44] [45]. Sirt 1 and its close involvement as a histone deacetylase may be involved with Klotho gene expression and Sirt 1 downregulation may be intimately involved in the secretion and release of the protein into the serum or CSF. Resveratrol is closely involved in Sirt 1 upregulation and studies indicate that Klotho gene expression and secretion is upregulated by resveratrol [46]. Klotho gene has been identified as an important regulator of age related diseases and is involved with cell senescence by upregulation of p21 [47]. Klotho is an anti-aging gene and in Klotho-deficient mice Klotho has been associated with a premature aging-like syndrome. These results demonstrate that Klotho normally regulates cellular senescence by repressing the p53/p21 pathway that is activated by DNA damage and causes G(1)-phase arrest in mammalian cells. Klotho has been reported as a secreted Wnt antagonist and a tumor suppressor [48]. Epigenetic silencing of klotho has been shown as a major pathway with the involvement of histone deacetylation in the transcriptional repression of Klotho is correlated with promoter CpG hypermethylation and linked to Sirt 1 gene silencing that involve CpG island methylation. Klotho protein has been indicated to be a hormone that inhibits the intracellular insulin/IGF-1 signaling cascade [49] [50]. In other studies Klotho has been shown not inhibit IGF-1 and/or insulin signaling in various cells such as HEK293, L6, and HepG2 cells and indicate against the role of Klotho in insulin resistance as an important regulator of aging. Klotho gene expression was not associated with telomere length and the association with aging via other mechanisms [51].
Klotho has been associated with cognition [52] and chronic kidney disease via the fibroblast growth factor 23 but klotho levels have remained unchanged [53].

2.2. p66Shc

The gene SHC1 is located on chromosome 1 and encodes 3 main protein isoforms: p66Shc, p52Shc and p46Shc and differ in molecular weight. p66Shc, a 66 kDa proto-oncogene Src collagen homologue (Shc) adaptor protein is a longevity protein and has many effects involved with cell receptor tyrosine kinase signal transduction, nutrient metabolism and increased levels of p66Shc (Ser phosphorylation) have been shown to block mitosis, inhibit glucose metabolism and associated with the regulation of reactive oxygen species induced cell apoptosis [54]-[57]. p66Shc antagonizes insulin and mTOR effects which limits glucose uptake and inhibits anabolic metabolism [58] [59]. The p66shc protein plays key role in oxidative stress, stroke, metabolic disease in various organs and tissues in obesity and diabetes [60]-[64]. The p66Shc isoform has inhibitory effects on the Erk pathway [65] in skeletal muscle myoblasts, actin cytoskeleton polymerization and glucose transport. p66Shc inhibits ERK1/2 activity and antagonize mitogenic and survival abilities of T-lymphoma Jurkat cell lines. The MAPK/Erk signaling cascade is activated by a wide variety of receptors involved in growth and differentiation including receptor tyrosine kinases (RTKs), integrins, and ion channels. Oxidized lipids and LDL have been shown to stimulate p66Shc expression that is associated with abnormal redox balance, endothelial dysfunction and cardiovascular disease [66]-[68]. p66Shc is involved with the expression of p53 and p53 isoform (p44/p53), oxidative stress and G2M cell cycle arrest [69]-[71]. The induction of angiotensin II regulated p66Shc is controlled by stress activated p53 and indicates that post transcriptional regulation by p53 of p66Shc is essential for endothelium dependent vascular relaxation [72]. Sirt 1 is primarily involved in the deacetylation of p53
with control of p66Shc cellular senescence associated with the progression of NAFLD. Repression of p66Shc expression by Sirt 1 has been shown to be involved with liver injury and hyperglycemia induced endothelium dysfunction [73]. Palmitic acid is an inhibitor of Sirt 1 and palmitate has been shown to increase p66Shc (Ser phosphorylation) in pancreatic beta cells [74]. p53 is closely involved with the palmitate-induced increase in p66Shc expression and beta cell apoptosis. Sirt 1 that is actively involved in Aβ metabolism in neurons and Aβ has now been connected to the phosphorylation of p66Shc at the serine 36 residue with increased oxidative stress that leads to cell death [75] [76]. Antioxidants have been shown to be involved with reduced oxidative stress by interfering with the phosphorylation of p66Shc. Sirt 1 has effects on brain and liver alpha-synuclein and Aβ metabolism closely linked metabolic disease [77] [78] with effects of p53 transcriptional regulation by intracellular alpha-synuclein and Aβ metabolism in the liver and brain linked to the regulation of anti-aging genes and cellular apoptosis [78] [79].

2.3. **FOXO3a**

FOXOs belong to the O subclass of the Forkhead family of transcription factors which are characterized by a Forkhead DNA binding domain. There are three main proteins (FOXO1, FOXO3a and FOXO4) from which FOXO3a protein is considered to be a regulator of cancer and aging [80]-[83]. FOXO1 proteins are involved with adipocyte lipid metabolism and ROS-dependent cascades. FOXO3a is found in the nucleus but is redistributed to the cytosol by the actions of ROS and activation of this pathway (insulin/insulin-like growth factor-1 (IGF-1)/phosphatidylinositol-3 kinase (PI3K)/Akt/FOXO3a) is associated with senescence [84]. p66Shc participates in Akt signaling pathway and is involved with inactivated FOXO3a and ROS effects that involve activated p38 and JNK and inactivated by Akt kinase in cells. Sirt 1 has been shown to
deacetylate FOXO3 and FOXO4 with the regulation of FOXO-induced apoptosis and cell-cycle arrest not connected to p53 deacetylation. Sirt 1 has been shown to interact with FOXO3a and induce cell apoptosis [85] [86]. Nuclear Sirt 1 actively involved in Aβ metabolism and possibly regulates FOXO associated senescent effects with control of cell survival. Klotho has been shown to activate FOXO and to inhibit the insulin/IGF-1/PI3K/Akt signaling cascade. The connections between Sirt 1 and Klotho for cell senescence possibly are connected via FOXO1/FOXO3a mediated glucose homeostasis and ROS pathways. Bacterial lipopolysaccharides (LPS) are involved in the repression of Sirt 1 with the actions on other anti-aging genes. Zinc is the activator of Sirt 1 function with LPS closely connected to zinc deficiency with zinc supplementation essential to reduce LPS toxicity [38] [39]. Sirt 1’s effects on cellular cholesterol homeostasis is by its deacetylase activity and ubiquitination of liver X receptor (LXR) proteins with the regulation of ATP-binding cassette transporter (ABCA1) and sterol regulatory element-binding protein 1 involved in cell cholesterol homeostasis [78] [79]. LPS interferes with Sirt 1 and ABCA1 interactions by inhibition of cholesterol flux via LXR-ABCA1 pathways [78] [79]. Sirt 1 regulation of PGC1 alpha is well understood with PGC1 alpha involved in the inactivation of prostaglandin E2 (PGE2) with fat accumulation [11]. LPS is involved in the biosynthesis of PGE2 with LPS effects in the liver and other cells that override Sirt 1 and PGC1 alpha effects in these cells [87] [88]. The major effects of Sirt 1 as a deacetylase is regulation of the transcription factor p53 involved in the regulation of cell glucose and cholesterol metabolism [79]. LPS is involved in the post-transcriptional regulation of p53 with interference of Sirt 1/p53 cell regulation pathways involved in cell maintenance [79]. LPS induces mitochondrial apoptosis with toxic effects on the SCN neurons involved with appetite regulation that involve Sirt 1 dysregulation linked to anti-aging genes [78] [79]. IGF-1 levels and its connections to Sirt 1 and the anti-aging genes possibly involve corruption by LPS with LPS effects that involve dysreg-
ulation of circadian regulation of IGF-1 with IGF-1 effects on nuclear genes (cancer) and mitochondria within cells [17]-[19] [89]-[91]. Sirt 1 and its regulation of the SCN and appetite centre are inhibited by LPS via interference of the Sirt 1/p53 pathways that involve the other anti-aging genes.

