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

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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 dysregulation, 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,

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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 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
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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].

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 endoctic 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 [94]-[96]. 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].

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 adiponectin gene expression and secretion

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**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.
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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 lipopolysaccharides (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 Aβ metabolism in diabetes with relevance to neurodegenerative diseases. LPS are endotoxins 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].

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 membranes with a preference for insertion and partition into cholesterol/sphingomyelin domains in cell membranes [159]-[161]. Lipid rafts containing sphingomyelin and cholesterol form microdomains in cell membranes for the recruitment of lipid modified proteins such as Aβ oligomers with the binding of these hydrophobic proteins to membranes. The essentiality of cholesterol 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 cholesterol-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 protein (PLTP) involved in vitamin E, phospholipid and Aβ transport in cell membranes [169]-[174] with LPS involved in PLTP transport that supersedes membrane 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 implicates LPS of central importance in the corruption of magnesium therapy that involves peripheral cholesterol metabolism, PLTP activity
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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.

and the role of various acute phase proteins involved in $\beta$ 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 $\beta$ 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 $\beta$ 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 $\beta$ 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 effects 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 myocardial 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 imbalances 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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