3. Dysregulation of Neuropeptides and Endocrine Hormones by LPS Determine Appetite and Metabolism Disorders

The SCN in the brain is closely involved with appetite regulation and LPS induced posttranscriptional regulation in neurons is now closely connected to appetite dysregulation. The SCN synchrony between neurons is essential to maintain circadian rhythms and disturbances between neurons are associated with autonomous neuron disease linked to appetite dysregulation. LPS has a number of effects on various cells and tissues in the periphery and in the brain. LPS induces dyslipidemia and NAFLD with effects on apolipoproteins (apo E, apo AI), acute phase proteins, cytokines, albumin, alpha synuclein and amyloid beta [77] [78]. Its preference for binding to cholesterol and sphingomyelin sites on cell membranes indicates its role in the electrostatic interaction of amyloid beta [23] [77]. LPS has marked effects on receptors and on the astrocyte-neuron interaction with the induction of neuroinflammation [77]. LPS effects on the sleep/wake cycle determines food intake regulation and LPS effects on appetite regulation involves Sirt 1 repression and alpha synuclein/IGF-1 metabolism [78] [92]-[95]. Neurons in the hypothalamus are responsible to various brain regions and LPS induction of nuclear, mitochondria and cell membrane interactions induces autonomous cell behaviour with appetite dysregulation linked to reorganization cell signalling and astrocyte-neuron synchrony in the brain. Autonomous disease interferes with the effects of neuropeptides and hormones that are no longer effective and are now connected to nuclear receptors dysfunction associ-
ated with the anti-aging genes. Appetite regulation has been associated with various neuropeptides such as BDNF and NPY, hormones such as insulin, adiponectin, leptin and various intestinal peptides [96].

The interests in LPS in the induction of autonomous neuron disease involve inflammation with the connections to poor neuropeptide/receptor and peripheral hormones interactions that promote appetite dysregulation in the brain. NO has been clearly linked to food intake regulation and autonomous neuron disease induced by LPS is relevant overeating and metabolic disease in global populations (Figure 2). The effects of LPS induce mitochondrial apoptosis with NO dyshomeostasis [97]-[100] and corrupt appetite regulation by interference with neuropeptides and peripheral hormones that are also involved in the maintenance of mitochondrial stability. The effects of LPS on nuclear Sirt 1 repression in neurons disturb Sirt 1 regulation of cell NO metabolism with Sirt 1 linked to mitochondrial biogenesis [79]. The effects of LPS in the brain and the liver corrupt the autonomic innervation of the liver by the brain [101] with the liver clocks under autonomous regulation with sensitivity to disturbed post-prandial metabolism, liver steatosis and NAFLD. Interest in metabolic disorders indicate that the communication between the gastrointestinal tract neuropeptides involve the hypothalamus and brain stem [3].

These regions of the brain integrate peripheral signals such as various factors released from the gut and adipose tissue that have effects on neuronal activity of the hypothalamus and brain stem that control appetite regulation. In response to food intake various gut and adipose tissue hormones have effects on the hypothalamus that release various neuropeptides that effect appetite, food intake and energy balance. Cholecystokinin (CCK) is an intestinal hormone and after a meal CCK levels rise to inhibit food intake. Other peptides involved in appetite regulation include glucagon like peptide (GLP-1) that increases in the blood plasma released from the L cells of the gastrointestinal tract. Pancreatic islet
beta cells release insulin and another peptide referred to as amylin is released with relevance to reduced food intake. Other proglucagon cleavage peptides including oxyntomodulin (OXM) and peptide YY (PYY) are secreted with GLP-1 in response to high calorie foods. Pancreatic polypeptide (PP) is secreted from the pancreatic islets and is similar in structure to PYY with reduction in food intake after administration to rodents and humans. PP has effects on gastric ghrelin and gene expression of hypothalamic peptides such as NPY and AGRP that control food intake. Ghrelin is 28 amino acid peptide hormone and has been characterized as an appetite stimulating hormone with effects on appetite control related to hypothalamic NPY/AgRP neurones which express the ghrelin receptors [3].

Future therapies that involve control of body size and adiposity will involve assessment of diets that reduce LPS absorption [23] with relevance to LPS effects on the hypothalamus and on the poor regulation of various intestinal and brain neuropeptides that influence appetite regulation. Influence on appetite regulation and feeding are also related to leptin, melanortin, adiponectin, melanin concentrating hormone (MCH), orexins and endocannabinoids that communicate with peripheral signals such as nutrients (glucose, amino acids, fatty acids) and gastrointestinal peptide hormones such as CCK and ghrelin. Thyroid hormones may act directly on the hypothalamic appetite circuits and signalling factors such as thyroid stimulating hormone, triiodothyronine (T3) and thyroxine (T4) have recently shown to directly influence food intake. Hypothalamic control of appetite regulation and energy expenditure not only involves the hypothalamus but also the hypothalamic pituitary axis (HPT). Recent evidence indicates that the HPT axis can control food intake and effects on appetite and body weight is mediated by thyroid hormones and LPS has become important to appetite regulation [102] [103]. Interests in the neuroendocrine system, energy metabolism and peripheral cholesterol metabolism have increased with the strong genetic identification and involvement NPY in plasma cholesterol regulation.
The CNS and its control of lipid metabolism has identified hypothalamic NPY with evidence that NPY has effects on Y1 receptors to promote hepatic lipoprotein secretion to promote VLDL secretion via the sympathetic nervous system [104] [105] and on Y2 receptors to promote feeding. Sirt1 regulation of BDNF [106]-[108] has been shown (Figure 4) and associated with altered NPY levels in the brain [109] [110] and several studies have indicated its involvement in neuronal plasticity, behaviour, appetite control and body weight regulation. BDNF is involved in the regulation of food intake and the levels of BDNF controlled by high fat diets. In mature neurons the BDNF peptide is involved with the regulation of synaptic plasticity and neuro transmission in the peripheral and central nervous system. BDNF is involved in regulation of CB1 receptor expression and the proliferation, survival and maintenance of neurons. In individuals with the metabolic syndrome Sirt1 downregulation is possibly related to BDNF levels [111], IGF-1 levels and abnormal NPY regulation involved with appetite dysregulation and neurodegeneration.

Figure 4. Bacterial LPS suppresses Sirt1 expression with effects on neuropeptides such as brain derived neurotrophic factor, neuropeptide Y and IGF-1 that are involved in the appetite regulation (food intake) in the brain and in the periphery LPS interrupts hepatic glucose, lipoprotein and cholesterol metabolism. LPS is involved in cell zinc homeostasis with the importance of zinc relevant to the maintenance of Sirt1 activity and the function of hormones such as insulin and the adipokines (adiponectin, leptin) involved in appetite regulation in the hypothalamus.
Zinc deficiency has marked effects on brain zinc homeostasis and is associated with alterations in behaviour, learning and mental function. Under stress, anxiety and depression disorders zinc levels alter with marked effects on health and well being of the individuals. Stress has been linked to body weight regulation and evidence suggests zinc’s involvement in the molecular mechanisms of brain function and appetite control. Zinc is involved with regulation of leptin, insulin and adiponectin levels, adipose tissue cytokines (interleukin 2 and tumour necrosis factor) with long term effects on appetite regulation in the brain.

In zinc deficiency NPY levels in the hypothalamus are increased and release of NPY from the paraventricular nucleus is impaired with effects on regulation of food intake [112] [113]. In zinc deficiency NPY is unable to bind to its receptors to initiate an orexigenic response. Zinc is involved in the expression of brain BDNF and NPY synthesis and its effects on insulin, leptin and adiponectin [3] in the periphery indicates its role in the close relationship between appetite control and cholesterol homeostasis. Zinc is an activator of Sirt 1 and plays a critical role in the biology of p53 that is involved in the binding of p53 to DNA [114]. Interests in alpha-synuclein and food intake have increased [92] [93] and its relevance to p53 transcriptional regulation has been shown with LPS involvement [78] [79]. LPS regulation of apo E (23) has become important with relevance to apo E suppression of food intake [115]-[117] and LPS effects on leptin synthesis may determine appetite regulation [118] [119]. Leptin is a 16 kda protein identified in 1994 (14) is synthesized by fat cells and acts as a satiety factor at the hypothalamus mediated through the leptin receptor. The amount of leptin released is proportional to the size of adipose tissue and regulates food intake. LPS has effects on adipose tissue with release of free fatty acids associated with insulin resistance [120]. Dietary fat that promotes LPS absorption may determine apo E and leptin synthesis in the hypothalamus with relevance to chronic autonomic disease that involves zinc deficiency, appetite dysregulation and insulin resistance.
4. Anti-Aging Therapy Involves Reversal of Appetite Disorders in Autonomous Chronic Diseases

In the aging process appetite dysregulation (overeating) is connected to the suppression of the anti-aging genes as a result of transcriptional dysregulation. Interests in the gene-environment interaction [121] [122] indicate that the anti-aging gene Sirt 1 that regulates food intake is repressed early in the aging process in various global populations. Repression of Sirt 1 and other anti-aging genes such as Klotho, p66Shc (longevity protein) and FOXO1/FOXO3a lead to abnormal regulation of glucose, lipid and amyloid beta metabolism that are associated with programmed cell death in the liver and brain. Dietary effects on stress sensitive anti-aging genes (repression) may be associated with Sirt 1 downregulation with appetite dysregulation and accelerated disease progression. Anti-aging therapy that maintains appetite regulation improves an individual’s survival against autonomous disease induced by the environment in various communities. Bacterial lipopolysaccharides, drugs, and xenobiotics consumed early in life induce autonomous chronic disease and corrupt the Sirt 1 circadian clock gene with dysregulation of other cellular anti-aging genes now associated with cell senescence and apoptosis. Furthermore the lack of ingestion of nutritional doses of phosphatidylinositol (appetite regulation) leads to liver steatosis and acceleration to NAFLD. In the current global NAFLD in developing countries [122] [123] the induction of autonomous liver disease by consumption of high calorie diets that contain LPS, xenobiotics and drugs is now relevant to neurodegenerative diseases such as PD and AD. LPS and xenobiotics inactivate liver cells (autonomous liver disease) with relevance to the defective peripheral sink abeta clearance pathway that is now relevant to many chronic diseases [11] [124] that before may have been previously only associated with neurodegeneration [77]. The role of anti-aging genes in various communities in the develop-
ing world may be altered early in life with the acceleration of various diseases [11]. In the developed world the xenobiotic free diet and appropriate zinc consumption may activate hepatic nuclear receptors and with the metabolic syndrome the malfunction of various organ diseases may not be associated with the insulin resistance epidemic [125]. To maintain the cell anti-aging gene mechanisms and prevent early programmed cell death diets that are very low carbohydrate diets need to be ingested to avoid the intestinal absorption of LPS into the blood that is found in various foods [14]. The low calorie diet will maintain the nuclear Sirt 1 activity with relevance to p66Shc mechanisms that are sensitive to the ingestion of high palmitic acid and leads to cell cycle dysregulation with cell apoptosis [74] [126]. Short chain fatty acids (SCFA) have become important to appetite regulation with the consumption of acetate, propionic acid and butyric acid at therapeutic doses applicable to central appetite regulation [127] [128]. Butyric acid has been associated with the inhibition of zinc associated HDACs and administration of butyric acid doses in man for the reduction of alpha-synuclein and Aβ oligomers [78] [129] may inhibit the zinc sensitive HDACs such as Sirt 1 involved in cell NO homeostasis [129]. LPS sensitive butyric acid events have been associated with T cell apoptosis and cancer (Figure 5) with butyric acid derivatives important to cancer treatment [130]. The use of SCFA in nutritional diets has attracted interest to appetite regulation but the doses of the SCFA have become of concern for use in man and administration of butyric acid may need to be assessed with relevance to plasma LPS levels that may corrupt the neuroprotective effects of a ketogenic diet [131].

Sirt 1 activators (nutrients) and inhibitors (drugs, alcohol) have been previously described [11] and their consumption in various countries will determine nuclear receptor function and insulin resistance and determine the origin of autonomous chronic disease associated with early liver dysfunction linked to organ disease progression. Diets that are high in NO override the Sirt 1/ p66Shc
Chapter 4. Anti-Aging Genes Improve Appetite Regulation and Reverse Cell Senescence and Apoptosis in Global Populations

Figure 5. The short chain fatty acid butyric acid has been shown to be involved in the inhibition of Sirt 1 activity with effects of butyric acid and LPS on T cell apoptosis and cancer. Butyric acid regulation of brain appetite signals involves other short chain fatty acids such as acetate and propionic that are important to central appetite regulation. Butyric acid inhibits Sirt 1 with effects on the metabolism of alpha synuclein and amyloid beta metabolism in cells. Administration of dietary phenyl butyric acid reduces alpha synuclein and amyloid beta oligomers in the brain in mice.

regulation of cell NO (Figure 5) and mitochondrial apoptosis linked to cell autonomous disease are possibly associated with the acceleration of obesity, diabetes and neurodegeneration [25] [132]. The major interest in cell anti-aging genes is relevant to specific dietary intake that allows Sirt 1 cell function to belinked to therapeutic neuropeptide and endocrine responses that lead to the maintenance of anti-aging cell processes with the prevention of NO related apoptosis [133]-[135]. Interactions between cells in various tissues such as the liver and brain have become important with the brain involved in the autonomic regulation of liver function. The liver clock [136] may override the autonomic regulation of brain control by autonomous behaviour between cells that may be induced by LPS, mycotoxins or xenobiotics [137] with dysregulation of neuropeptides and endocrine hormones. Mycotoxins, LPS and xenobiotics that may be transported to the brain may induce cell desynchrony with appetite dysregulation and overeating related to dysregulation of neuropeptides and endocrine hormones important to insulin and the IGF-1 signaling cascade. The synergism
between LPS, mycotoxin and xenobiotics in diets may override the function of the anti-aging genes with the liver autonomous to brain regulation with the development of obesity and diabetes. The intestine and its release of lipid particles such as chylomicrons after a meal [14] has become important to human disease with intestinal release of lipid particles that contain LPS, xenobiotics and mycotoxins. The fat content of diet that releases the number and size of the intestinal particles has become important [138] to the function of the anti-aging genes in liver cells and food restriction (chylomicron release) that allows maintenance of anti-aging gene function is required. Under fasting conditions or timed meal conditions the release from the intestine of chylomicrons with LPS, xenobiotic or mycotoxin to the liver may allow rapid hepatic metabolism and elimination of various drugs into the bile [122] [137]. Tests for postprandial lipid metabolism in obesity indicate that in the fed and the fasting conditions dietary chylomicron remnant metabolism is defective with liver programmed cell death [14]. The various blood tests [22] and tests for postprandial lipid metabolism [14] may not allow early diagnosis of autonomous liver disease independent of appetite regulation that may be the primary disease associated with the current global obesity linked diabetes epidemic relevant to neurodegeneration [3] [22] [139]. The addition of zinc to the diet may not reverse the cell autonomy and may require the addition of various nutrients and the removal of various Sirt 1 inhibitors required for anti-aging cell processes. In the developing world, abnormal blood lipids (cholesterol, triglyceride) and liver enzymes may not interpret the effects of LPS and mycotoxin on anti-aging genes in the liver and brain that are defective and the effects of the anti-aging therapy such as consumption of a very low carbohydrate or a low fat diet [11] are possibly able to reverse the autonomous cell behaviour (nuclear-mitochondria interactions) that is linked to the nuclear senescence with mitochondrial apoptosis [79]. The use of diet as therapy for reversal of the aging process may stabilize the apelinergic system [25] that is defective in individuals with insulin resistance and important to the
optimal function of the brain and peripheral organs. The anti-aging genes in people at risk for various diseases in global populations may be defective early in life and not connected to DNA methylation profile associated with aging and longevity [140].

5. Discussion

In Western countries and the developing world the metabolic syndrome and NAFLD and neurodegenerative disease has reached approximate 30% of the global population. Accelerated age related disease associated with cell senescence interfere the anti-aging genes that are involved with cell growth and healthy aging. Dietary interventions with calorie restriction early in life prevent the tissue accumulation of LPS, mycotoxin, xenobiotics and drugs by maintenance of post-prandial lipid metabolism associated with delivery of various foreign compounds to the liver relevant to facilitate many tissue cell to cell communications with the prevention of autonomous organ diseases. Anti-aging strategies that involve nutritional diets allow neuropeptides and endocrine hormones to maintain cell and mitochondrial functions to facilitate nutrient metabolism in the liver and brain. Prevention of insulin resistance has become the major prevention program in global populations with improvement in zinc intake and maintenance of nitric oxide homeostasis in cells central to prevent early alterations in multiple anti-aging genes, neuropeptides and endocrine hormones that are associated with appetite regulation, insulin resistance and cell apoptosis.

6. Conclusion

The regulation of food intake and calorie restriction is important to appetite regulation with relevance to the progression of chronic disease and neurodegen-
Appetite dysregulation involves neurons associated with the suppression of the anti-aging gene Sirt 1 and other anti-aging genes such as Klotho, p66Shc and FOXO1/FOXO3a that are connected to the programmed cell death (mitochondrial apoptosis) and dysregulation of glucose, lipid and amyloid beta metabolism. Nutritional intervention early in life with the consumption of very low carbohydrate diets has been recommended that allows maintenance of the autonomic innervation of the liver by the brain. In the aging process unhealthy diets disconnect the liver from the brain with the ingestion of LPS, mycotoxin and xenobiotics that induce autonomous liver disease, metabolic disease and neurodegeneration. The brain and liver dysregulation are connected to various chronic diseases associated with abnormal post-prandial lipid metabolism, cardiovascular disease, obesity and diabetes. The anti-aging therapy involves low calorie diets that do not contain LPS, mycotoxin or xenobiotics and these diets maintain brain and liver Sirt 1 activity with appetite regulation closely linked to zinc and nitric oxide homeostasis connected to the autonomic control of the liver by the brain.

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Chapter 5.

Magnesium Therapy Prevents Senescence with the Reversal of Diabetes and Alzheimer’s Disease

Ian James Martins\textsuperscript{1,2,3}

\textsuperscript{1}Centre of Excellence in Alzheimer’s Disease Research and Care, School of Medical Sciences, Edith Cowan University, Joondalup, Australia
\textsuperscript{2}School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Nedlands, Australia
\textsuperscript{3}McCusker Alzheimer’s Research Foundation, Holywood Medical Centre, Nedlands, Australia

Abstract: In the current global epidemic for Non Alcoholic Fatty Liver Disease (NAFLD), diabetes and neurodegenerative diseases such as Alzheimer’s disease there has been a major interest in magnesium therapy to delay the severity of NAFLD, Type 3 diabetes and neurodegeneration in the developing and developed world. The objective of magnesium therapy is to activate the anti-aging gene Sirtuin 1 (Sirt1) to prevent cardiovascular disease, NAFLD and diabetes. Reduced consumption of nutrients such as fatty acids, glucose, cholesterol and increased magnesium consumption is closely linked to reduced bacterial lipopolysaccharides (LPS) and activation of Sirt1 relevant to active nuclear and mitochondria interactions with the prevention of myocardial infarction and Type 3 diabetes. Magnesium deficiency and its effects on Sirt1 regulation have become important with magnesium deficiency associated with appetite dysregu-
lation, senescence, glucose/nitric oxide dyshomeostasis, increased ceramide and toxic amyloid beta formation. Magnesium therapy activates the peripheral sink amyloid beta clearance pathway with the reversal of cell senescence associated with various chronic diseases such as cardiovascular disease, Type 3 diabetes and Alzheimer’s disease.

**Keywords:** Magnesium, Cholesterol, Amyloid Beta, Infarct, Lipopolysaccharides

### 1. Introduction

Interests in chronic diseases have increased globally with the release of the World Health Organization (WHO, 2013) which reported that the global death related to chronic disease was 63% with 48% attributed to cardiovascular disease, 21% to cancer and 12% to chronic respiratory disease. The global epidemic in obesity and diabetes has affected both the developing and developed world with neuroendocrine disease that involves insulin and leptin resistance linked to kidney disease, thyroid dysfunction, Non Alcoholic Fatty Liver Disease (NAFLD) and rheumatoid arthritis [1] [2]. The early senescence of cells in global populations has recently been associated with the anti-aging gene Sirtuin 1 (Sirt1) and its down regulation has been associated with mitochondrial apoptosis with relevance to diabetes and neurodegeneration [3] [4].

Sirt1 is a Nicotinamide Adenine Dinucleotide (NAD) + dependent class III histone deacetylase protein that targets nuclear receptors to regulate several cell functions by deacetylating both histone and non-histone targets [5]. Sirt1 regulation of transcription factors adapts gene expression to metabolic activity, insulin resistance and inflammation in chronic diseases [6]-[10]. Nutritional regulation (calorie restriction and high fat feeding) of Sirt1 that is involved in the hypothalamic and suprachiasmatic nucleus control of food intake with regulation
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of the central melanocortin system via the fork head transcription factor has been reported [11]-[14]. Sirt1 dysregulation has been closely linked with alterations in appetite regulation and low adiponectin levels with circadian clock disorders that are now important to Type 3 diabetes [3] [15] [16]. In support of Sirt1’s role in circadian rhythms subjects carrying minor alleles at Sirt1 and clock loci, displayed a higher resistance to weight loss as compared with homozygotes for both major alleles, suggesting links between the circadian clock and Sirt1 function [17]-[19]. Sirt1 is involved in neuron proliferation and glucose homeostasis with effects on cellular cholesterol and lipid homeostasis by the regulation of Liver X Receptor (LXR) proteins [3] [4].

The rate of the most prevalent chronic disease such as cardiovascular disease and acute myocardial infarction is linked to the metabolic syndrome and interest in magnesium/Sirt1 interactions associated with the development of coronary artery atherosclerosis has become important [20]-[23] (Figure 1). Reversal of cell senescence involves magnesium and Sirt1 interactions that improve appetite dysregulation connected to autonomous disease and Type 3 diabetes in a population by activation of other anti-aging genes that may delay the rate of chronic diseases [24] [25] (Figure 1). Autonomous disease that involves magnesium and Sirt1 dysregulation may be relevant to defective calcium ion channel activity and linked to emergency acute myocardial infarction and ischemic heart disease [26]-[28] and may not be relevant to levels of CK-MB and statin use [29]-[32]. Other anti-aging genes [24] [25] may be involved with magnesium therapy and the regulation of mitochondrial apoptosis in various cells and tissues [25]. Appetite dysregulation and Type 3 diabetes have been linked to higher brain dysregulations (higher cerebral cortex areas) that corrupt the hypothalamus, sympathetic and non-sympathetic nervous system with close connections between magnesium and Sirt1 in the regulation of the circadian rhythm [4] [33], stroke [34]-[37], NAFLD [38]-[40] diabetes [41]-[47] and neurodegenerative diseases [48]-[52].
Figure 1. Anti-aging therapy that involves magnesium and Sirt1 interactions are required to improve appetite dysregulation and brain-liver connections with relevance to chronic diseases and Type 3 diabetes in global populations. Nutritional diets are required to prevent Sirt1 dysregulation that occurs with aging and associated with emergency acute myocardial infarction. Nutrition and magnesium therapy prevent bacterial lipopolysaccharides and xenobiotics to induce post-transcriptional modifications with the prevention of magnesium/Sirt1 dysregulation in diabetes and Alzheimer’s disease that involve glucose dyshomeostasis, hypercholesterolemia and calcium associated toxic amyloid beta formation with relevance to myocardial infarction in global populations.

Detailed studies have previously shown the involvement of magnesium therapy in cholesterol metabolism with relevance to cardiovascular disease that is associated with low plasma High Density Lipoprotein (HDL), and high Low Density Lipoprotein (LDL) cholesterol levels [26] [27]. Stress, diet and lifestyles are closely linked to imbalances [53] in magnesium therapy that may accelerate aging with disturbances in eating [54], growth and nutrient metabolism that may involve dietary fat/carbohydrate [55]-[58] (Figure 1). Diets that contain xenobiotics [39]/bacterial lipopolysaccharides (LPS) are involved in post-transcriptional modifications with magnesium/Sirt1 dysregulation in diabetes and Alzheimer’s disease that may involve toxic amyloidogenic pathways and myocardial infarction in global populations [59]-[63].
2. Magnesium Therapy Regulates Amyloid Beta Metabolism with Implications for NAFLD and Cardiovascular Disease

In the developing and developed world NAFLD now afflicts 60% of the global population with the metabolic syndrome as the major disorder in these obese/diabetic individuals [3][39][40]. The increased risk for acute myocardial infarction has become of concern with NAFLD associated with poor hepatic xenobiotic and LPS [63]-[66] that may now be the factors involved in the induction of toxic amyloid beta (Aβ) associated with NAFLD and cardiovascular disease in global populations. Sirt1 down regulation promotes abnormal hepatic cholesterol homeostasis that exist as the primary cellular mechanism involved in the inactivation of the peripheral sink (Aβ) clearance pathway with generation of toxic Aβ involved in cardiovascular disease and the risk for death [59]-[62].

Aβ [67] is a proteolytic product of a larger protein, the amyloid precursor protein (APP). The Aβ (1-40) is synthesized in the early secretory and endocytic cellular pathways and the Aβ (1-42) is generated mainly in the secretory pathway [68]. APP is cleaved by three proteases, classified as α, β and γ secretases and formation of Aβ from APP is thought to occur via a two step process involving the β-site cleaving enzyme (BACE) and the putative γ-secretases [69]-[71]. The APP protein is cleaved into βAPPs (amino acids 18-671 of APP) and Aβ (amino acids 672-711/713 of APP). Apolipoprotein E (apo E) is important in lipid metabolism with multiple roles in cell biology and is involved in the understanding of how apo E4 promotes risk of neurodegeneration [72]. The understanding of apo E mediated hepatic Aβ [72] clearance has become important with the alterations in apo E/Aβ interactions responsible for defective peripheral clearance of Aβ associated with various chronic diseases [4].

Magnesium and its involvement in apo E/Aβ interactions determine cellular
apo E expression [73] [74] and cholesterol metabolism [75]-[77] with relevance to Aβ oligomer formation and magnesium alterations determine Aβ flux from the brain to the liver [4]. Cholesterol has been shown to be directly involved in membrane APP/Aβ interactions and magnesium levels have been shown to determine cholesterol metabolism involved in the early stages of organ disease and amyloidosis [78]-[80]. Magnesium has been shown to regulate APP and Aβ processing with dietary levels of magnesium important to maintain synaptic plasticity, cognitive decline with the prevention of Alzheimer’s disease (AD) [81]-[85]. Magnesium and its involvement in hypercholesterolemia, toxic amyloid beta formation also include ceramide formation with relevance to cardiovascular disease [86] [87].

Interests in magnesium homeostasis with relevance to intestinal magnesium absorption and kidney excretion provide important evidence of the relevance of the global kidney epidemic to magnesium deficiency in cells [88]. Obese and diabetic individuals are at increased risk for kidney disease with obvious implications of magnesium disturbances in various cells and tissues. The absent peripheral sink amyloid beta pathway in insulin resistant individuals may be relevant to kidney disease and magnesium imbalance. Magnesium play an important role in ATP formation in the mitochondria with ATP critical to Aβ misofolding and APP and Aβ involved in ATP generation in the mitochondria [89]-[92]. Magnesium imbalance in cells are associated with mitochondrial apoptosis [93] and Aβ oligomer formation with defective energy metabolism that indicate induction of NAFLD and obesity in global populations [3] [39] [40].

The anti-aging gene Sirt1 is involved in Aβ metabolism [3] and the biogenesis of the mitochondria and magnesium/Sirt1 interactions are possibly essential for maintenance of energy metabolism in various cells and tissues [3]. Magnesium/Sirt1 interactions involve anti-aging effects by telomere length regulation in the nucleus with both magnesium and Sirt1 involved in telomerase activity
The role of magnesium in RNA interactions and stability are critical to Sirt1 regulation of cellular lipid metabolism and energy expenditure [97]-[101]. Sirt1 is involved with the transcription factor p53 deacetylation with post-transcriptional regulation of cells (Figure 2) in the liver (NAFLD), adipose tissue (obesity) and brain (neurodegeneration) that involve both lipid and glucose metabolism [3] [4]. The relevance of p53/Sirt1 interactions and magnesium/p53 interaction [102] have become critical with relevance to Sirt1 down regulation by inhibitors [25] that override magnesium transactivation of Sirt1 (Figure 2) with acceleration of myocardial infarction in global populations [103]-[108]. Furthermore magnesium regulation of neuron and mitochondria apoptosis via N-methyl-d-aspartate (NMDA) receptor calcium loading involves p53/Sirt1 interactions with relevance to transcriptional regulation by magnesium of neuron and mitochondria apoptosis in Type 3 diabetes and AD [109]-[113].

Figure 2. The importance of magnesium and RNA interactions in the post-transcriptional regulation of Sirt1 has become important to the maintenance of the peripheral sink amyloid beta clearance pathway. Magnesium and Sirt1 are involved in telomere length and mitochondrial biogenesis and regulate cholesterol and ceramide contents of cells. p53/Sirt1 downregulation and kidney disease (low magnesium) are associated with low adiponectin levels with relevance to hyperglycemia, toxic amyloid beta formation and abnormal nitric oxidemetabolism.
Sirt1’s role in vasodilation of the coronary arteries has become important with the discovery of apelin that with Sirt1 are involved with nitric oxide (NO) regulation (Figure 2) in endothelial cells [114]. Sirt1 inhibitors prevent magnesium independent regulation of NO in endothelium with the development of coronary artery vasoconstriction [115]-[117]. Apelin and release from adipose tissue [114] involves conversion to angiotensin II (Ang II) and magnesium supplementation is essential to prevent Ang II induced myocardial damage [118]-[122]. Interests in Ang II and magnesium regulation of cell calcium homeostasis [123] [124] has accelerated with the role magnesium in the regulation of myocardium calcium channel function and now is associated with apelin’s regulation of sarco endoplasmic calcium [125]-[129].

Magnesium and its regulation of adiponectin levels [130] [131] and adiponectin connections to myocardial infarction in man [132]-[134] has become of importance with the role of magnesium involved in cell calcium homeostasis (mitochondrial function) and formation of high molecular weight adiponectin [135] [136]. 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 regulation of glucose homeostasis, NMDA glutamate receptor [137] and appetite regulation (Figure 2). Dysregulated Sirt1 in adipocyte differentiation and senescence [138]-[142] involve the down regulation of adiponection gene expression and secretion [143]-[145]. Sirt1 is clearly involved in adiposity with adipocyte size negatively correlated with adiponectin levels, adipose tissue ceramide metabolism and HDL levels [146]-[149]. The connections between magnesium/Sirt1 interactions involve adiponectin levels with relevance to calcium and toxic amyloid beta metabolism [41], NAFLD and myocardial infarction in man.
Magnesium therapy in age related diseases has become essential with magnesium deficiency involved in mitochondrial apoptosis with relevance to diseases of the heart, liver, brain, immune system and reproductive system [27] [150]-[155]. In the current global kidney epidemic the loss of magnesium in the urine is the inducing factor in magnesium deficiency involved in Sirt1 dysregulation and induction of apoptosis of various cells. The interactions of magnesium with Sirt1 (Figure 2) has become important with magnesium therapy involved with Sirt1 regulation of mitochondrial biogenesis and prevention of toxic amyloid beta formation relevant to the reduced susceptibility to senescence in various cells and tissues. The connections between magnesium and cancer has become important with magnesium therapy essential to maintain magnesium/Sirt1 interactions with the prevention of insulin resistance and cancer [156]. Dysregulation of miRNA/Sirt1 interactions by magnesium deficiency induces cancer [157] by downregulation of p53 induced by decreased intracellular magnesium levels with the corruption of nuclear and mitochondria connections.

3. LPS Disrupts Magnesium Therapy with Relevance to Albumin and Amyloid Beta Oligomer Metabolism

Atherogenic diets that contain high fat contents have been discouraged in various communities with the role of these fat diets in the transport of gut microbiota [15] that increase plasma endotoxins such as lipopolysaccarides (LPS) (Figure 3) in the blood plasma [15]. LPS has been associated with metabolic diseases and diabetes [63]-[66]. Lipoproteins such as chylomicrons that are produced after a high fat diet contain the LPS binding protein (LBP) that bind LPS and essential interactions of LPS to apo B containing cholesterol-rich lipoproteins clearly implicate dietary fat and LPS [63]-[66] in peripheral A/β metabolism in diabetes with relevance to neurodegenerative diseases. LPS are endo-
toxins 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 [158].

Figure 3. Atherogenic diets that are high in fat transport LPS into the blood plasma associated with metabolic diseases and diabetes. LPS interfere with magnesium therapy and regulation of hepatic cholesterol and peripheral amyloid beta metabolism with relevance to diabetes and neurodegenerative diseases. LPS, xenobiotics, Sirt1 inhibitors (alcohol, palmitic acid, butyric acid) interferes with magnesium therapy via p53/Sirt1 regulation of cells with increased inflammation and with relevance to cardiovascular disease. Ang II interfere with magnesium homeostasis with effects on Sirt1 actions that involve adiponectin, toxic amyloid beta formation, mitochondrial apoptosis and myocardial infarct size.

Cholesterol is an essential membrane component and in association with phospholipids, glycosphingolipids such as ceramide or gangliosides, glycerophospholipids (plasmalogen) and sterols make up the membrane bilayers in cells. LPS may influence membrane cholesterol by binding to cell membranes and lipoproteins and its packing in the membrane allows the increased interaction or displacement of the Aβ peptide. LPS can rapidly insert into cell mem-
branes with a preference for insertion and partition into cholesterol/sphingo-
myelin domains in cell membranes [159]-[161]. Lipid rafts containing sphin-
gomyelin and cholesterol form microdomains in cell membranes for the re-
cruitment of lipid modified proteins such as Aβ oligomers with the binding of
these hydrophobic proteins to membranes. The essentiality of cholesterol de-
determines Aβ binding to membranes [72] with cholesterol and magnesium now
important to effects of LPS on the metabolism of toxic Aβ oligomers in cells
(Figure 3).

LPS alter magnesium regulation of hepatic cholesterol metabolism and the
immune response [162]-[164] with an increase hepatic cytokines and APPs [66]
with effects on cholesterol mediated amyloidosis. Magnesium and its relevance
to hepatic cholesterol metabolism is associated with the structure and stability
of cholesterol/ sphingomyelin domains with magnesium deficiency associated
with increased ceramide [86] [87] that interferes with membrane cholesterol
(alkyl chain/C17 position) metabolism with decreased clearance of cholester-
ol-rich lipoproteins [165]. In LPS induced membrane alterations the magnesium
regulation of membrane fluidity is altered [166]-[168] with increased cholesterol
and ceramide contents that promote Aβ aggregation and fibril formation with
increased risk for myocardial infarction (Figure 3). LPS and its regulation of
hepatic membrane cholesterol metabolism involves phospholipid transfer pro-
tein (PLTP) involved in vitamin E, phospholipid and Aβ transport in cell mem-
branes [169]-[174] with LPS involved in PLTP transport that supersedes mem-
brane vitamin E transport [64] with relevance to magnesium therapy and hepatic
lipid metabolism. Increased levels of vitamin E administration in rats prevent
LPS mediated hepatic damage [175] with facilitation of peripheral amyloid beta
clearance.

The understanding of the role of the peripheral sink Aβ hypothesis in AD im-
plicates LPS of central importance in the corruption of magnesium therapy that
involves peripheral cholesterol metabolism, PLTP activity and the role of various acute phase proteins involved in \( \text{A} \beta \) aggregation [72]. LPS corruption of magnesium therapy involve the reduced release of albumin [176]-[181] from the liver with effects on albumin mediated fatty acid transport with plasma albumin important to maintain therapeutic free magnesium levels in cells such as the liver and brain and therapeutic levels of albumin important to prevent peripheral and brain \( \text{A} \beta \) aggregation [64]. The plasma magnesium levels need to be corrected with relevance to albumin (Albumin-corrected magnesium = magnesium + 0.005 (40-albumin) and values expressed as mg/albumin contents [176] [177] with relevance to LPS induced \( \text{A} \beta \) oligomer formation and size of the myocardial infarct [182]-[184]. LPS interferes with p53/ Sirt1 regulation of cells with increased inflammation and hepatocyte apoptosis [185] with importance to the p53 regulation of cardiac rupture [103] [104] (Figure 3).

4. Unhealthy Diets, Exercise and Stress Prevent Magnesium Therapy and Accelerate Chronic Diseases

Stressors that disturb adaptive functions early in life may not protect the organism from the environment and magnesium imbalance linked to stress, exercise [186]-[188], diet (high carbohydrate) and lifestyle have become important to prevent NAFLD and Type 3 diabetes with elevated risk of early myocardial infarction [182]-[184]. A low calorie diet is essential and recommended for the treatment of NAFLD and obesity and the benefit of this dietary regime is quite likely to lead to Sirt1 activation with improved peripheral cholesterol metabolism and reduced effects of LPS. Diet that are high in fat promote LPS absorption [4] and high fat diet have been also associated with magnesium deficiency. Sirt1 inhibitors such as alcohol, palmitic acid and butyric acid [24] (Figure 3) should be avoided with low palmitic acid diets essential for prevention of
NAFLD and for rapid liver metabolism of glucose, cholesterol and amyloid beta. Stress and the neuroendocrine system are closely involved in appetite regulation with the corruption of the apelinergic pathway [114] associated with kidney disease (magnesium deficiency), NAFLD and reduced Aβ oligomer metabolism [114].

Healthy food consumption an exercise may not eradicate the obesity epidemic or chronic diseases in the Western world since various xenobiotics (Figure 3) present in the food [39] such as the phthalates which affect the nuclear receptors (PPAR-Sirt1) are possibly involved in the induction of NAFLD, insulin resistance and chronic diseases associated with obesity. Antioxidants and minerals (magnesium, zinc) that improve genomic stability and reduce free radical damage of cells include vitamins such as C, D and E essential for cell function. Xenobiotics interfere with magnesium binding to DNA with effects on zinc/Sirt1 protection and risk for damage to various cells with chronic disease [189]-[192]. Addition of resveratrol to the diet has been shown to activate Sirt1 with the prevention of NAFLD in animal models [4]. Magnesium needs to be consumed at a dose of 260 mg/day (males) and 220 mg/day (females) in global communities that involve exercise as a daily basis and essential for individuals from developed countries/developing countries to avoid xenobiotic toxicity from elevated xenobiotic exposure present in food, water and air [39]. Xenobiotics have been shown to override magnesium related regulation of calcium homeostasis by interference of calcium channels and pumps with relevance to cardiac contraction [189]-[191].

High fibre diets [78] that contain fruit and vegetables and have become important for the treatment of NAFLD with therapeutic potential to the heart and brain and these diets prevent adverse affects on magnesium dysfunction and calcium-membrane lipid interactions [41] have become important to the prevention of accelerated aging associated with NAFLD, toxic Aβ formation and my-
Cardiac infarction. Specific polyphenols found in vegetables and fruits need careful evaluation since high doses [40] may cause increased oxidative stress with toxicity to the liver and induction of NAFLD and chronic disease. Nutritional interests in pyruvic acid consumption (6 - 44 g/day) [40] have increased with pyruvic acid as a Sirt1 activator and leucine consumption associated with increased adiponectin levels and reduced cholesterol levels in rats and glucose levels in obese mice [40]. Interest in leucine administration in man has increased with the effects of leucine on appetite regulation and Sirt1 activation [40].

Magnesium dysfunction versus magnesium deficiency in cell and tissues has become important to the treatment of various diseases with Sirt1 inhibitors (Figure 3) that corrupt magnesium DNA effects in various cells. Otherwise in various cells and tissues chronic disease may be related to calcium dyshomeostasis that involve calcium ion channel dysfunction by xenobiotics and not related to magnesium imbalance within cells. In the aging process magnesium deficiency is the most common disorder associated with poor intestinal absorption magnesium and associated with various chronic diseases. Magnesium therapy now involves the use of various products that stimulate the absorption of magnesium into the blood and magnesium supplementation has been introduced to manage insulin resistance, NAFLD and cardiovascular disease [192] [193]. Magnesium dysfunction induces Type 3 diabetes [15] [16] with brain insulin resistance (Figure 3) closely connected to magnesium levels (Sirt1 regulation), glucose dyshomeostasis, LPS induced repression of Sirt1 [194] with relevance to Aβ oligomer formation. High fibre diets that contain short chain fatty acids [195] [196] have been shown to stimulate magnesium absorption with relevance to management of insulin resistance and NAFLD. The anti-aging protein Sirt1 is involved with the intestinal absorption of nutrients [197] and with the aging process Sirt1 down regulation is now linked to cell senescence and apoptosis and possibly connected to malabsorption, intestinal disease and magnesium im-
balances in man. Sirt1 has been closely linked to Aβ metabolism in AD (Figure 1) and α-synuclein metabolism in PD [65] with circadian dysregulation that is associated with protein aggregation and with implications to magnesium/Sirt1 research and therapeutics in the regulation of α-synuclein/Aβ aggregates in the prevention of early cell senescence in and cardiovascular disease [198] [199].

5. Conclusion

Early cell senescence with relevance to Sirt1 has become important to the prevention of various chronic diseases that include cardiovascular disease, NAFLD and Type 3 diabetes. Interest in magnesium therapy has accelerated to maintain Sirt1 activity that may prevent mitochondrial apoptosis that afflicts many of the global chronic diseases. Magnesium/Sirt1 interactions are critical to cellular cholesterol metabolism, glucose metabolism, energy expenditure and defective post-transcriptional regulation of cells via the p53/Sirt1 pathway corrupt magnesium therapy with relevance to toxic Aβ formation and myocardial infarction. Magnesium therapy and Sirt1 regulation of adiponectin and Aβ formation are closely linked maintenance of the adipose-liver interactions that maintain the peripheral Aβ clearance pathway with the prevention of NAFLD, Type 3 diabetes and AD. Ang II down regulation of magnesium/Sirt1 interactions connects calcium dyshomeostasis to toxic amyloid beta formation and to myocardial infarction. Diets high in fat/carbohydrate are connected to magnesium deficiency and these diets promote the absorption of bacterial lipopolysaccharides that interfere with magnesium/Sirt1 regulation of hepatic membrane cholesterol homeostasis with relevance to toxic Aβ formation. Lifestyles that involve stress, exercise and unhealthy diets lead to abnormal magnesium therapy with inactivation of Sirt1 with early cell senescence and induction of autonomous disease associated with cardiac rupture, NAFLD and Type 3 diabetes.
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Chapter 6.
Indian Spices and Biotherapeutics in Health and Chronic Disease

Ian James Martins\textsuperscript{1,2,3,4}

\textsuperscript{1}Centre of Excellence in Alzheimer’s Disease Research and Care, Sarich Neuroscience Research Institute, Edith Cowan University, Nedlands, Australia
\textsuperscript{2}School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Nedlands, Australia
\textsuperscript{3}McCusker Alzheimer’s Research Foundation, Hollywood Medical Centre, Nedlands, Australia
\textsuperscript{4}School of Medical and Health Sciences, Edith Cowan University, Nedlands, Australia

Abstract: The acceleration in the rate of chronic disease that involves insulin resistance has become of concern in various countries. The rate of the most prevalent chronic diseases involves the metabolic syndrome and non alcoholic fatty liver disease (NAFLD) that is closely associated to diabetes and neurodegenerative diseases. Biotherapeutics and nutritional biotherapy have become important to reverse these global diseases. Biotherapeutics that involves Indian spice therapy requires assessment with relevance to insulin therapy, immunotherapy, antimicrobial therapy and drug therapeutics. Combined insulin therapy and Indian spice therapy regulates human insulin biological activity with relevance to the prevention of uncontrolled intracellular glucose levels and mitochondrial apoptosis. Biotherapeutics with nutritional biotherapy that involves the use of various nutrients such as magnesium and phosphatidylinositol...
sitol (gm/day) is essential to insulin therapy. Factors such as stress, core body temperature and food quality influence biotherapeutics and Indian spice therapy with delayed spice clearance associated with mitochondrial dysfunction (cell apoptosis) and altered drug/caffeine therapy with relevance to the global diabetes pandemic.

Keywords: Spices, Biotherapeutics

1. Editorial

Biotherapeutics has become of importance to global chronic diseases to prevent accelerated aging associated with uncontrolled immune reactions that determine treatment and disease progression. In the global burden of disease connections between nutritional therapy and the immune system [1] [2] [3] have become of medical interest with primary immune dysregulation related to obesity, diabetes and neurodegenerative diseases. Nutritional diets are essential to maintain immunotherapy/antimicrobial therapy [2] [4] [5] [6] relevant to community factors and global antibiotic resistance [7] [8]. Drug biotherapeutics is essential to stabilize chronic disease with dietary interventions and fat consumption that determine biotherapeutics important to the treatment of endocrine and metabolic diseases. Nutritional interventions with Indian spices [9] [10] and insulin therapy [11] [12] (Figure 1) have become of critical importance to the global diabetic pandemic with human insulin and its biological activity (Figure 1) of major relevance to the global burden of disease progression.

Indian spices have been reported to exhibit a wide range of physiological and pharmacological properties that produce beneficial health promoting/protective effects for various chronic diseases [13]-[19]. Identification of spices such as five commonly used dietary spices include saffron, curcumin, pepper family, zingiber and cinnamon has been used for the treatment of hypercholesterolemic,
Figure 1. Biotherapeutics and nutritional biotherapy have become important to reverse global diseases such as non alcoholic fatty liver disease (NAFLD), diabetes and neurodegenerative diseases. Biotherapeutics that involve Indian spice therapy require assessment with relevance to immunotherapy, antimicrobial therapy and drug therapeutics. Combined insulin therapy and Indian spice therapy regulate human insulin biological activity with relevance to intracellular hyperglycemia and mitochondrial apoptosis. Databases searched for medical literature in this study include Pubmed database, Medline database, Research Gate Researcher Network, Mendeley Research Network and Academia.edu database.

cardiovascular disease, obesity, inflammation/metabolic disease, diabetes and Alzheimer’s disease [13]-[19]. Indian spices as a biotherapy have become important in the developed and developing world with specific spices such as cinnamon and curcumin involved in the control of the immune system and the antimicrobial therapy [20] [21] [22] [23]. Cinnamon and curcumin as nutritional interventions have major effects on drug and hormone biotherapy with doses of these spices [9] important to determine stabilization and reversal of global chronic disease. Insulin therapy is one of the most important treatments in diabetes with cinnamon and curcumin involved in the improvement of plasma hyperglycemia and involved with the regulation of insulin dose/type and frequency of use in diabetes therapeutics [24] [25] [26] [27]. Cinnamon has been shown to regulate insulin levels [24] [25] with therapeutic effects on hyperglycemia induced mitochondrial apoptosis [26]. Curcumin effects on the insulin receptor and beta cell function [26] [27] modulates human insulin therapy with critical consideration of Indian spice therapy required with relevance to human insulin
administration and diabetes treatment [28]. Diabetes and mitochondrial dysfunction are closely connected [1] [29] with Indian spice and Insulin therapy to be carefully assessed with relevance combined therapy and increased cellular glucose levels related to hyperglycemic mitochondrial apoptosis [30].

Biotherapeutics for diseases (Figure 2) are now ineffective with malfunction of nutrient sensitive genes involved in mitochondrial survival [1] [3] [4] [30]. Indian spices (curcumin) as a biotherapy in health and disease should be carefully controlled with higher doses not associated with activation of anti-aging genes [31] involved in mitochondrial biogenesis [3]. Biotherapeutics that involve nutritional biotherapy with phosphatidylinositol (gm/day) [4] and magnesium contents [32] improves insulin therapy but combined therapy with Indian spices need to be assessed in clinical trials. Biotherapeutics that include other nutrients [33] are essential for biotherapy to maintain genomic stability in diabetes (Figure 2). Foods that contain essential nutrients include protein, eggs, cottage cheese, dairy, red meat, chicken, legumes, duck, nuts, and seeds. These essential nutrients include methionine, methylsulfonylmethane, sulphur, choline, and trimethylglycine as building blocks that allow regulation of genes by appropriate telomeres. Vitamins such as vitamin B12, folic acid, and vitamin B6 play multiple roles in genomic stability. Antioxidants and vitamins C, D and E are essential and maintain genomic stability. A lack of antioxidants leads to increased free radical damage and more risk for damage to telomeres essential to cell survival. Minerals such as magnesium and zinc are required for the prevention of DNA strand breakage and the prevention of accelerated cell aging. Nutrients such as quercetin, green tea catechins, grape seed extract, resveratrol and omega 3 fatty acids (eicosapentaenoic acid/docosahexaenoic acid) are important as basic nutrients to preserve biological aging and reverse diabetes. Poor food quality [4] [5] [34] interferes with drug biotherapeutics associated with Indian spice inactivation (Figure 2). Biotherapeutics that involves caffeine has been extensively studied in obesity and diabetes [35] [36] with curcumin doses
and caffeine intake important to hyperglycemia induced cell apoptosis. Indian spices that induce cell apoptosis [37] [38] [39] prevent cancer include curcumin (turmeric) and piperine (black pepper) with interference with caffeine metabolism [40] and active spice component pharmacokinetic data is still not available.

Figure 2. Biotherapeutics with nutritional biotherapy involve the use of various nutrients such as magnesium and phosphatidylinositol (gm/day) are essential to maintain genes involved in insulin therapy. Factors such as stress, core body temperature and food quality influence biotherapeutics and Indian spice therapy with delayed spice clearance associated with mitochondrial dysfunction (cell apoptosis) and altered drug/caffeine therapy.

Core body temperature connections to the immune system and mitochondrial cell function [41] indicate that with heat/cold stress induce toxic immune reactions [42] that are relevant to mitochondrial apoptosis in non alcoholic fatty liver disease, obesity, diabetes and neurodegenerative diseases. Factors such as core body temperature and stress [41] [43] may override Indian spice therapy and various biotherapeutics that are of prime importance in the stabilization of the global chronic disease epidemic [31] [44]. Indian spice therapy requires further assessment with relevance to hormone therapy, reversal of NAFLD with poor Indian spice metabolism possibly relevant to adverse drug reactions [9].
(Indian spice-drug interactions) with the aging process but higher doses are therapeutic for cancer treatment with relevance to induction of cell apoptosis [29] [30] [31]. Furthermore diets that contain Indian spices may alter the apernergic system [43] involved in stress reactions, co-ordination of the neuroendocrine system and the development of chronic disease.

2. Conclusion

Biotherapeutics for chronic diseases has accelerated to prevent the progression of the current global chronic disease epidemic. Indian spice therapy has become an important biotherapeutic involved in the reversal of global diabetes and neurodegeneration. Mitophagy in chronic disease requires attention with Indian spice therapy and insulin therapy as a combined therapy to regulate cell glucose levels to prevent hyperglycemic induced mitochondrial apoptosis. Specific nutrients need to be consumed with Indian spices to allow stabilization of uncontrolled toxic reactions that lead to cell death. Core body temperature, stress and inappropriate food quality will inactivate Indian spice therapy with excessive Indian spice intake over many years that may be connected to ineffective human insulin biological activity/drug biotherapeutics with long term Indian spice use more relevant to cell apoptosis and the treatment of cancer. Monitoring of long term Indian spice therapy may be required in future clinical trials in man with relevance to safety compared to diabetic individuals with insulin therapy and without Indian spice therapy.

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